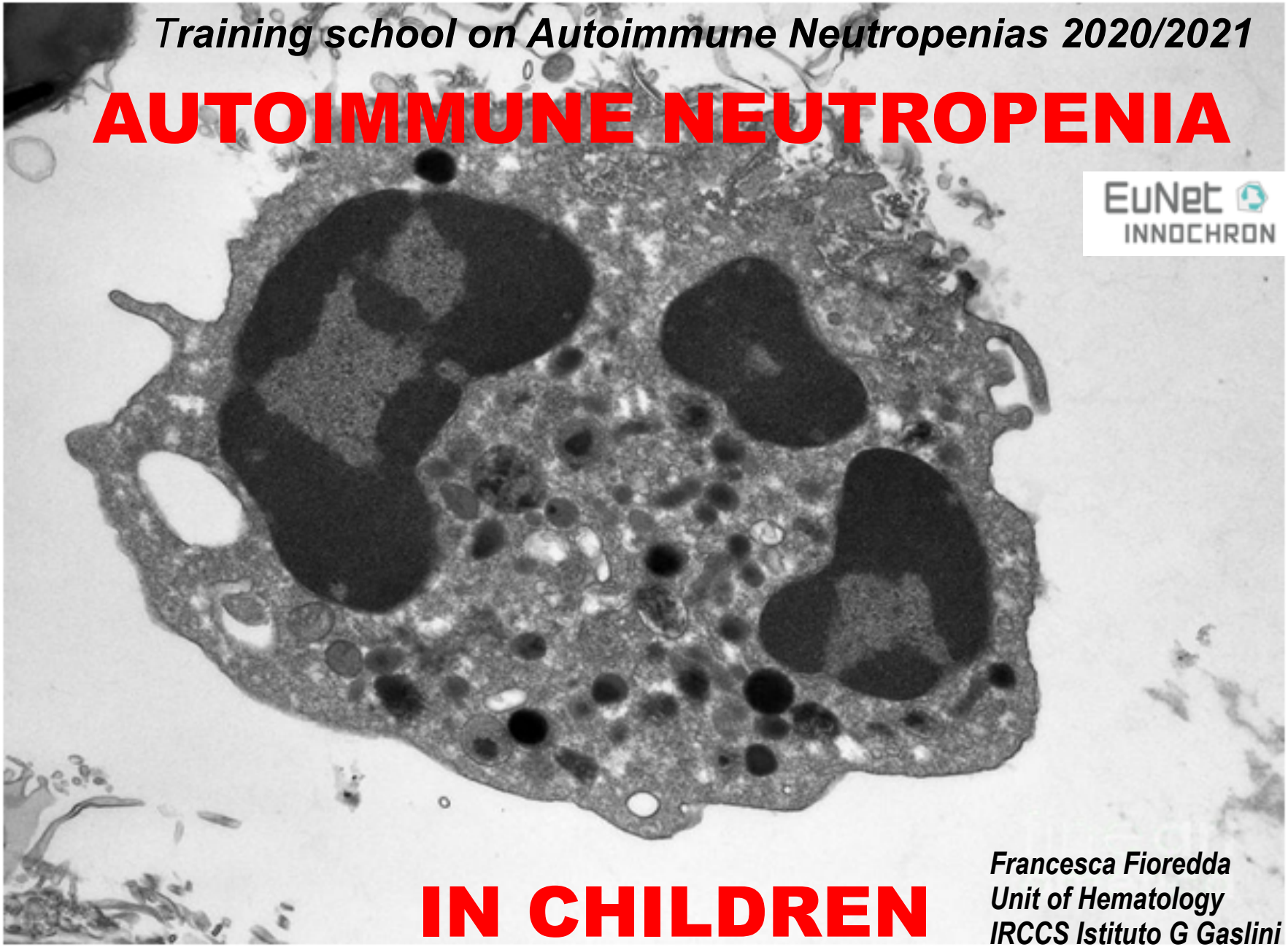
Training school on Autoimmune Neutropenias 2020/2021

AUTOIMMUNE NEUTROPENIA

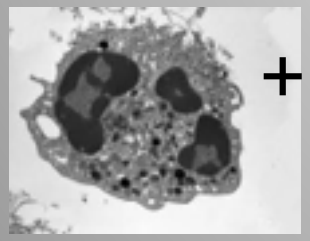


IN CHILDREN

Francesca Fioredda
Unit of Hematology
IRCCS Istituto G Gaslini

NEUTROPENIA

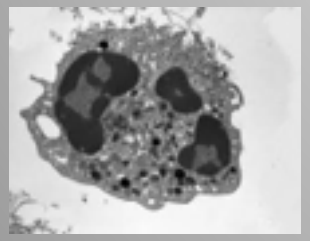
Mild	**ANC 1000-1500/mmc**
Moderate	**ANC 500-1000/mmc**
Severe	**ANC 500-200/mmc**
Very severe	**ANC <200/mmc**



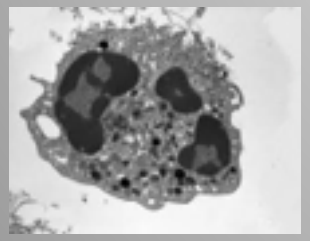
+ Antibodies against neutrophils

AUTOIMMUNE NEUTROPENIA

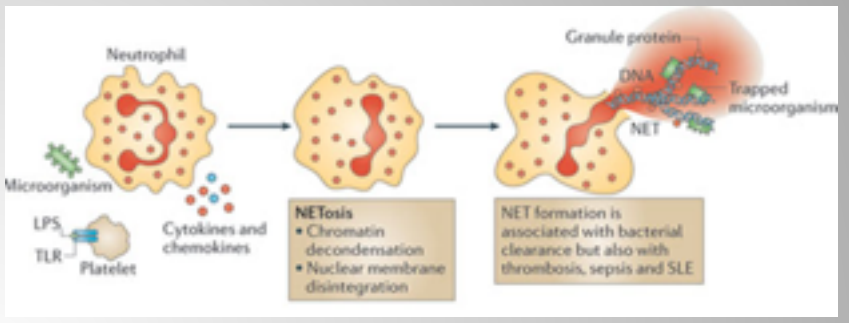
- ✓ Neutrophil, Antigens and Antobodies
- ✓ Diagnosis and classification
- ✓ Clinical features
- ✓ Management and Follo w up



Neutrophils
antigens
antibodies



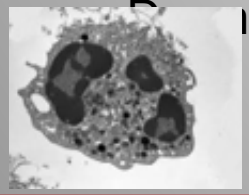
NEUTROPHIL: LINCHPIN between INNATE and ADAPTIVE immune function



INNATE

- Phagocytosis
- Intracellular degradation
- Extracellular discharge of antimicrobial factors
- Formation of neutrophil extracellular traps (NETs)
- Cytokines and chemokines release recruit monocytes, DCs

- Block of maturation of NK cells at an immature stage
- regulation of NK cells reactivity



Jaeger BN et al JEM 2012

ADAPTATIVE

- Induction of Th 1 cell responses during infection

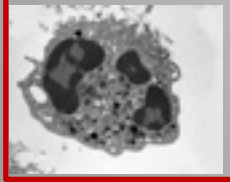
- Potentiation or down regulation of T cell response

  - throught secretion of IL 10 by the TRL stimulous

  - throught inducible nitric oxide synthase (iNOS)

- Binding to B cell-derived immunoglobulin G (IgG) and IgA on opsonized microbes
- Promotion of survival of B cells differentiation and immunoglobulin secreting cells

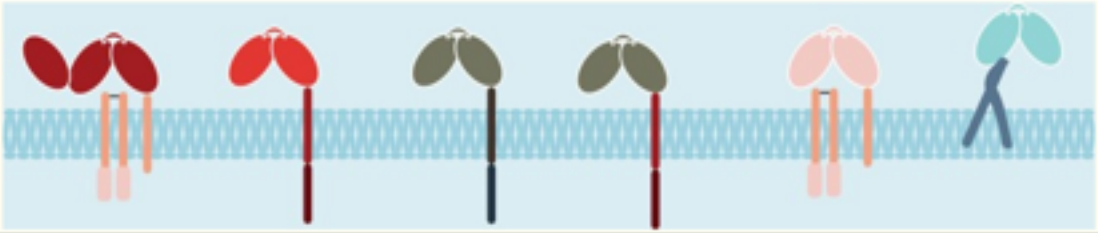
- Promotion of Immunoglobulin class switching and antibodies production via a mechanism BAFF, APRIL and IL 21 mediated



Puga I et al, Nat Immunol 2012, Leliefeld PHC

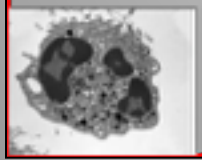
SURFACE ANTIGENS

Classical FcγRs and their expression on neutrophils.

