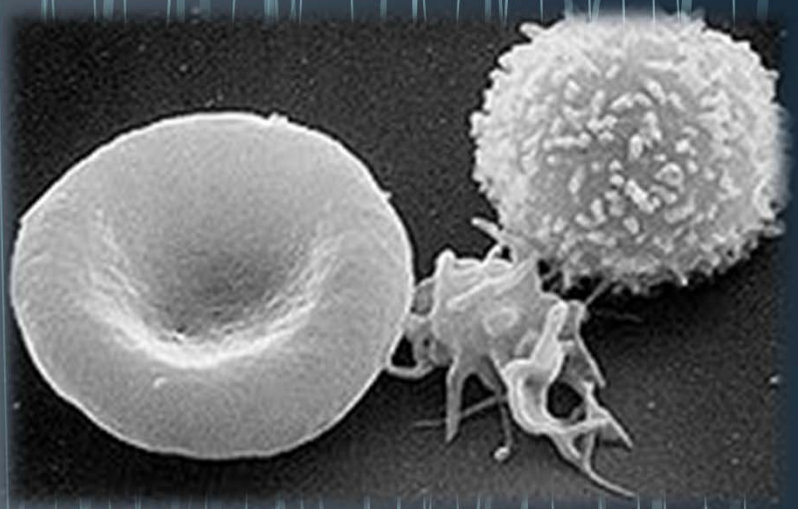
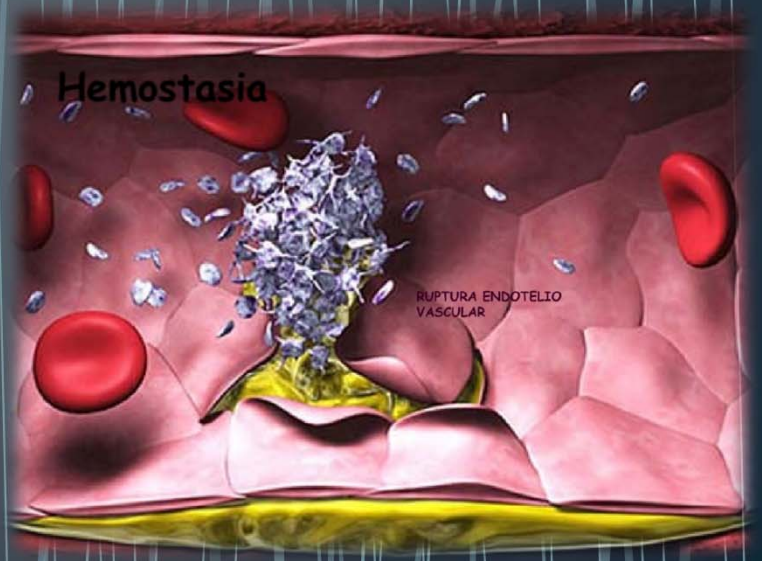
Trombocitopenia neonatal

Alexis Vidal Alarcón
Interno de Medicina
Uss Puerto Montt





Contenido:

- Definición
- Fisiopatología y diferencias con adultos.
- Recuentos.
- Aproximación diagnóstica.
- Causas.
- Tratamiento en relación a plaquetas.
  - ¿Cuándo?

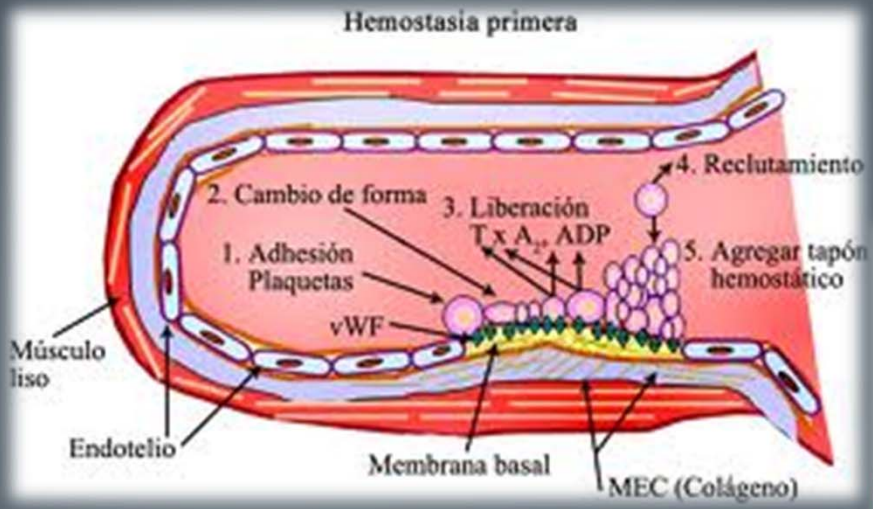
Definición:

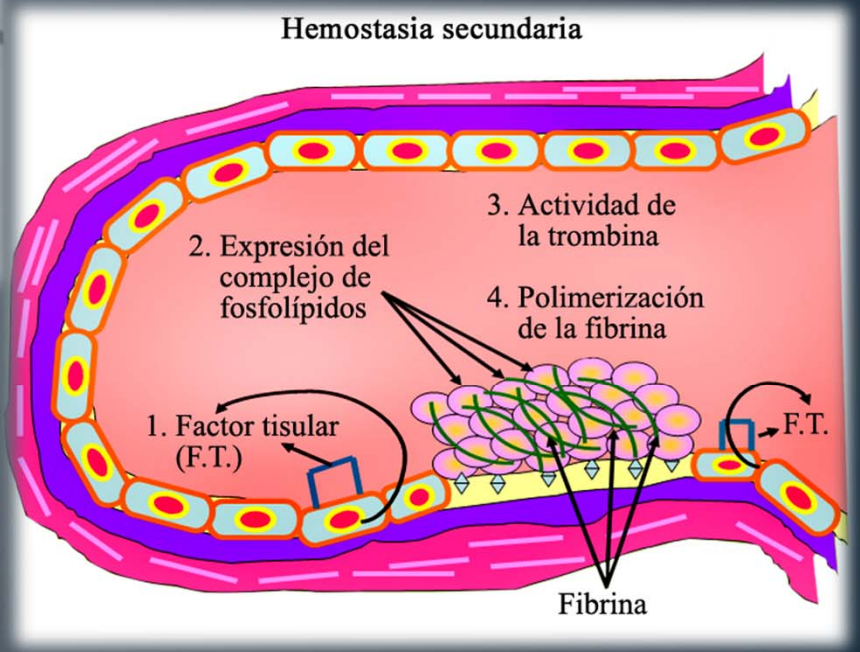
- Las plaquetas son pequeños fragmentos celulares producidos por los megacariocitos.

- < 150.000 plaquetas.
- <1% RN sanos
- Problemas más comunes en RN
  - 25% a 30% → UCIN.

Robert D. Christensen, Platelet Transfusion in the Neonatal Intensive Care Unit: Benefits, Risks, Alternatives, Neonatology 2011;100:311–318

