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NEONATAL IMMUNE NEUTROPENIAS

I have No financial disclosure or conflicts of interest
with the presented material in this presentation

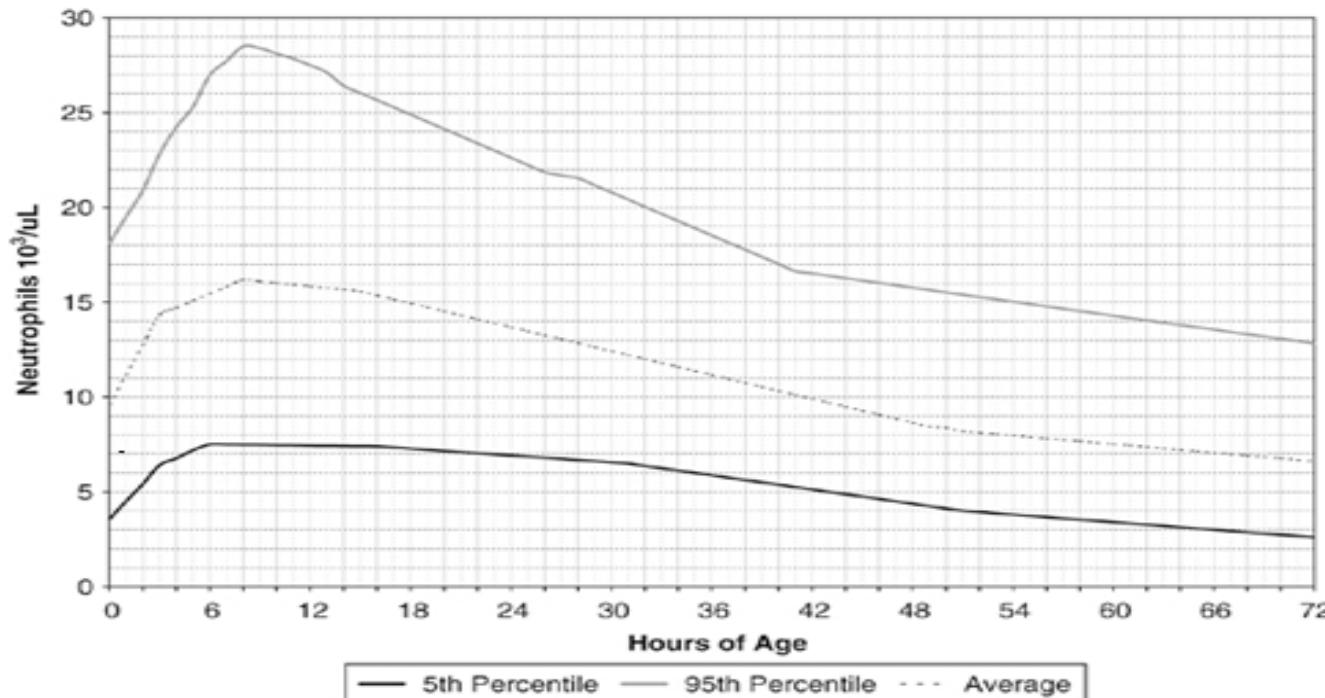
Cutoff

Age	WBC $\times 10^9/L$	Neutrophils $\times 10^9/L$
Birth	18 (9.0-30.0)	11 (6.0-26.0)
7 days	12.2 (5.0-21.0)	5.5 (1.5-10.0)
14 days	11.4 (5.0-20.0)	4.5 (1.0-9.5)
30 days	10.8 (5.0-19.5)	3.800 (1.0-9.0)