Structure						
						
Name	**FcγRI**	**FcγRIIA**	**FcγRIIB**	**FcγRIIC**	**FcγRIIIA**	**FcγRIIIB**
CD	CD64	CD32A	CD32B	CD32C	CD16A	CD16B
Gene	*FCGR1A*	*FCGR2A*	*FCGR2B*	*FCGR2C*	*FCGR3A*	*FCGR3B*
Alleles	–	H_{131} R_{131}	I_{232} T_{232}	Q_{57} $stop_{57}$	V_{176} F_{176}	NA1 NA2 SH
Affinity	High	Low to medium	Low to medium	Low to medium	Low to medium	Low to medium
Expression on resting neutrophils	< 2,000 copies	30,000–60,000 copies	Low to none; increase when 2B4 promotor haplotype	Low to none	Low to none	100,000–200,000 copies
Neutrophil expression in inflammatory conditions	Up to 10-fold increased expression in presence of IFN-γ and G-CSF	Upregulated in presence TNF-α	Low to none; increase when 2B4 promotor haplotype	Low to none	Low to none	100,000–200,000 copies, subject to shedding

Fcy IIIB trigger neutrophil activation
Bind to the complement rector CD11b/CD18
Inihit the tranendotelial migration

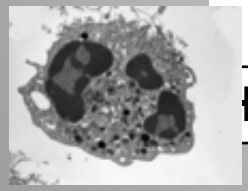
Fcy IIIA trigger NET
produce RO



Wang Y , Frontiers Immunol 2019

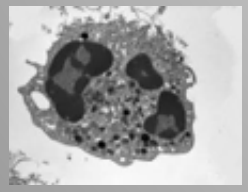
Disorders caused by neutrophil specific antibodies

Antibody	Clinical Condition
HNA-1	Alloimmune neonatal neutropenia
	Autoimmune Neutropenia
	TRALI
HNA-2a	Alloimmune neonatal neutropenia
	Autoimmune Neutropenia
	TRALI
	Graft failure after HSCT
	Drug Induced Neutropenia
HNA-3a	TRALI
HNA-4a	Alloimmune neonatal neutropenia
	Autoimmune Neutropenia
HNA-5a	Unknown



HNA Frequency

Antigen	Italy	Germany	Turkey	Brasil	Black-USA	Hispanic
HNA1a	49%	39%	42%	65%	31%[4]	53%
HNA1b	84%	60%	56%	83%	69%[4]	47%
HNA1c	7%				23%[5]	
HNA2a	96%			97%		
HNA3a	95%	74%	73%	81%		
HNA3b	41%	25%	26%	19%		
HNA4a	97%	90%	88%	94%		
HNA4b	25%	9%	11%			
HNA5a	92%	73%	75%			
HNA5b	47%	26%	24%			

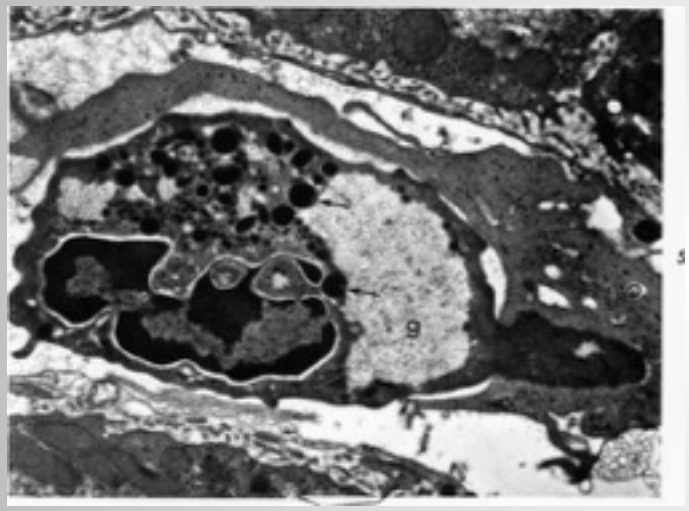


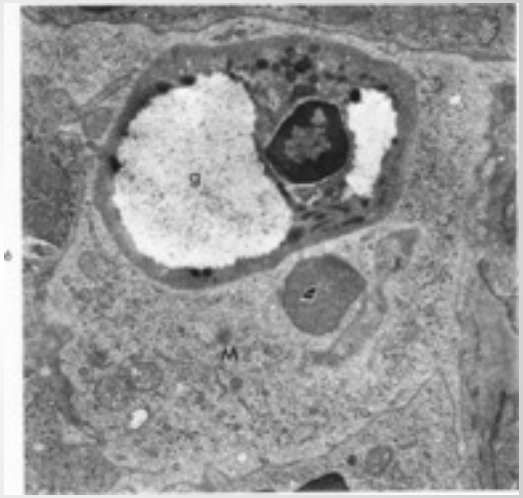
Porretti et al, Blood Transf 2012; Hauck et al, Tissue Antigens 2011;
Norcia et al, Tissue Antigens 2009; Hessner et al, Transfusion 1996;
Lopes LB et al, Transfusion 2013; Kissel et al, Tissue Antigens 2000.

ANTIBODIES «EFFECT»

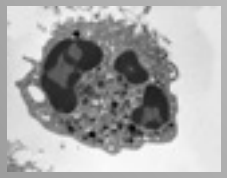
QUANTITATIVE

- Neutrophil phagocytosis by Ab detection or by complement activation (C3) (Ab or Immunocomplex)





- Neutrophil hypoproduction for inihibition of granulocyte marrow precursor



Simpson Dm, Am J pathol 1971 Rustagi PK I Clin Invest 1982, Shastri KA , Blood 1993

ANTIBODIES «EFFECT»

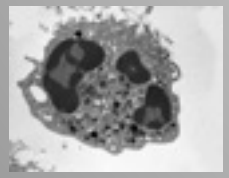
QUALITATIVE

Impairment in CO_2 production (LAD , CD11/CD18)

Abnormal aggregation-disaggregation

Reduced ROS production

Motility defect



PATHOGENESIS of AUTOIMMUNE NEUTROPENIA

Immune reaction against a "foreing" antigen

Molecular mimicry of microbial antigen

Modification of antigen after drug exposure

HLA alleles more frequently associated with disease (HLADR2, HLADQB1 *0503

Loss of suppression of a "self reaction "

Immaturity of the suppressor system

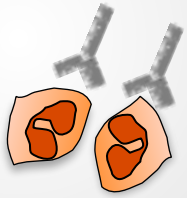
T reg deficiency

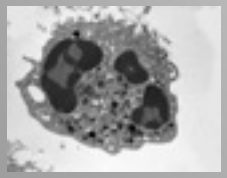
Bux J, Human ImmLoss of supprunology 1991, Wang L, Transfusion 2009, Nakamura K, Br J Hematol 2009, Shastri KA , Blood 1993

ANTIBODIES DETECTION METHODS

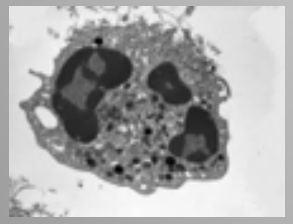
Indirect

Direct





Diagnosis and classification



Useful elements

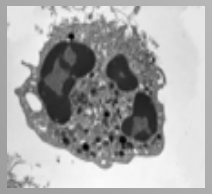
Age at onset

Family historyethnic origin, consanguinity, occurrence of other neutropenia cases, neoplasm, cytopenias and autoimmunity

Personal history previous blood count and number, type, site, **frequency and recurrence of infections (i.e. apthae, skin infections)**

Symptoms: even extra –haemaoltological and compatible with autoimmune, metabolic, gastrointestinal, nutritional diseases

Physical examination weight, stature, psychomotor development, skin, nails, hair characteristic somatic dysmorphisms, hearth function, liver, and **spleen size,** presence of **enlarged lymphonodes,** joints and neurological abnormalities



Curtis R ASH 2017, Fioredda F Ped Blood and cancr 2011

DIAGNOSTIC ALGORITHM

CONFIRMED NEUTROPENIA (3 samples)

severe symptoms

moderate symptoms

mild/absent symptoms

Recent infection/ resolution 4-6 w

POST INFECTIOUS NEUTROPENIA

BONE MARROW

morphology cytogenetic,immunophenotype coltures

hepatic and renal function, immunoglobulin dosage and blood smear

Suspect of cyclicity

ELANE

POS

2 WBC / week (6-sett)

NEG

3 WBC / week (6-weeks)

CYCLIC NEUTROPENIA

Any extrahematological sign associated to neutropenia

Isolated Neutropenia

BLOCK AT PROMYELOCYTE

YES

NO

Second levels investigations and molecular analysis for selected cases

Indirect test Ab AN

NEG

POS

Repeat at least 4 test

AUTOIIMUNE/ ALLOIMMUNE NEUTROPENIA

Follow-up

SEVERE CONGENITAL NEUTROPENIA

CONGENITAL NEUTROPENIA associated to

IMMUNODEFICOENCY
IMMUNEDYSREGULATION
METABOLIC DISEAES
BONE MARROW FAILURE

not essential, but contributive to add informative elements

BONE MARROW

morphology cytogenetic,immunophenotype coltures

molecular analysis

Possible appearance of symptoms during follow up +/- additional cytopenias

LONGLASTING > 24-36 months

NEG

POS

IDIOPATHIC NEUTROPENIA

YES

Resolution within 24-36mesi

YES

AUTOIMMUNE NEUTROPENIA

NO

Stop controls

modified from Fioredda F et al 2011

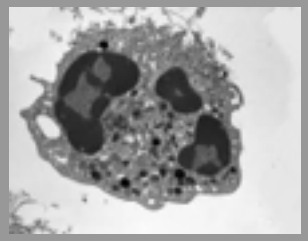
Key Lecture

DEGREE OF SEVERITY

More severe scenario

Intermediate severe scenario

Less severe scenario



More severe scenario

Isolated neutropenia
Severe infections
Persistent count of neutrophil <500/mmc
Early infancy