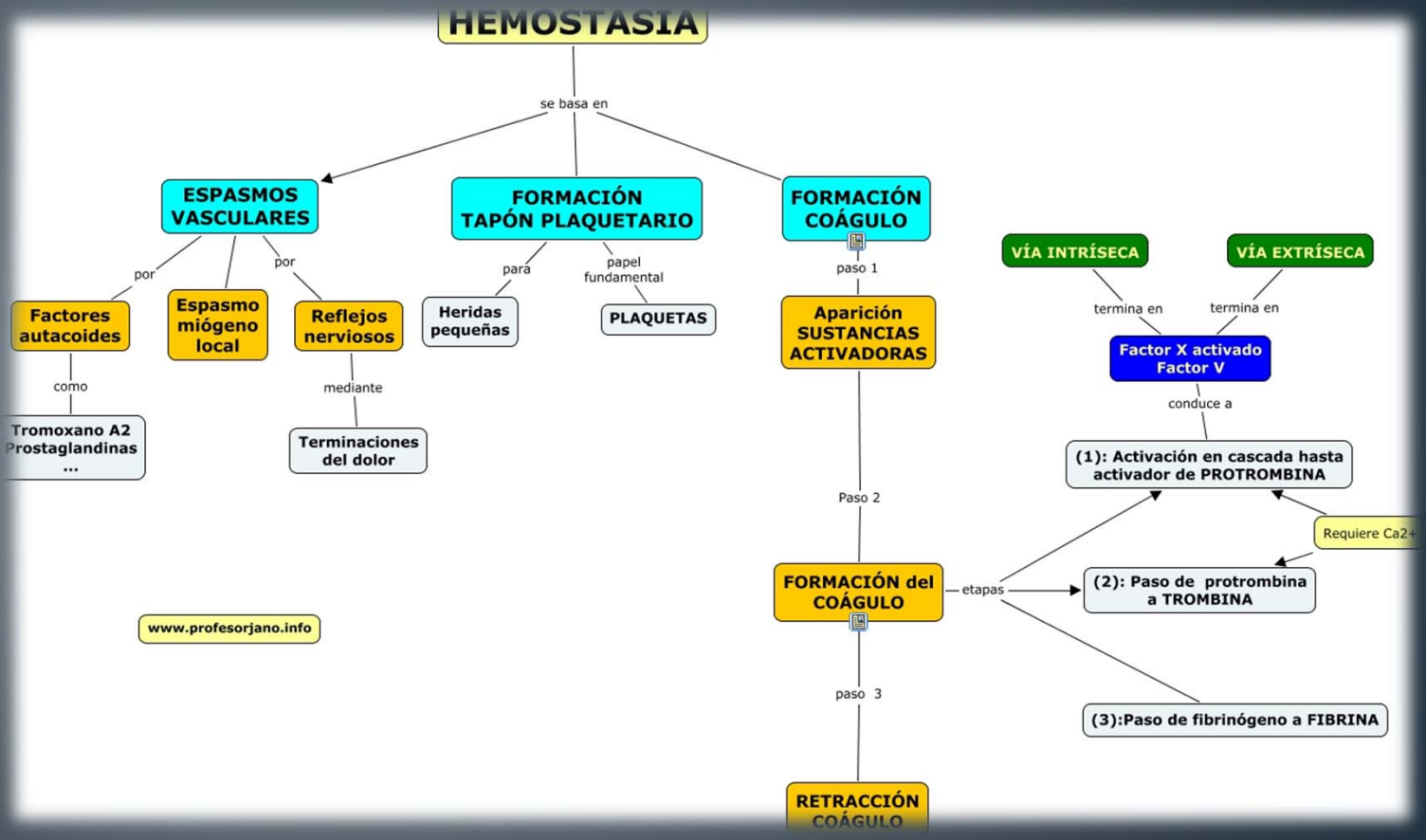
Fisiología:





http://skat.ihmc.us/

Hemostasia



http://skat.ihmc.us/

Journal of Perinatology (2009) 29, 130–136

www.nature.com/jp

ORIGINAL ARTICLE

Platelet reference ranges for neonates, defined using data from over 47 000 patients in a multihospital healthcare system

SE Wiedmeier[1,2,3], E Henry[1,4], MC Sola-Visner[5] and RD Christensen[1,6]