Dallmann, 1977

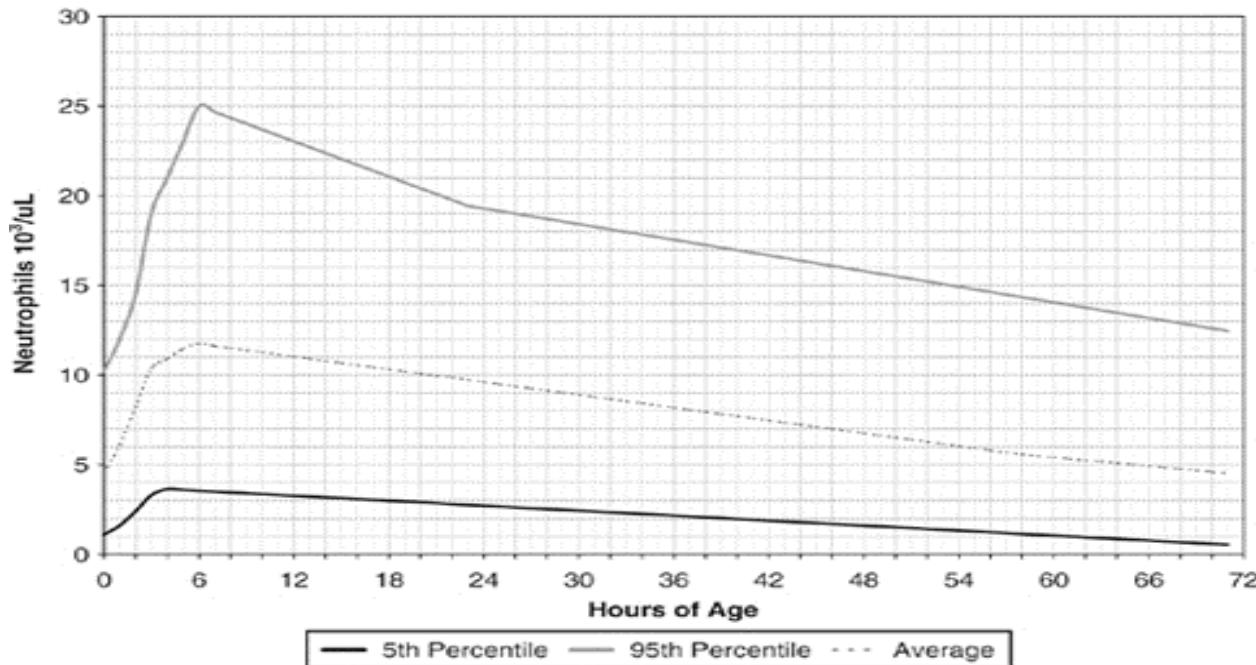
The cutoff of $1.0 \times 10^9/L$ becomes significant after 14 days of age, but.....