CONFIRMED NEUTROPENIA (3samples)

severe symptoms

moderate symptoms

mild/absent symptoms

BONE MARROW morphology cytogenetic,immunophenotype coltures

hepatic and renal function, immunoglobulin dosage and blood smear

Any extrahematological sign associated to neutropenia

Second levels investigations and molecular analysis for selected cases

BONE MARROW morphology cytogenetic, immunophenotype coltures

not essential, but contributive to add informative elements

SEVERE CONGENITAL NEUTROPENIA associated to

IMMUNODEFICOENCY
IMMUNEDYSREGULATION
METABOLIC DISEAES
BONE MARROW FAILURE

molecular analysis

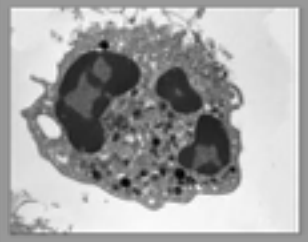
BLOCK AT PROMYELOCYTE

YES

NO

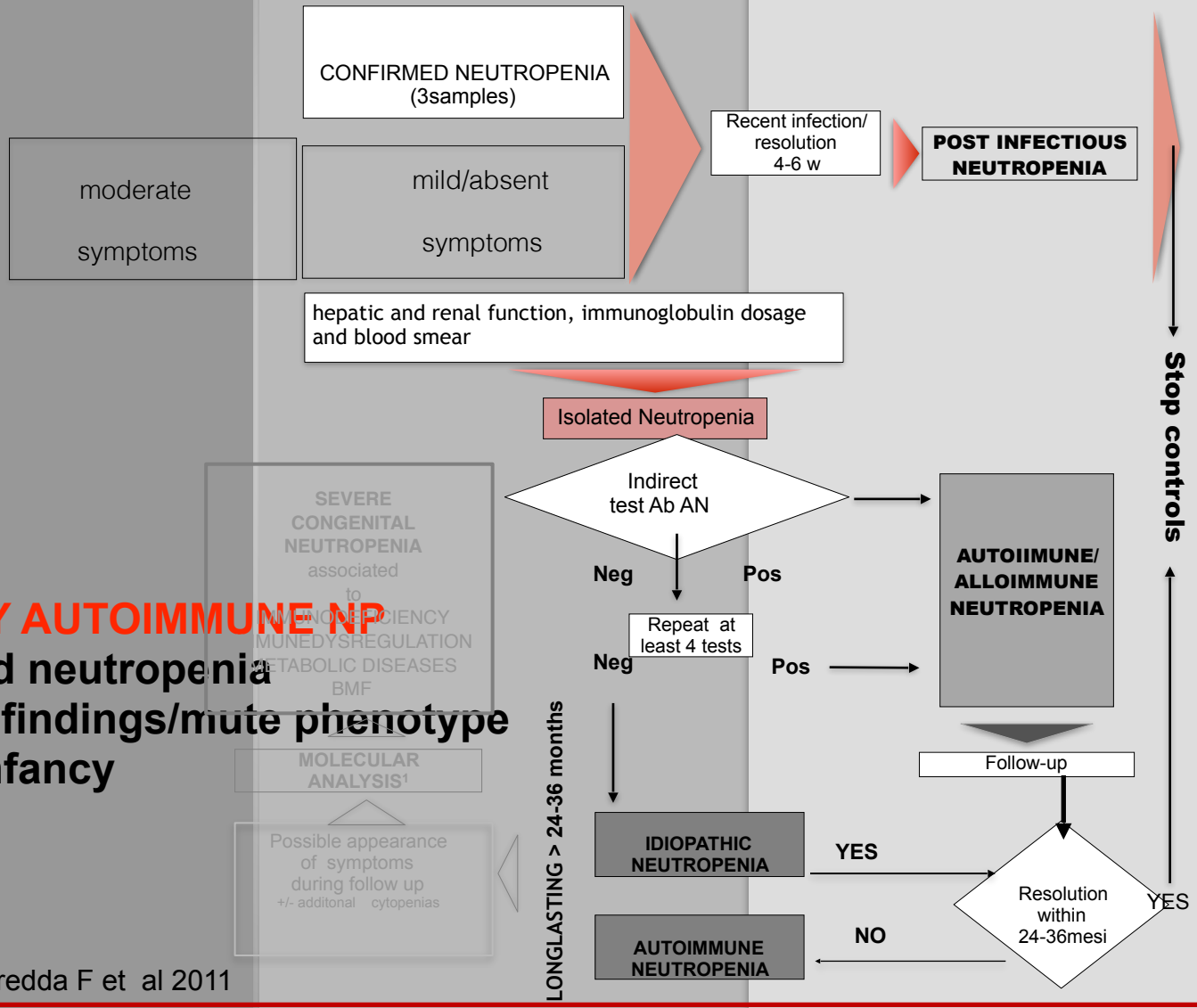
SEVERE CONGENITAL NEUTROPENIA

Molecular analysis



modified form Fioredda F et al 2011

Less severe scenario

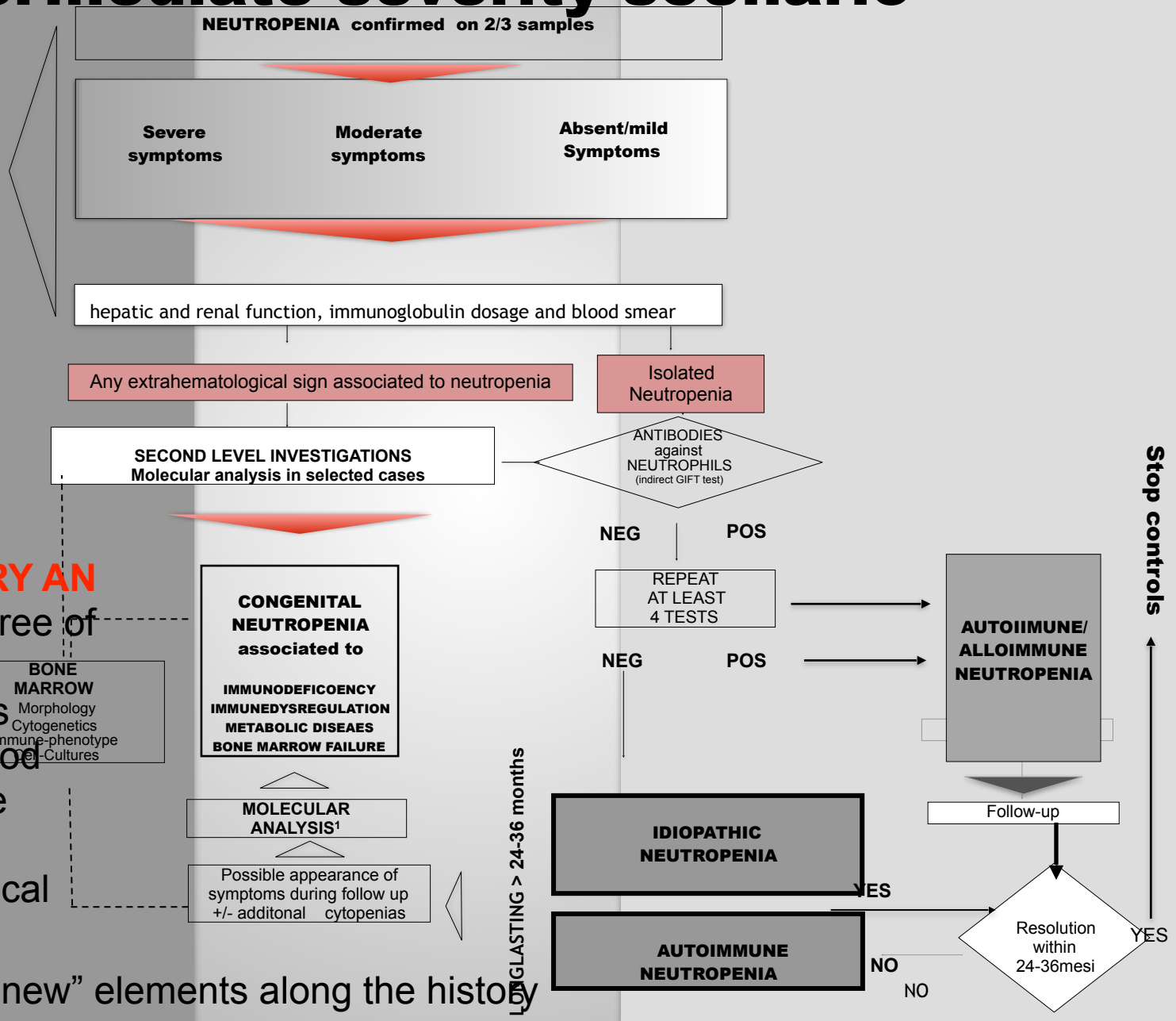


PRIMARY AUTOIMMUNE NP

- **Isolated neutropenia**
- **Casual findings/mute phenotype**
- **Early infancy**

modified form Fioredda F et al 2011

Intermediate severity scenario



NON PRIMARY AN

- Variable degree of neutropenia and infections
- Late childhood adolescence
- Extra-haematological signs

Acquisition of “new” elements along the history

modified from Fioredda F et al 2011

Classification

idiopathic neutropenia

Congenital neutropenia

ISOLATED NEUTROPENIA
ELANE, CSF3R, CXCR2, WAS

ASSOCIATED NEUTROPENIA
Mixed non-haematological signs
HAX1 G6PC3, GFI1,TAZ,USB1, VPS13.
VPS45, SMARCAL1,JAG1, DNM2 ,
Pearson syndrome, SBDS, GATA1, SEC61A1
Metabolic diseases
TCN2, SLC37A, PCCA-PCCB,
MMUT-MMAA-MMAB-MCEE-MMADHCIVD
Immunodef/immunodisregulation
AK2 , CD40L, AP3B1, RAB27A,PRF1-UNC13D-ST
STXBP2
RMRP ,LYST,STK4 CXCR4,GATA2
Genetic Bone Marrow Failure
FANCAnemiaDKC1, NHP2, NOP10, RTEL1, TERC
TERT,
TINF2, WRAP53 RPS-RPL (Blackfan Diamond A
SAMD/SAMD9L

Acquired neutropenia

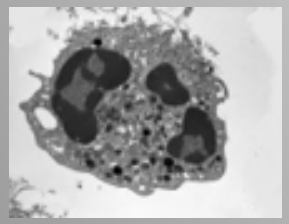
Primary Autoimmune Neutropenia
Secondary Autoimmune Neutropenia
Primary Alloimmune Neutropenia
Secondary Alloimmune Neutropenia