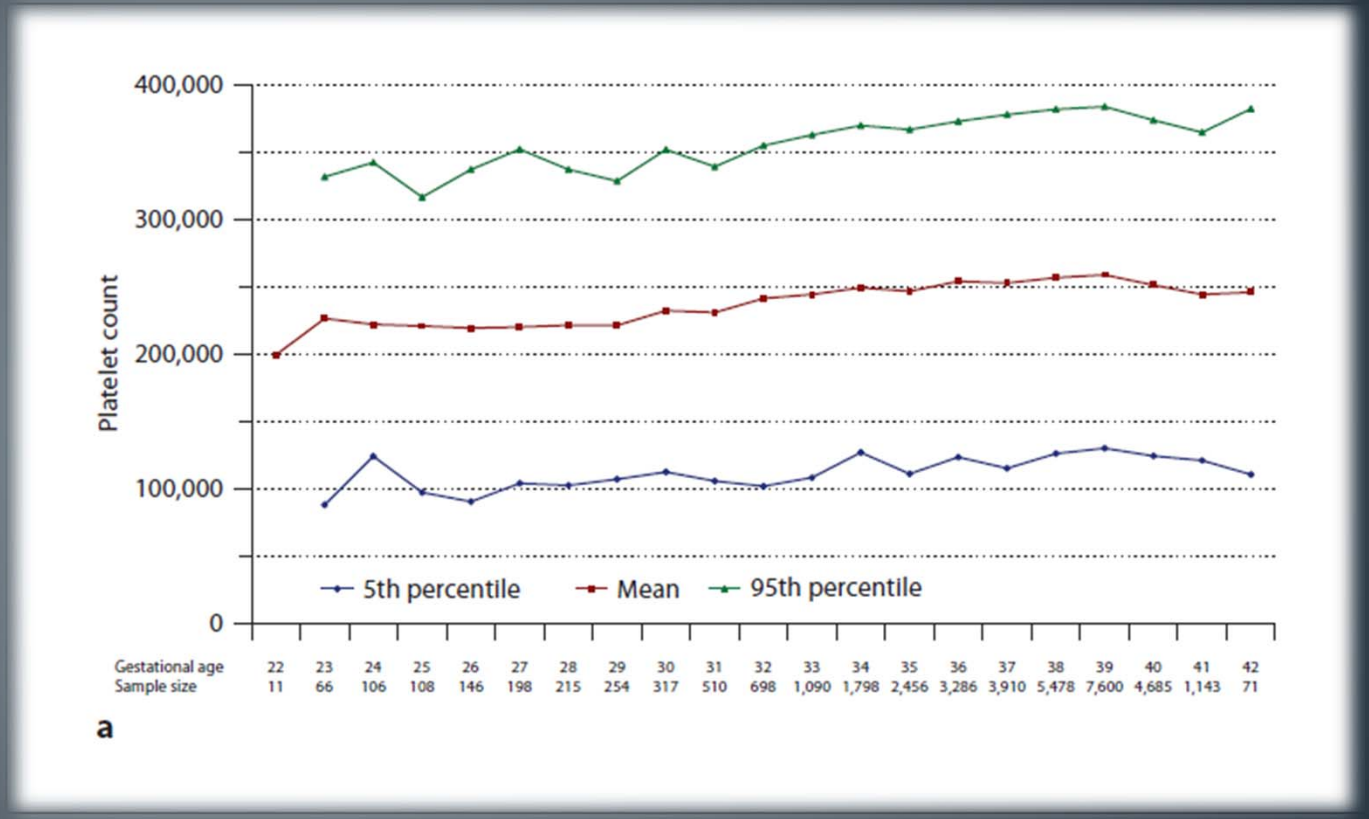
[1]Intermountain Healthcare, Salt Lake City, UT, USA; [2]Intermountain Medical Center, Murray, UT, USA; [3]The University of Utah School of Medicine, Salt Lake City, UT, USA; [4]The Institute for Healthcare Delivery Research, Salt Lake City, UT, USA; [5]Children's Hospital and Harvard Medical School, Boston, MA, USA and [6]McKay-Dee Hospital Center, Ogden, UT, USA

Rangos

- Est. Multicéntrico retrospectivo 47291 pacientes:
- 22 a 42 sem.
  - P<5
    - <32 sem
      - 104.000 plaq.
    - > 32 sem
      - 123.000 plaq.