Full-term newborns



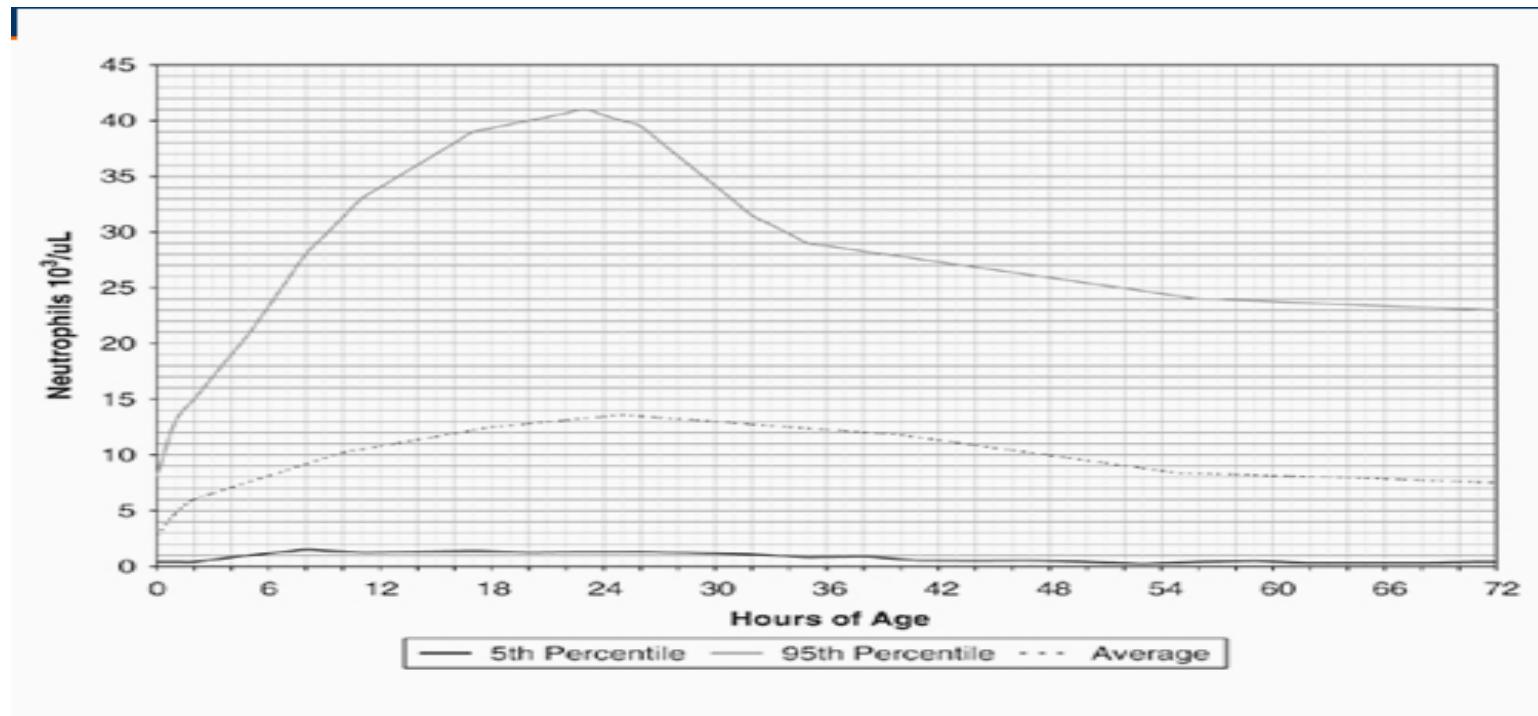
Schmutz N et al, J Perinatol 2008

Preterms (28–36 weeks)



Schmutz N et al, J Perinatol 2008

Preterms (less than 28 weeks)



Schmutz N et al, J Perinatol 2008

Cutoff

Sex¹

Female: on average $2.0 \times 10^9/L$ neutrophils higher.

Delivery¹

Labor: on average $3.5 \times 10^9/L$ neutrophils higher.

IUGR^{2,3}, altitude⁴ and others

¹Schmutz N et al, J Perinat 2008

²Wirbelauer J et al, Am J Perinatol 2010

³Troger B et al, Neonatology 2013

⁴Lambert RM et al, J Perinat 2009

Pregnancy or delivery related neutropenias¹

Perinatal asphyxia²

Hypertension/Pre-eclampsia²

Rh and ABO incompatibility^{3,4}

Feto-Fetal Transfusion Syndrome⁵

Maternal viral infections

Maternal drugs

¹Farruggia and Dufour, Ther Adv Hematol 2015

²Engle WD et al, J Pediatr 1984

³Koenig JM et al, J Pediatr 1989

⁴Blanco E et al, Pediatr Blood Cancer 2012

⁵Koenig JM et al, J Perinatol 1991

Neonatal immune neutropenias

Autoimmune neutropenias (AIN)

Alloimmune neutropenias

Human Neutrophil Antigen (HNA)