Neutropenia associated to acquired bone marrow failure
Neutropenia associated to myeloprolyphe rative disorders

Pregnancy or delivery related neutropenias
Others (para/post infectious, drugs and nutritional disturbances related)

Feulle et al, 2018, Farruggia et al 2018

Clinical features



Focus on

Autoimmune Neutropenia

Primary (pAIN)

- ✓ Infancy/childhood
- ✓ Adulthood

Secondary (sAIN)

- ✓ Infancy/childhood
- ✓ Adulthood

Primary Alloimmune Neutropenia (only pediatric)

- ✓ Alloimmune neonatal neutropenia
- ✓ Alloimmune neonatal neutropenia in newborn of mother with autoimmune neutropenia

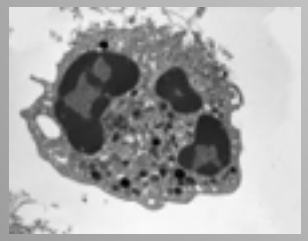
Secondary Alloimmune Neutropenia (any age)

- ✓ Transfusion related acute lung injury (“TRALI”)
- ✓ Transfusion related alloimmune neutropenia
- ✓ Febrile transfusion reactions

P. Farruggia,
World J Pediatr 2015

PRIMARY AUTOIMMUNE NEUTROPENIA of infancy

- ✓ Early infancy
- ✓ Detection by chance
- ✓ Low rate of severe infections
- ✓ Self limited course within 24 -36 mo



Cohorts of pAN affected children

First Author	No pts	Age at diagnosis(mo)	Female%	Severe Infections	Sensitivity Ab Anti N	Resolution	Resolution Age/Lenght (mo)
Lalezari P 1986	121	8 (3-30)	60%	---	---	95%	Lenght 20
Bux J 1998	240	8 (5-15)	54%	12%	74%	80%	Lenght 7-24
Bruin M1999	21	<	---	No	100% (selected +)	86%	Lenght 30 (16-52)
Chung BHY2004	24	9	50%	10%	21%	55% At 3y	Lenght 28.6
Wang L 2008	55	9.8 (4-28)	45%	No	100% (selected +)	100% on 24 available pts	Age 22.5 (13-44) Lenght 12,7
RutiSella B 2010	72	10 (0-42)	37%	15%	62,5%	100 % On available pts (74%)	Lenght 4.4 (0.5-30)
Audrain M 2011	116	16 (3-59)	48%	----	60%	----	---
Farruggia P 2015	157	8 (0–54):	36%	9.6%	62%	90% at 5 y	Age 25.7 Lenght 15.6

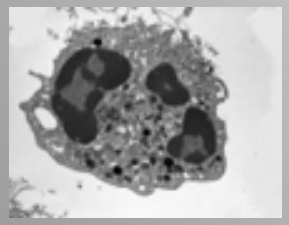
Bux J , Blood 1998, Audrain M Ped All Immunol 2011, Brun MC Blood 1999 , Chung B Hong Kong Med J 2004, Wang L Transfusion 2009, Lalezari J Ped 1986, Ruti Sella IMAJ 2010 , Farruggia P Am J Hem 2015

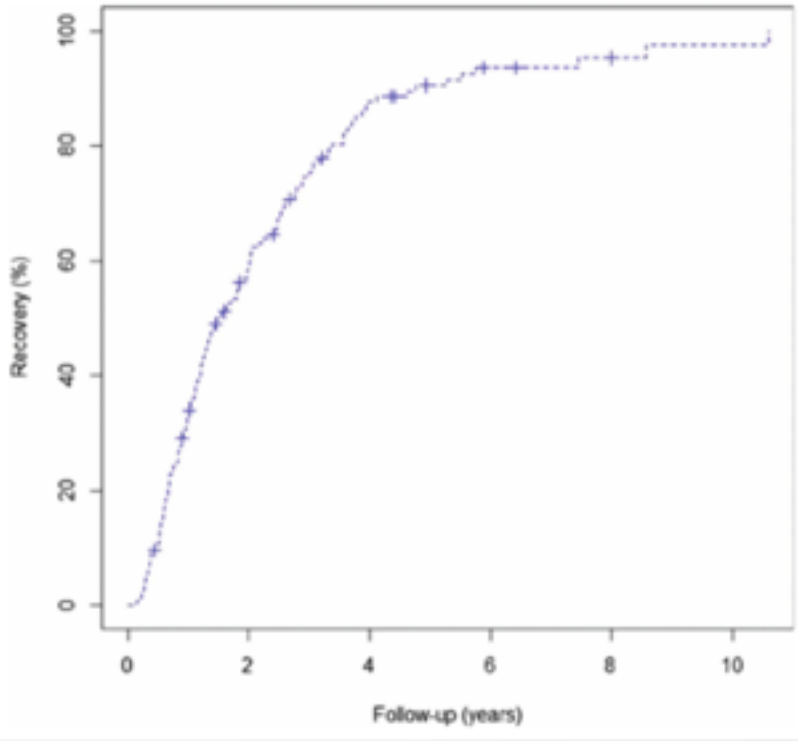
ITALIAN REGISTRY

157 patients pAN
Median age at onset: 7-8 months. Very rare at less <1 month (2%).1
More frequent in former preterms: 13.2% of pAIN patients.1

	Autoimmune neutropenia of infancy (157)
Male	64.3%
Median age at onset (years)	0.70
Median age at diagnosis (years)	1.06
Median age at resolution	2.14
Median duration (years)	1.30
Recovery	89.1%
Median WBC at onset ($\times 10^9$/L)	6.1
Median ANC at onset ($\times 10^9$/L)	0.45
Leucopenia at onset	41.7%
Monocytosis at onset	19.3%
Increased IgG at onset[a]	6.0%
Selected IgA deficiency[a]	3%
Severe infections	9.6%

[a] Data available on 133/157 patients.



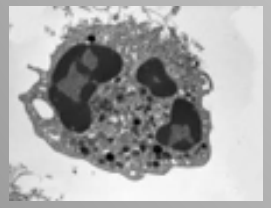


Primary AUTOIMMUNE NEUTROPENIA in adults

> Females

Association with other cytopenia (40%)

Approximately one third of adult patients with idiopathic neutropenia have IgG and/or IgM antineutrophil antibodies demonstrable in their serum.



Logue GL, Am J Med 1991

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P. Farruggia,
World J Pediatr 2015

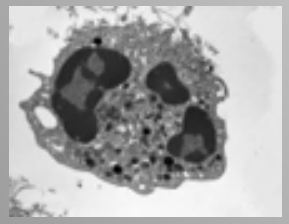
Secondary autoimmune neutropenia

In Childhood

- ✓ Other autoimmune diseases
- ✓ Immunodeficiency
- ✓ Drug
- ✓ Neoplasm
- ✓ BMT

In adulthood:

- ✓ Evans
- ✓ Autoimmune Thyroiditis
- ✓ SLE
- ✓ Sjogren syndrome
- ✓ Rheumatoid arthritis
- ✓ Felty's syndrome
- ✓ Crohn disease
- ✓ Autoimmune hepatitis
- ✓ Multiple sclerosis

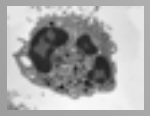


P. Farruggia, World J Pediatr 2015

ITALIAN REGISTRY

Secondary Autoimmune Neutropenia 26 patients

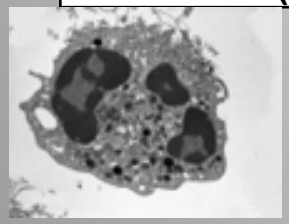
Sex	Age at onset (y)	Recovery	Age at recovery (y)	Associated autoimmunity
F	2	yes	7,44	Autoimmune hepatitis; ES (bilineage: thrombocytopenia)
M	15,12	yes	15,89	ES (bilineage: thrombocytopenia)
F	13,8	yes	14,12	Celiac disease; Autoimmune thyroiditis (anti-TPO+)
M	8,09	no		Celiac disease
M	10,6	no		Celiac disease; ES (bilineage: thrombocytopenia); DAT +
M	10,82	no		ES (trilineage)
F	3,76	no		ES (trilineage); autoimmune encephalitis
M	13,43	no		ES (bilineage: thrombocytopenia)
M	4,02	no		ES (bilineage: thrombocytopenia); ANA 1:320
M	0,5	no		ES (bilineage: AIHA)
M	17,17	no		ES (trilineage); ANA 1:160
F	12,42	no		ES (bilineage: thrombocytopenia); ANA 1:640; SLE
F	13,33	no		ES (trilineage); ANA 1:160;
F	15,55	no		Autoimmune thyroiditis (anti-TPO +; anti-TG +)
F	13,43	no		Autoimmune thyroiditis (anti-TPO +; anti-TG +)
F	7,45	no		Autoimmune thyroiditis (anti-TG +)
M	7,49	no		Autoimmune thyroiditis (anti-TPO +)
F	16,47	no		Autoimmune thyroiditis (anti-TPO +; anti-TG +); ANA 1:1280
M	9,54	no		Autoimmune thyroiditis (anti-TG +); ANA 1:320
F	11,98	no		GH deficiency; ANA 1:320
F	7,4	no		GH deficiency; ANA 1:320
M	12,49	no		IDDM
F	0,63	no		ANA 1:160; arthralgia; ASMA +; anti-GAD
F	7,2	no		ANA 1:1280; arthralgia