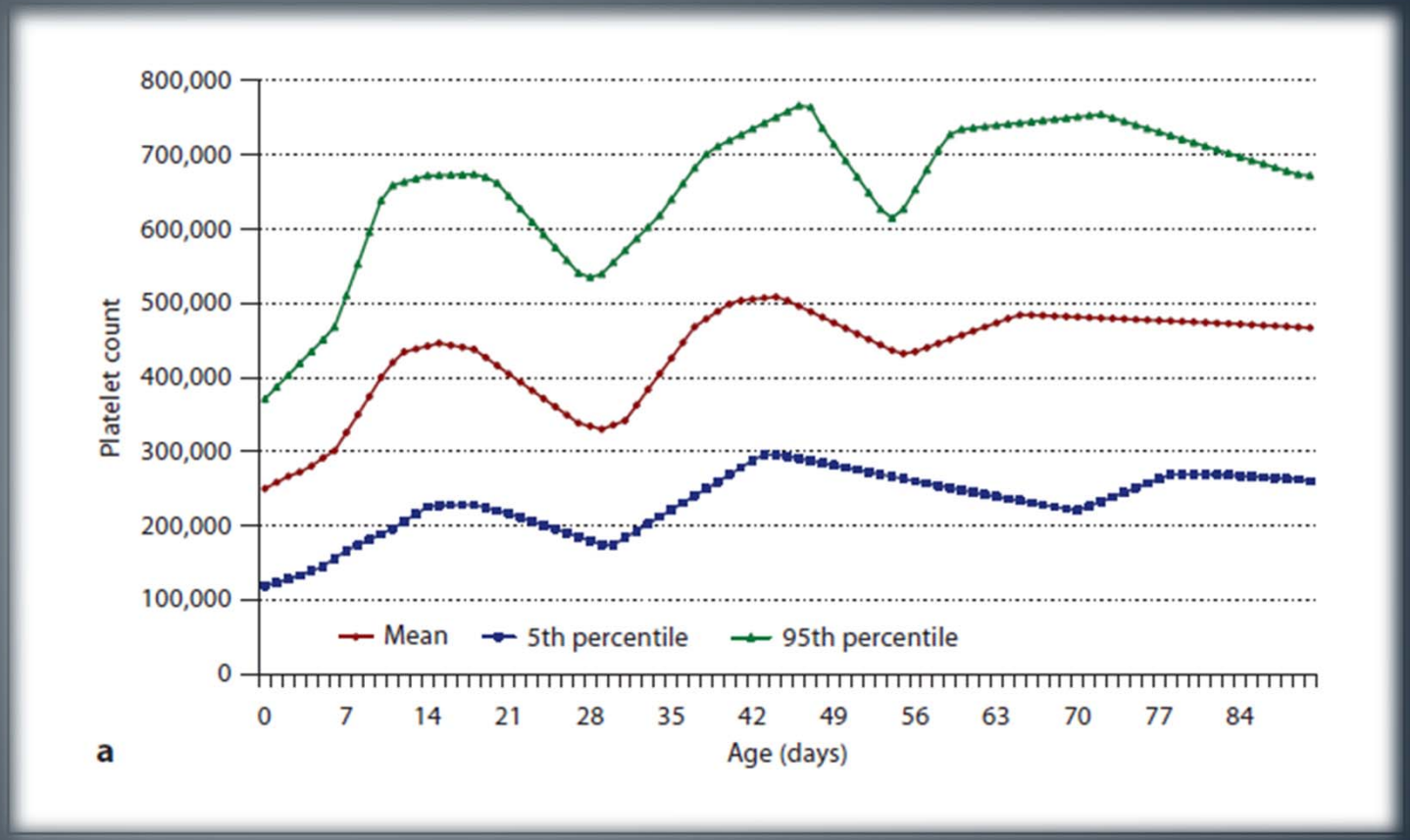
Wiedmeier SE, Henry E, Sola-Visner MC, Christensen RD. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system J Perinatol 2009;29:130–136

Recuento de plaquetas vs semanas de vida



- < 3 primeros DDV. - Emb de 22 a 42 s.

Robert D. Christensen, Platelet Transfusion in the Neonatal Intensive Care Unit: Benefits, Risks, Alternatives, Neonatology 2011;100:311–318



Robert D. Christensen, Platelet Transfusion in the Neonatal Intensive Care Unit: Benefits, Risks, Alternatives, Neonatology 2011;100:311–318

Riesgo de sangramiento

- Proporcional al número de plaquetas en circulación.
- Sin riesgo >100.000 / ml.
- Un riesgo mínimo ó leve → 20.000 y 100.000 / ml.
- El riesgo es moderado, → < 20.000 / ml.
- El riesgo es grave y/o hay hemorragia espontánea → <5.000/ml.