Glycoprotein	Antigens (5)	Old name	Allele (14)
FcγRIIIb (CD16b)	HNA-1a	NA1	<i>FCGR3B*01/FCGR3B*04</i>
	HNA-1b	NA2	<i>FCGR3B*05</i>
	HNA-1c	SH	<i>FCGR3B*03</i>
	HNA-1d		<i>FCGR3B*02</i>
No glycoprotein	HNA-1 null		<i>FCGR3B*null</i>
CD177	HNA-2	NB1	<i>CD177</i>
No glycoprotein	HNA-2 null		<i>CD177</i>
Choline transporter-like protein 2 (CTL2)	HNA-3a	5a	<i>SLC44A2*01/SLC44A2*03</i>
	HNA-3b	5b	<i>SLC44A2*02</i>
CD11b ($\beta 2$ integrin)	HNA-4a	MART	<i>ITGAM*01</i>
	HNA-4b		<i>ITGAM*02</i>
CD11a ($\beta 2$ integrin)	HNA-5a	OND	<i>ITGAL*01</i>

Neonatal immune neutropenias

Autoimmune neutropenias (AIN)

Alloimmune neutropenias

Primary autoimmune neutropenia of infancy

- Incidence: in Sicily 1/6.300 newborns.¹
- More frequent in former preterms: 13.2% of pAIN patients.¹
- At diagnosis: neutrophils $\leq 0.5 \times 10^9/L$ in 56%.¹
- At diagnosis: monocytosis in 19.3%.¹
- Infection rate: ~ 1/10 of SCN.² Fortuitous finding: in Italy 29%.¹
- Spontaneous remission: ~ 90% at < 5 years of age.^{1,3}
- Fluctuating neutropenia in recovery phase: 32.5%.¹
- Median age at onset: 7-8 months.
- Very rare at less <1 month (2%).¹

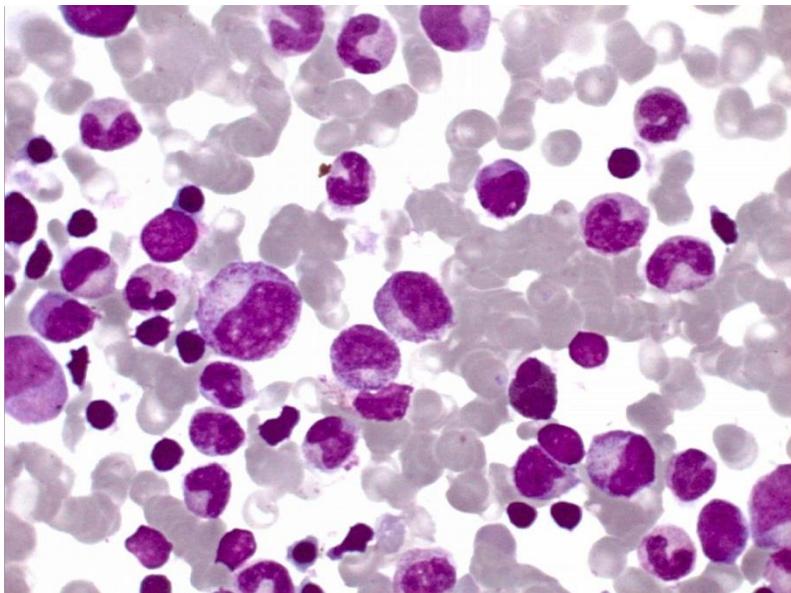
¹Farruggia P et al, Am J Hematol 2015

²Fioredda F et al, Pediatr Infect Dis J 2013

³Bux J et al, Blood 1998

Primary autoimmune neutropenia of infancy

Bone Marrow



Therapy

None

Rarely G-CSF at 5-10 mcg/kg/day

Antibiotic prophylaxis?^{1,2,3}

¹Kobayashi et al, J Ped Hem Onc 2003

²Azuma et al, J Gen Fam Med 2019

³Farruggia – Dufour, Ther Advances Hematol 2014

Neonatal immune neutropenias

Autoimmune neutropenias (AIN)

Alloimmune neutropenias

Typical neonatal immune. **Alloimmune neutropenias**

Primary

- Alloimmune neonatal neutropenia
- Alloimmune neonatal neutropenia secondary to autoimmune maternal neutropenia

Secondary

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



39⁺ week; 2,540 gr



5th day: onphalitis, inguinal abscess, N

310/mmc

7th day: BM (normal) + start G-CSF

12th day: diagnosis (anti HNA-1a)