ITALIAN REGISTRY

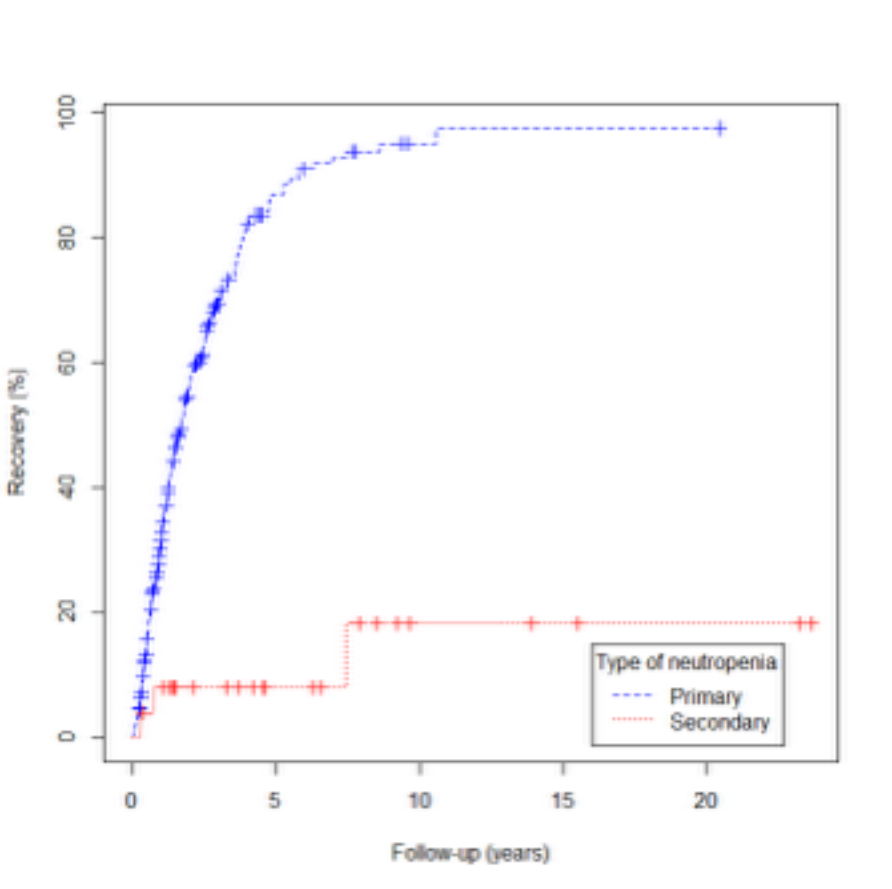
Comparison between primary AIN and secondary AIN

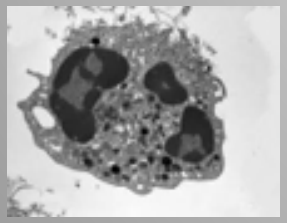
	pAIN (263)	sAIN (26)	*p*
Sex (F%)	41%	61%	0.049
Onset (y; median)	0.77	10.07	1.12e-12
Diagnosis (y; median)	1.09	10.98	2.03e-13
G-CSF	6.9%	23.1%	0.0045
Severe infections	11.8%	40.0%	0.0001
Recovery	74.9%	7.7%	2.26e-12
Recovery (median age)	2.14	14.11	0.0035
WBC (median) at onset	5.93 x 10^9/L	2.48 x 10^9/L	2.81e-11
ALC (median) at onset	4.36 x 10^9/L	1.58 x 10^9/L	6.29e-11
AMC (median) at onset	0.62 x 10^9/L	0.34 x 10^9/L	9.89e-07
ANC (median) at onset	0.45 x 10^9/L	0.63 x 10^9/L	0.035



Farruggia P et al, Am J Hematol 2017

Recovery: primary vs secondary AIN of infancy

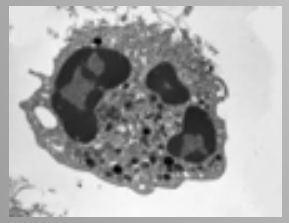




Farruggia et al, Am J Hematol 2017

	sAIN of childhood	Adult AIN (primary and secondary)
Female sex	~ 60%	~ 70%
Spontaneous recovery	~ 10%	~ 10%
Leucopenia at onset	~ 80%	~ 80%
Monocytosis at onset	~ 5%	~ 5%
Severe infections	~ 40%	~ 40%
Continuous G-CSF treatment	~ 15%	~ 20%

Pediatric sAIN =Adult sAIN =
Adult pAIN

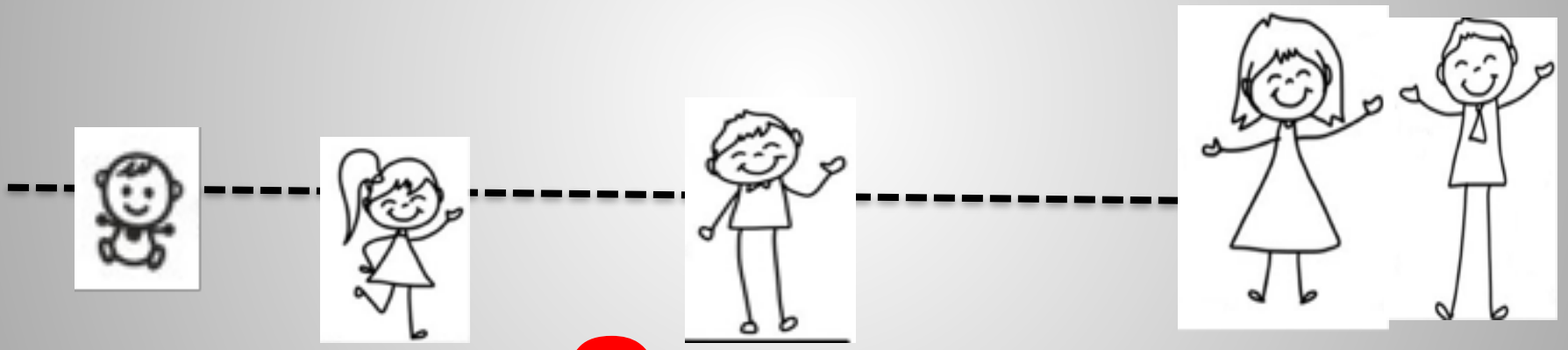


ONE DISEASE!!

Autoimmune Neutropenia

«natural history»

Primary AUTOIMMUNE NP **secondary AUTOIMMUNE NP**



Long lasting **Late onset**

Long Lasting and Late Onset

Autoimmune Neutropenia

Registry Study

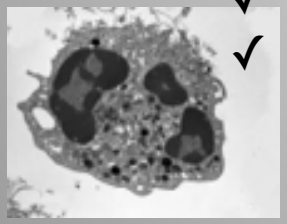
INCLUSION CRITERIA

Neutropenia + Ab against Neutrophil (indirect test)

- ✓ Lasting more than 36 months from onset
- ✓ Diagnosis after 5 y of life , up to 18 y

EXCLUSION CRITERIA

- ✓ Association at diagnosis with autoimmune/disimmune disorders
- ✓ Concomitant additional cytopenias
- ✓ Association with drug assumption, neoplasms
- ✓ Np occurred after HSCT



Fioredda F,Blood Advances 2020, in press

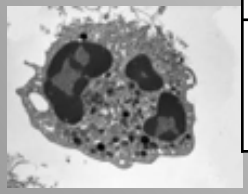
RESULTS 1

	PrimaryAN pAN = 135 pts	Late Onset Np LO =31pts	Long Lasting Np LL = 48 pts	P value
Sex (F)	41/135 (30%)	16/31 (52%)	25/48 (52%)	0.001
Age at diagnosis (y) [median (IQR)]	0.6 (IQR 0.3-1.3) .	11.5 (IQR 7.6-14.6)	1.18 (IQR 0.6-2.2)	<0.001
Lenght of Neutropenia (y) [median (IQR)]	1.03 (IQR0.54-1.7)	2.1 (IQR1.4-4.4)	4.5(IQR 3.5-7.09)	<0.001
Resolution of Neutropenia	135/135 (100%)	4/31(13%)	28/48(58%)	<0.001
ANC at onset [median (IQR)]	430 (IQR 230-716)	649 (IQR 430-970	552(IQR350-790)	<0.001
Leukocyte x 10^9/l at onset [median (IQR)]	6125 (IQR 5010-7920)	3180 (IQR 2670-3710)	5030 (IQR3440-6900)	<0.001
Lymphocyte x 10^9/l value [mediana(IQR)]	4740(IQR 3500-5880)	1680(IQR1240-1900)	2370 (IQR 1920-3400)	<0.001
Monocitosis x 10^9/l at onset	15/120(12.5%)	5/26(19%)	10/38 (26%)	ns

Fioredda F,Blood Advances 2020, in press

RESULTS 2

	PrimaryAN pAN = 135 pts	Late Onset Np LO =31pts	Long Lasting Np LL = 48 pts	P value
Low CD3	7/72 (10%)	2/24 (8%)	11/39(28%)	0.02
Low CD4	8/72(11%)	4/25(16%)	11/38(29%)	0.06
Low CD8	11/71(15%)	4/25(16%)	7/40(17,5%)	ns
Low CD19	6/64(9%)	12/25(48%)	13/37(35%)	<0.001
Low NK (CD3+CD16+CD56+)	10/62(16%)	9/23(39%)	10/34(29%)	0.06
Immunoglobulin depletion	7/113(6%)	4/26 (15%)	3/44(7%)	ns
Infectious epysodes	65/130 (50%)	14/29(48%)	18/47 (38%)	0.4
Severe infections	16/65 (25%)	3/14(21%)	3/18 (17%)	0.2
GCSF therapy	7/135(5%)	3/21 (14%)	7/42(17%)	0.04
Autoimmune diseases/markers	2/135(1%)	16/29 (55%)	8/48(17%)	<0.001



Fioredda F,Blood Advances 2020, in press

Primary Autoimmune Neutropenia (pAN)