Karen S. Ferna´ndez, MD, Neonatal Thrombocytopenia, NeoReviews Vol.14 No.2 February 2013

- RN no se ha establecido la correlación del recuento de plaquetas con sangramiento.

- El trauma y el estrés de nacimiento pueden precipitar , aunque raramente, hemorragia intracraneal ó interna cuando las plaquetas están por debajo de 30.000 / ml.
- <50.000/ml en prematuros

Karen S. Ferna´ndez, MD, Neonatal Thrombocytopenia, NeoReviews Vol.14 No.2 February 2013

Producción de plaquetas

Trombopoyetina

Formación de plaquetas y liberación de nuevas plaquetas a la circulación.

Generación y proliferación de progenitores de megacariocitos.

Maduración de megacariocitos

- > progresivo de la ploidía nuclear
  - (N° de sets de cromosomas en una célula dada)
- Madurez citoplasmática
  - Grandes megacariocitos poliploides (8 N - 64 N).

Karen S. Fernández, MD, Neonatal Thrombocytopenia, NeoReviews Vol.14 No.2 February 2013

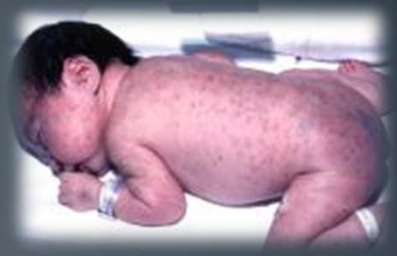
Diferencias entre neonatos y adultos

	Neonatos	Adultos
Trombopoyetina	Leve aumento en RN sanos	Menor en en Adultos Sanos
Progenitores megacariocíticos	Abundantes en sangre y muy sensibles a TPO	Escasas en sangre y menos sensibles a TPO
Megacariocitos	Pequeños y poca ploidía	Normal (<250 pg/ml)
Plaquetas	Mas pequeñas VPM 8	VPM 7,5-11,5

Susanne Holzhauer, Diagnosis and managment of neonatal thrombocytopenia, Seminars in Fetal and Neonatal Medicina 16 (2011) 305-310

Clínica:

- Púrpura.
- Petequias.
- Equimosis.
- Sangrado de mucosas.
- Sangrado gastrointestinal
- Sangrado umbilical.
- **Hemorragia intracraneal.**



Susanne Holzhauer, Diagnosis and managment of neonatal thrombocytopenia, Seminars in Fetal and Neonatal Medicina 16 (2011) 305-310

Categories	Subtypes	Differential Diagnoses (Where Applicable)	Severity	Onset
Immune	Alloimmune	Neonatal alloimmune thrombocytopenia	Severe	Early
	Autoimmune	Maternal ITP, lupus, other collagen vascular disorder	Severe-moderate	Early
Infectious	Bacterial	GBS, Gram-negative rods, *Staphylococcus*, etc.	Variable	Variable
	Viral	CMV, HSV, HIV, enteroviruses	Variable	Usually early
	Fungal	*Candida*, other	Severe	Usually early
	Parasite	Toxoplasmosis	Variable	Early
Placental insufficiency		Preeclampsia, eclampsia, chronic hypertension	Mild-moderate	Early
		Intrauterine growth restriction due to placental insufficiency	Mild-moderate	Early
DIC		Asphyxia	Severe	Early
		Sepsis	Severe	Variable
		Congenital TTP (rare)	Severe	Variable
Genetic disorders	Chromosomal	Trisomy 13, Trisomy 18, Trisomy 21, Turner syndrome, Jacobsen syndrome	Variable	Early
	Familial	Macrothrombocytopenias, Wiskott-Aldrich syndrome, X-linked thrombocytopenias, Amegakaryocytic thrombocytopenia, TAR, Fanconi anemia[a]	Variable	Early*
	Metabolic	Proprionic acidemia, methylmalonic acidemia, etc.	Mild-moderate	Variable
Medication induced	Antibiotics	Penicillin and derivatives, vancomycin, metronidazole, etc.	Variable	Late
	Heparin		Variable	Late
	Anticonvulsants	Phenytoin, phenobarbital	Variable	Late
	H_2 receptor antagonists		Variable	Late
Miscellaneous	Thrombosis	RVT, line-associated thrombosis, sagittal sinus thrombosis	Moderate	Variable
	Vascular tumor	Kasabach Kasabach-Merritt, hepatic hemangioendothelioma	Moderate	Variable
	NEC		Severe-moderate	Usually late
	ECMO		Variable	Variable