30th day: recovery

6 doses of G-CSF

Patient: HNA 1a/1b

Genotypes Mother: HNA 1b/1b

Father: HNA 1a/1b

Neonatal Alloimmune Neutropenia (1)

Incidence of feto-maternal incompatibility: 19.6% of pregnancies.¹

Incidence of maternal alloantibody: 0.6-1.1% of newborns.^{1,2,3}

Incidence of neutropenia: 1/6.000-10.000 newborns^{1,4}

All HNA involved.⁵ Especially:^{2,6,7}

- HNA-1a and HNA-1b
- HNA-2

Possible at first pregnancy^{7,8}

¹Zupanska et al, Transf Med 2001

²Bux et al, Transf Med 1992

³Williams et al, J Paediatr Child Health 2006

⁴Doan et al, J Pediatrics Child Health 2019

⁵Lopes et al, Transfusion 2018

⁶Tomicic et al, Am J of Reproductive Immunology 2014

⁷van den Tooren-de Groot R et al, Acta Paediatr 2014

⁸Curtis, Transfusion 2016

Neonatal Alloimmune Neutropenia (2)

ANC < 500/ μ L^{1,2,3}

Infections:

- Above all of skin and umbilical cord (frequent delayed separation).^{1,2,3}
- In up to 60% of patients^{2,5}
- Severe in 20-40% of patients.^{1,2} Can NAN be lethal today?

Lasting 1-4 months (max 6): median 7-11 weeks.^{1,5}

Therapy:

- None: if asymptomatic
- G-CSF 5-10 mcg/kg: not always efficient^{6,7,8,9}
- IVIG (if no response to G-CSF). Efficacy: 30%^{9,10}

¹Bux et al, Transf Med 1992; ² van den Tooren-de Groot R et al, Acta Paediatr 2014

³Porcelijn – de Haas et al, Transf Medicne and Hemotherapy 2018; ⁴Doan et al, J Paediatrics child health 2019

⁵Tomicic et al, Am J reproductive Immunology 2016; ⁶Bedu et al, J Pediatr 1995; ⁷Maheshwari et al, Pediatrics 2002

⁸Latini et ala, Acta Ped 1999; ⁹Desenfants et al, Am J Perinatology 2011; ¹⁰Gilmore et al, J Pediatr 1994

HLA related Neonatal Alloimmune Neutropenia?

Simultaneous thrombocytopenia and neutropenia

Bux et al , Transfusion Medicine 1992	2 newborns
Marin et al, Pediatr Allergy Immunology 2005	1 newborn
Gramatges et al , Ped Blood Cancer 2009	1 newborn
Meler et al, Transfusion and apheresis science 2016	1° twin: thrombocytopenia; 2° twin thrombocytopenia+neutropenia
Gimferrer, 2018	1 newborn (of 2 twins)*

In all reports but Marin negative searching for anti-HNA and anti-HPA

In all reports high titer anti HLA-1 antibodies

* high levels of complement-fixing antibodies against paternal HLA in maternal and newborn serum

Isolated neutropenia

Hagimoto et al, Transfusion 2001	Anti HLA-2
Tomicic et al, Transf Medicine 2003	Anti B49
Tomicic et al , Am J Reprod Immunol. 2014	13 patients (various HLA-I)

Typical neonatal immune neutropenias

Alloimmune neonatal neutropenia

Alloimmune neonatal neutropenia

secondary to autoimmune maternal

neutropenia

Alloimmune neonatal neutropenia in newborn of mother with Autoimmune neutropenia

Only 14 patients described (11 mothers).¹

Risk of infections significantly higher in newborns.^{1,2,3}

G-CSF for the mother must be considered.

ANC normalized in 1-4 months.

¹Seguier A et al, J Clinical Immunol 2019

²Davoren et al, Transfusion 2004

³Fung YL et al, Transfus Med 2005



Thanks