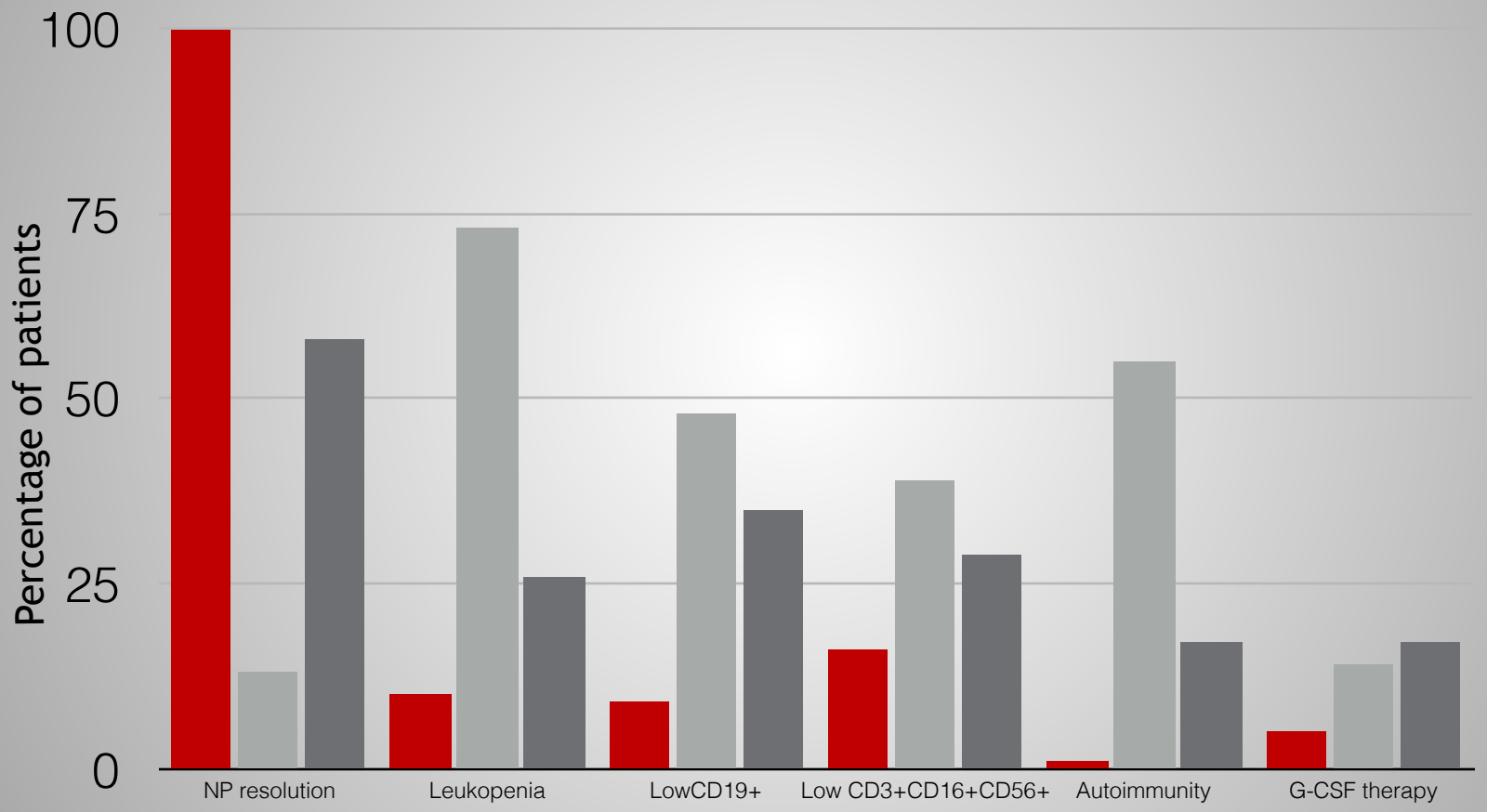
Early Onset and resolution within 3 years
135 patients

Late Onset Neutropenia (LONp)

Neutropenia Onset > 5-18 years
31 patients

Long Lasting Neutropenia (LLNp)

Neutropenia Lasting >3 years
48 patients



Fioredda F,Blood Advances 2020, in press

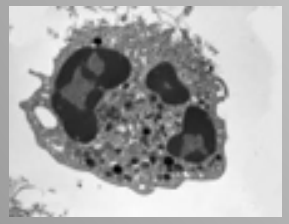
RESULTS 4

PT n	LO/ LL	Assoc Leukopenia	Infections/ type	Other symptoms	Auto immune Markers	Lymphocyte subclasses Deficiency	Gene Variants	Variants classif
7	LO	Y	Hydroadenitis	No	ANA 1:160	↓ CD19+	TINF2 § p.Ser245 Tyr	VUS°
11	LO	Y	Skin abscesses	Recurrent diarrhea	No	No	TACI p.Cys193Ter	Likely Pathogenic°
12	LO	Y	Recurr aphtae Pneumonia	Malar rash, legs pain	No	↓ CD8+	TACI p.Ala181Glu	VUS°
15	LL	N	Adenitis Colecistitis	Diarrhea	ASMA	↓ CD8+↓ CD19+ ↓ NK	LRBA p.Gln2561X +c. 1359+1G>A	Pathogenic+ Pathogenic°

Fioredda F,Blood Advances 2020, in press

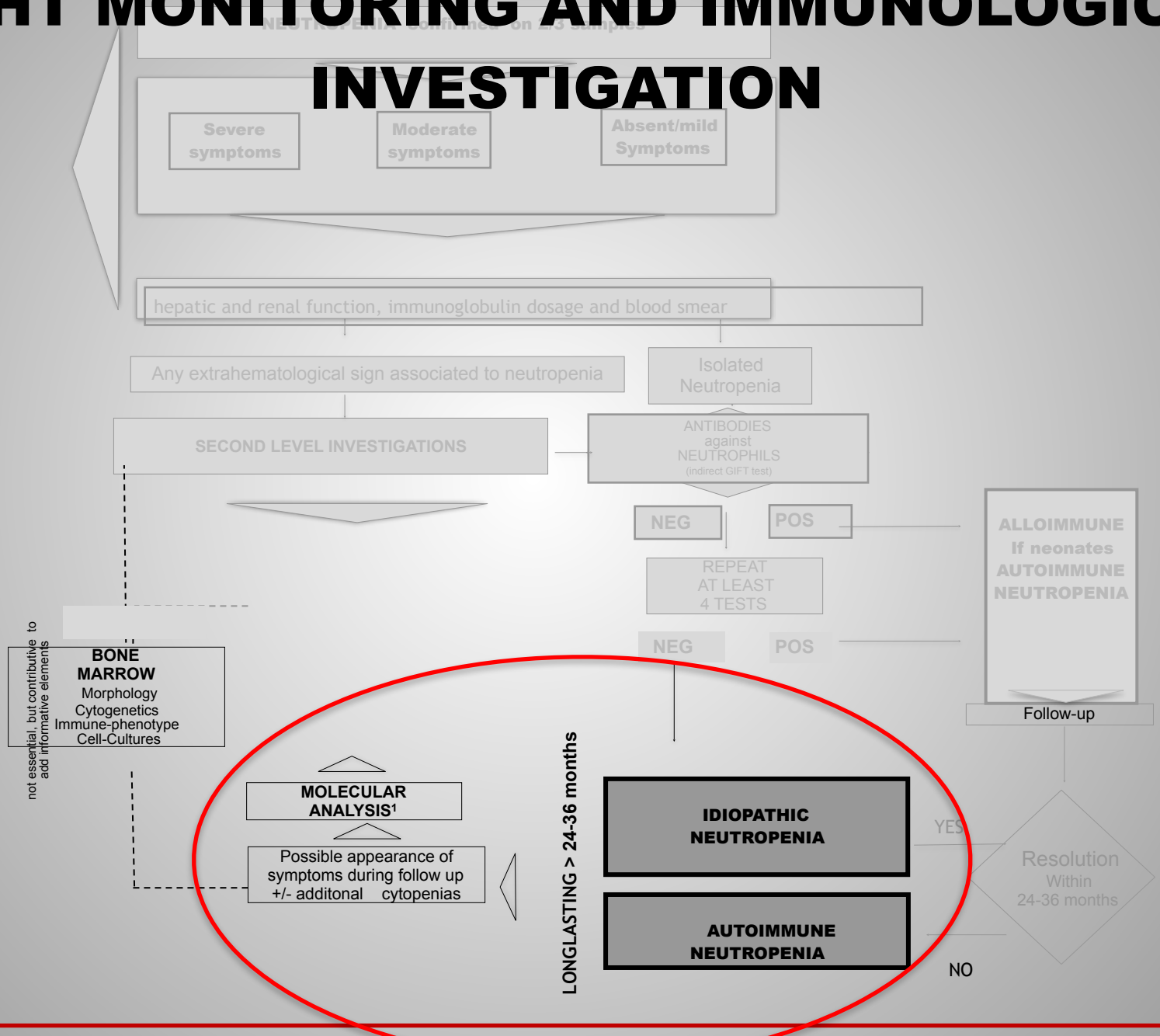
CONCLUSIONS

- ✓ LL/LO neutropenia anticipatory phenomena of an immunodeficiency/ dysregulation disease
- ✓ Tight monitoring and extensive immune investigations to identify underlying immunological disease
- ✓ Early diagnosis of an immunological disease for prevention of complication and application of targeted therapies