Karen S. Fernández, MD, Neonatal Thrombocytopenia, NeoReviews Vol.14 No.2 February 2013

Enfoque diagnóstico

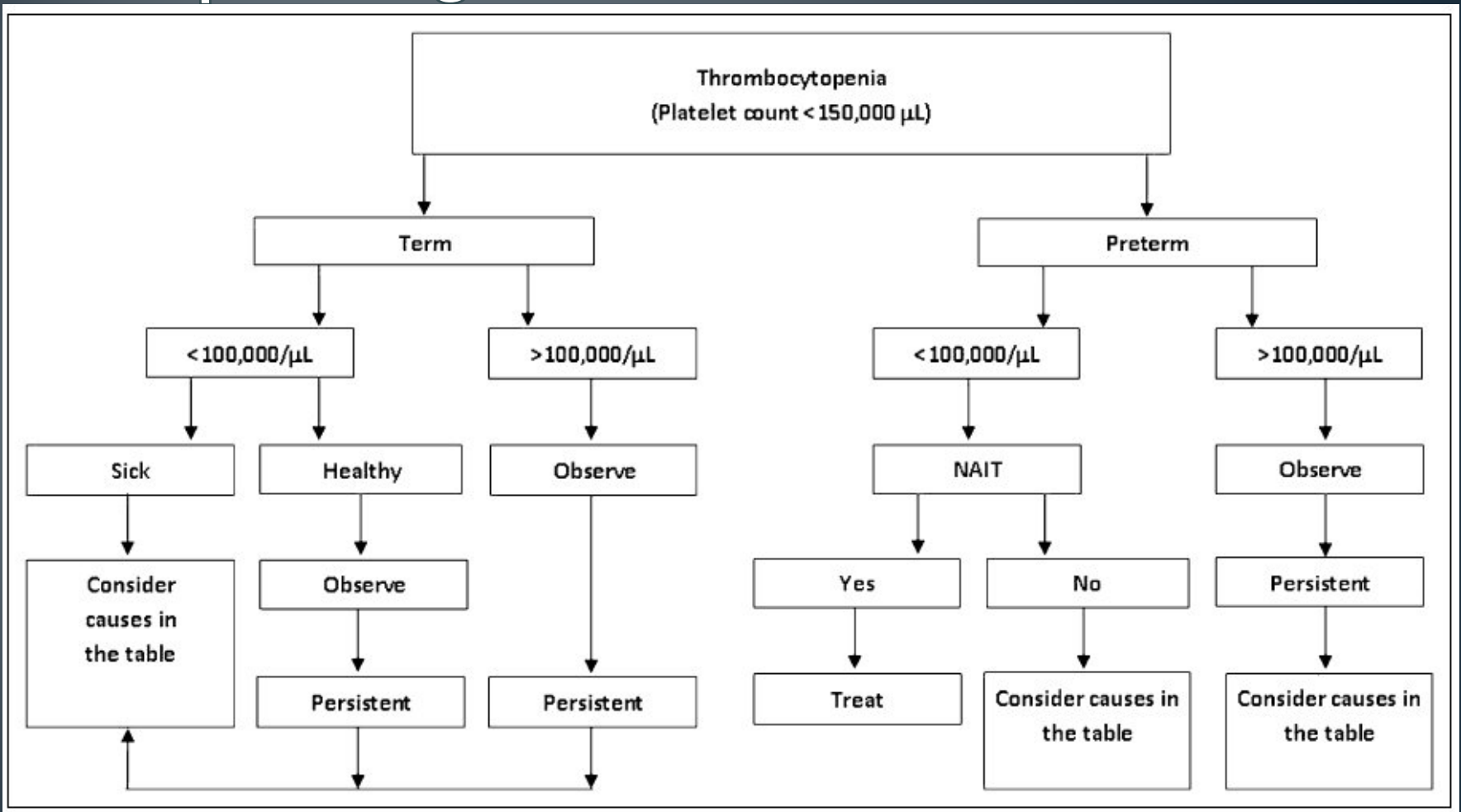


Figure. Diagnostic approach to an infant with thrombocytopenia. NAIT=Neonatal alloimmune thrombocytopenia.

Karen S. Fernández, MD, Neonatal Thrombocytopenia, NeoReviews Vol.14 No.2 February 2013

Categories	Subtypes	Differential Diagnoses (Where Applicable)	Severity	Onset
Immune	Alloimmune	Neonatal alloimmune thrombocytopenia	Severe	Early
	Autoimmune	Maternal ITP, lupus, other collagen vascular disorder	Severe-moderate	Early
Infectious	Bacterial	GBS, Gram-negative rods, *Staphylococcus*, etc.	Variable	Variable
	Viral	CMV, HSV, HIV, enteroviruses	Variable	Usually early
	Fungal	*Candida*, other	Severe	Usually early
	Parasite	Toxoplasmosis	Variable	Early
Placental insufficiency		Preeclampsia, eclampsia, chronic hypertension	Mild-moderate	Early
		Intrauterine growth restriction due to placental insufficiency	Mild-moderate	Early
DIC		Asphyxia	Severe	Early
		Sepsis	Severe	Variable
		Congenital TTP (rare)	Severe	Variable
Genetic disorders	Chromosomal	Trisomy 13, Trisomy 18, Trisomy 21, Turner syndrome, Jacobsen syndrome	Variable	Early
	Familial	Macrothrombocytopenias, Wiskott-Aldrich syndrome, X-linked thrombocytopenias, Amegakaryocytic thrombocytopenia, TAR, Fanconi anemia[a]	Variable	Early*