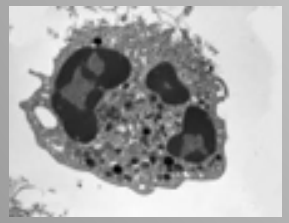


Fioredda F,Blood Advances 2020, in press

TIGHT MONITORING AND IMMUNOLOGICAL INVESTIGATION



Management
And
Follow up



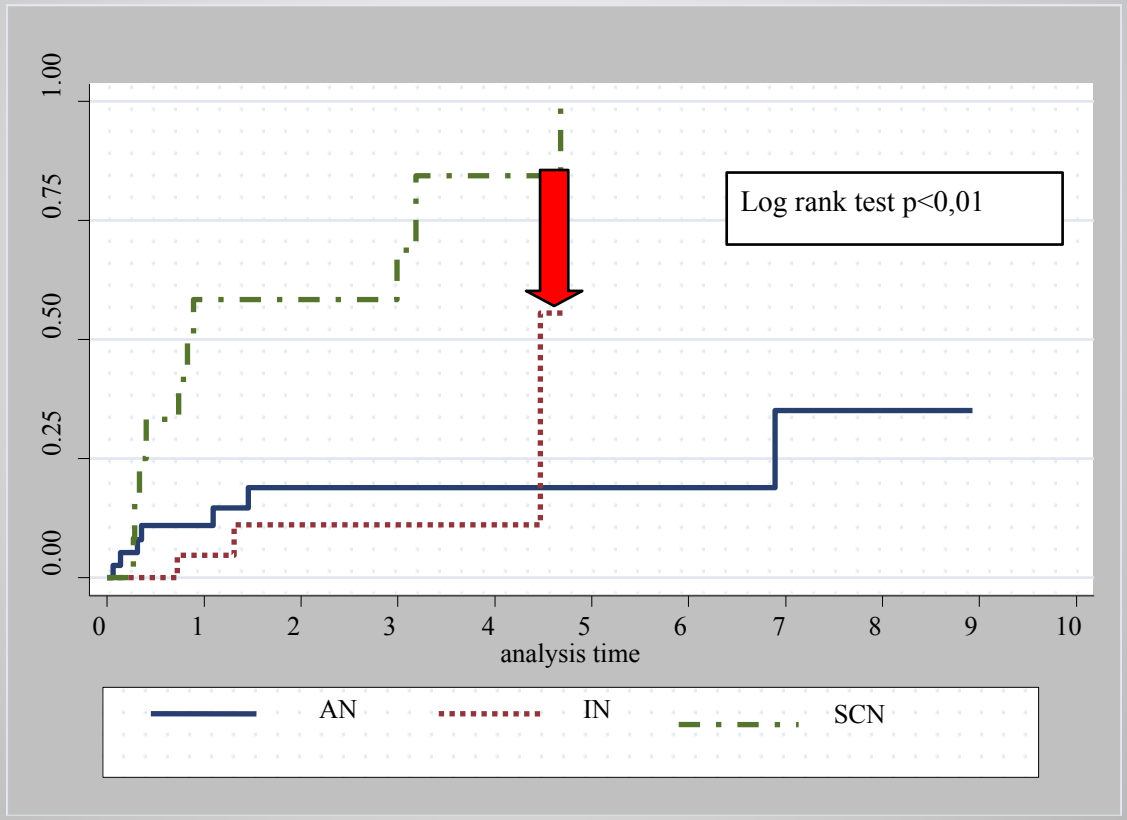
Cohorts of pAN affected children

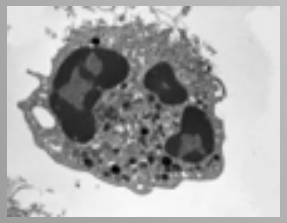
First Author	No pts	Age at diagnosis(mo)	Female%	Severe Infections	Sensitivity	Resolution	Resolution Age/Lenght (mo)
Lalezari P 1986	121	8 (3-30)	60%	---	---	95%	Lenght 20
Bux J 1998	240	8 (5-15)	54%	12%	74%	80%	Lenght 7-24
Bruin M1999	21	<	---	No	100% (selected +)	86%	Lenght 30 (16-52)
Chung BHY2004	24	9	50%	10%	21%	55% At 3y	Lenght 28.6
Wang L 2008	55	9.8 (4-28)	45%	No	100% (selected +)	100% on 24 available pts	Age 22.5 (13-44) Lenght 12,7
RutiSella B 2010	72	10 (0-42)	37%	15%	62,5%	100 % On available pts (74%)	Lenght 4.4 (0.5-30)
Audrain M 2011	116	16 (3-59)	48%	----	60%	----	---
Farruggia P 2015	157	8 (0–54):	36%	9.6%	62%	90% at 5 y	Age 25.7 Lenght 15.6

Bux J , Blood 1998, Audrain M Ped All Immunol 2011, Brun MC Blood 1999 , Chung B Hong Kong Med J 2004, Wang L Transfusion 2009, Lalezari J Ped 1986, Ruti Sella IMAJ 2010 , Farruggia P Am J Hem 2015

ITALIAN REGISTRY
CUMULATIVE INCIDENCE OF INFECTIONS

Infectious ratio= (no of infections/period at risk) x1000)



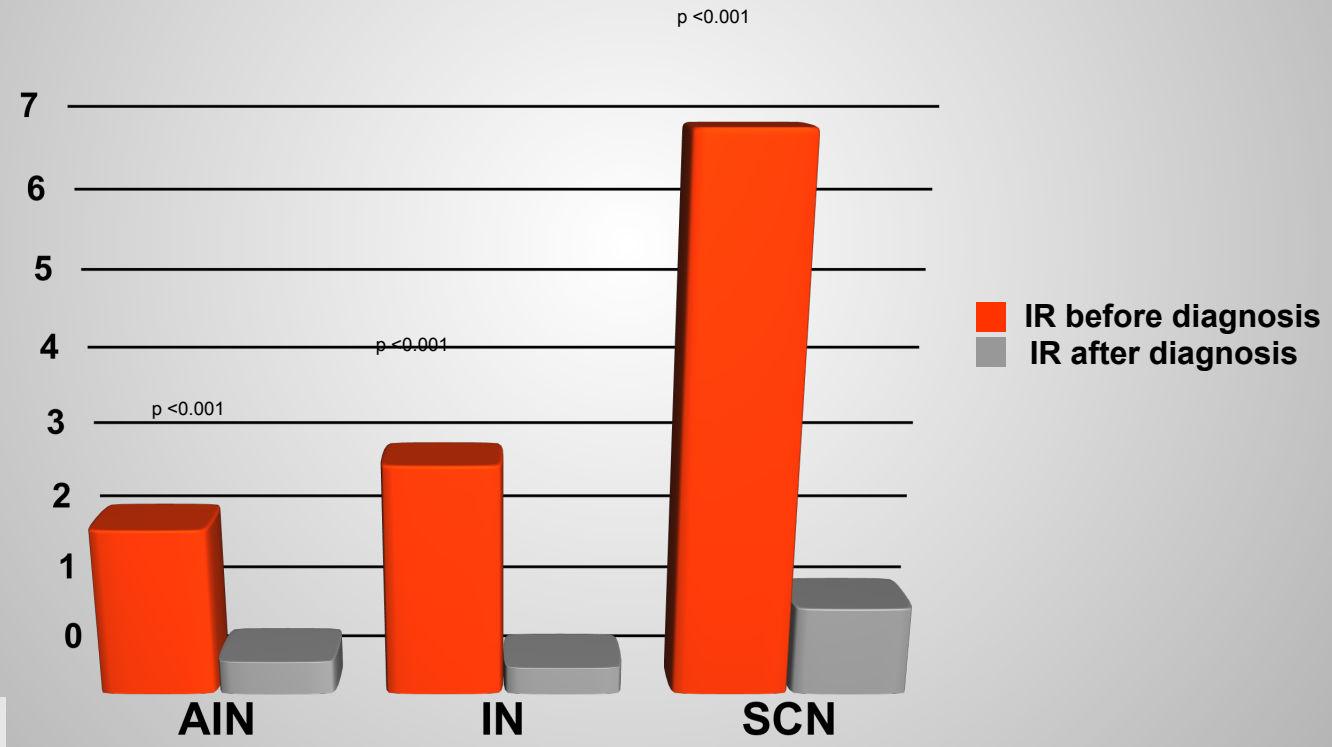


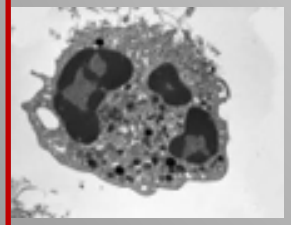
F. Fioredda et al. Pediatr Infect Dis J. 2013

ITALIAN REGISTRY

INFECTIOUS RATIO

Before and after diagnosis





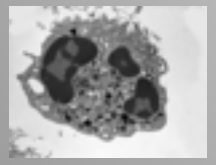
F. Fioredda et al. Pediatr Infect Dis J. 2013

Italian Neutropenia Registry

INFECTIOUS EPISODES

- ✓ pharyngitis, tracheobronchitis (53%)
- ✓ otitis (30%)
- ✓ apthous gengivostomatomatitis (23%)
- ✓ skin and subcutaneous infectious (17%)
- ✓ pneumonia (8%)
- ✓ IVU (6%)
- ✓ bacteremia (3%)
- ✓ sinusitis (2%)

NEVER LETHAL



Hospitalization for infection 40% on all the episodes

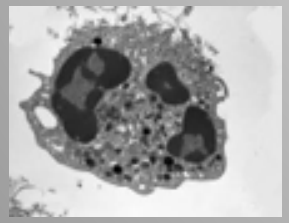
UP TO DATE

data from the Italian Neutropenia Registry

Infectious episodes and hospitalization according to ANC count (<500/cmm, 500-1000/cmm,>1000/cmm)

UTI significantly related to low neutrophils level
(p=0.049)

Non signicant association between hospitalization/patient and ANC
(p=0.47)



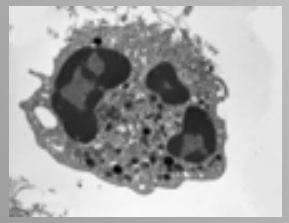
F. Fioredda et al. Pediatr Infect Dis J. 2013

PRIMARY AUTOIMMUNE NEUTROPENIA

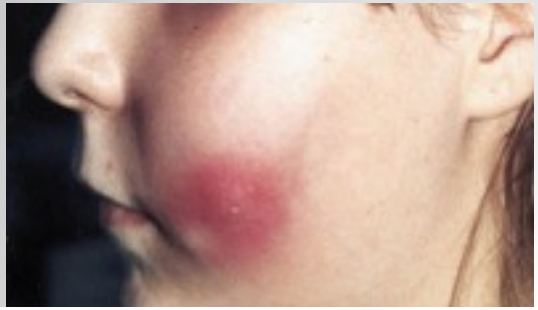
BENIGN DISEASE CHARACTERIZED BY **MINOR INFECTIOUS RISK** AND SPONTANEOUS RECOVERY

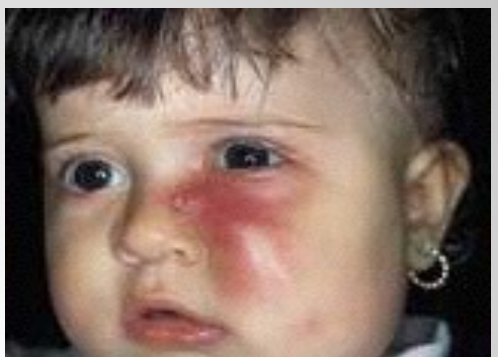
NON NEGLIGIBLE PERCENTAGE OF HOSPITALIZATION

STRICT SURVEILLANCE of EMERGING INFECTIONS EVEN DESPITE ANC COUNT



NON NEGLIGIBLE PERCENTAGE OF HOSPITALIZATION

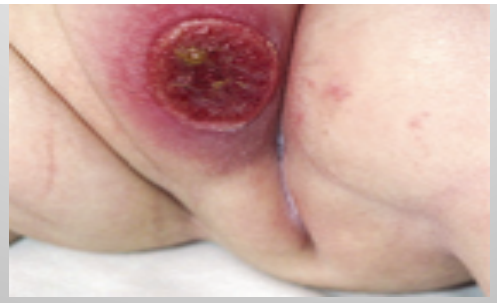


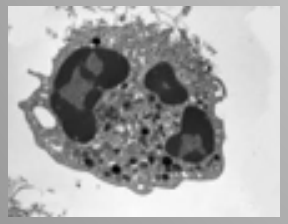


› Pediatr Infect Dis J. 2020 Sep 22. doi: 10.1097/INF.0000000000002915. Online ahead of print.

Infant Pyogenic Liver Abscess Complicated With Autoimmune Neutropenia: Two Cases

Shogo Otake [1], Rin Tamashiro [1], Naoya Morisada [2], Masashi Kasai [1]





SURVEILLANCE of EMERGING INFECTIONS

Granulocyte Colony Stimulating Factor
use in autoimmune NP

- ✓ **ANC < 0·5 × 10^9/l and recurrent fever and infections**
- ✓ **Minimal effective dose (usually 0·5–3·0 µg/kg/day**
- ✓ **Daily or alternate day basis**
- ✓ **The least dose for the best effect (1·0 × 10^9/l)**

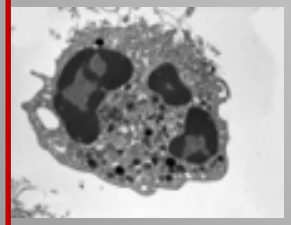
Dale D , BJH 2017, Fioredda F Am J Hematol 2012

Granulocyte Colony Stimulating Factor
G-CSF test

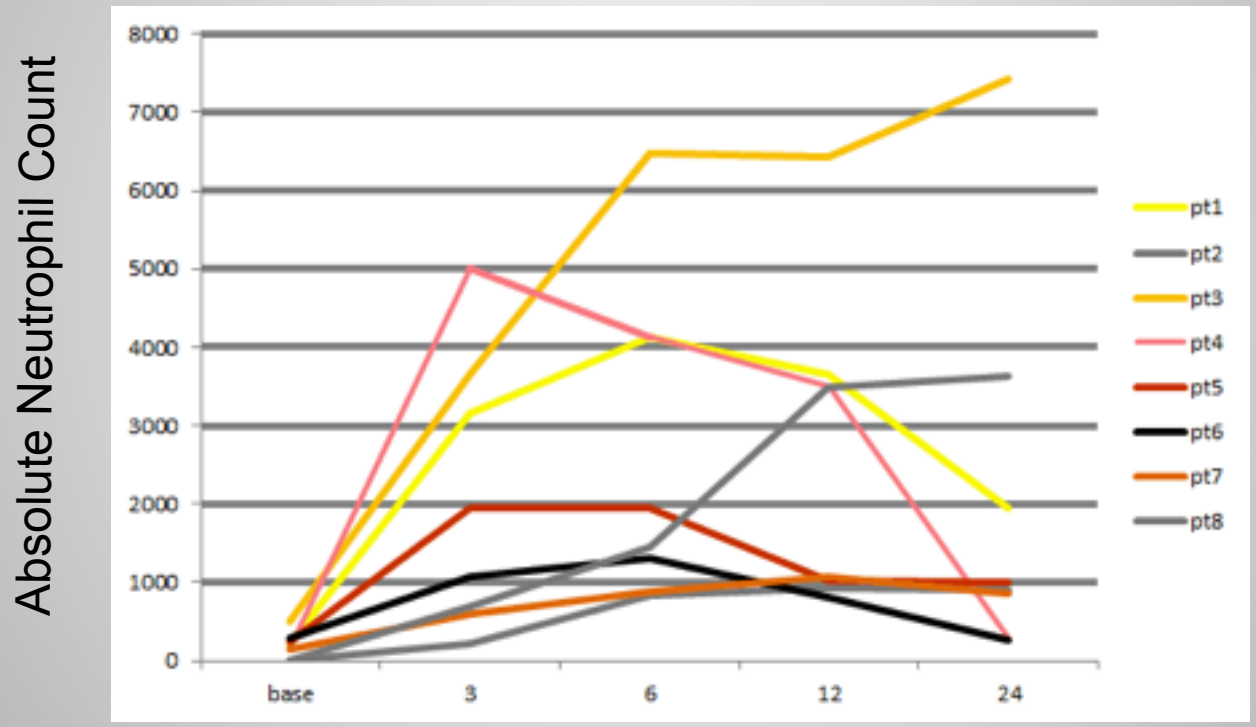
G-CSF 5 γ /Kg s.c.

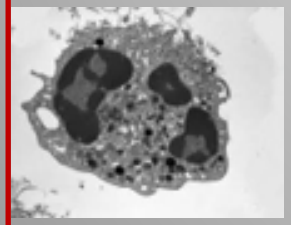
Baseline ANC value
+3h
+ 6 h
+12 h
+24 h

Doubling ANC (> 500/cmm)

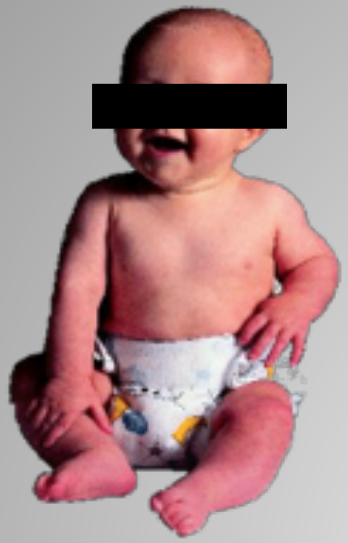


Granulocyte Colony Stimulating Factor
G-CSF test





Hours from G-CSF administration



After diagnosis….

Counselling and contact

- Family reassurance (time of resolution not always short…)
- Avoid overtreatment (blood count 3-4 times/y, repeat Ab against neutrophils if negative, no basically BM)
- On demand use of G-CSF
- Improvement of quality of life

Indication to bone marrow exam

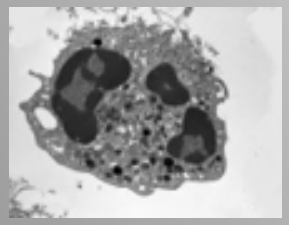
a) neutropenia associated with **severe, very severe or torpid infections** or recurrent sthomatitis or gingivitis

b) neutropenia associated with **any other cytopenia** (anemia, thrombocytopenia and lymphopenia) **with or without lymphoprolipheration**

c) Chronic neutropenia in **adolescents/ young adults** in diagnostic work up phase

d) Idiopathic neutropenia lasting **more than 24 months**

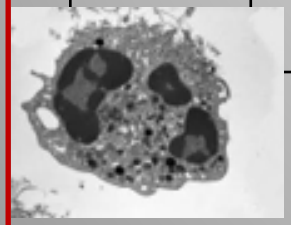
e) Autoimmune neutropenia lasting more than 24 months in subjects **aged > 5 years**



modified from Fioredda F et al 2011

Recommended Follow up

	Full blood count	Biochemical parameters	Bone marrow	Abdomen Ultrasound Scan	Bone density	Further consideration
AN G-CSF Treated Continuously	At least 3/y	At least 2/y	At least 1	12 -24months	24 months	If a spontaneous resolution of neutropenia does not occur deepen immunological features and consider to perform an enlarged panel of autoimmunity If neutropenia is persistent and strongly suggestive of AN repeat indirect antibodies against neutrophils (at least 4 times) In AN lasting more than 36 months think of immune deficiency/ dysimmunity and perform NGS for PID
AN Not treated with G-CSF	At least 3/y	At least 2/y	Not indicated routinely , see the clinic	-----	---------	



Fioredda F, modified Ped Blood Cancer 2011


THANKS!!