	Metabolic	Proprionic acidemia, methylmalonic acidemia, etc.	Mild-moderate	Variable
Medication induced	Antibiotics	Penicillin and derivatives, vancomycin, metronidazole, etc.	Variable	Late
	Heparin		Variable	Late
	Anticonvulsants	Phenytoin, phenobarbital	Variable	Late
	H_2 receptor antagonists		Variable	Late
Miscellaneous	Thrombosis	RVT, line-associated thrombosis, sagittal sinus thrombosis	Moderate	Variable
	Vascular tumor	Kasabach Kasabach-Merritt, hepatic hemangioendothelioma	Moderate	Variable
	NEC		Severe-moderate	Usually late
	ECMO		Variable	Variable

Karen S. Fernández, MD, Neonatal Thrombocytopenia, NeoReviews Vol.14 No.2 February 2013

¿Diagnóstico?

- 72 hrs.
- Edad gestacional.
- Mecanismo
- Inmune, no inmune o hereditaria.

RNT o RNPT

	RNPT	RNT
Causa mas importante	**Insuficiencia placentaria.** Asfixia Infección connatal.	**Trombocitopenia neonatal aloinmune** Sepsis - ECN
Causa secundaria	Frecuente asociación multifactorial.	Poco frecuente. Mas frecuente si se asocia a cromosomopatías.
Recuperación	10 días.	Depende de la causa

Karen S. Fernández, MD, Neonatal Thrombocytopenia, NeoReviews Vol.14 No.2 February 2013

Inicio: …72 hrs

Precoz	Tardía
Hipoxia crónica	Sepsis tardía
Asfixia perinatal	ECN
CID	Infecciones congénitas
TCP aloinmune	
TCP autoinmune	
Infecciones congénitas	

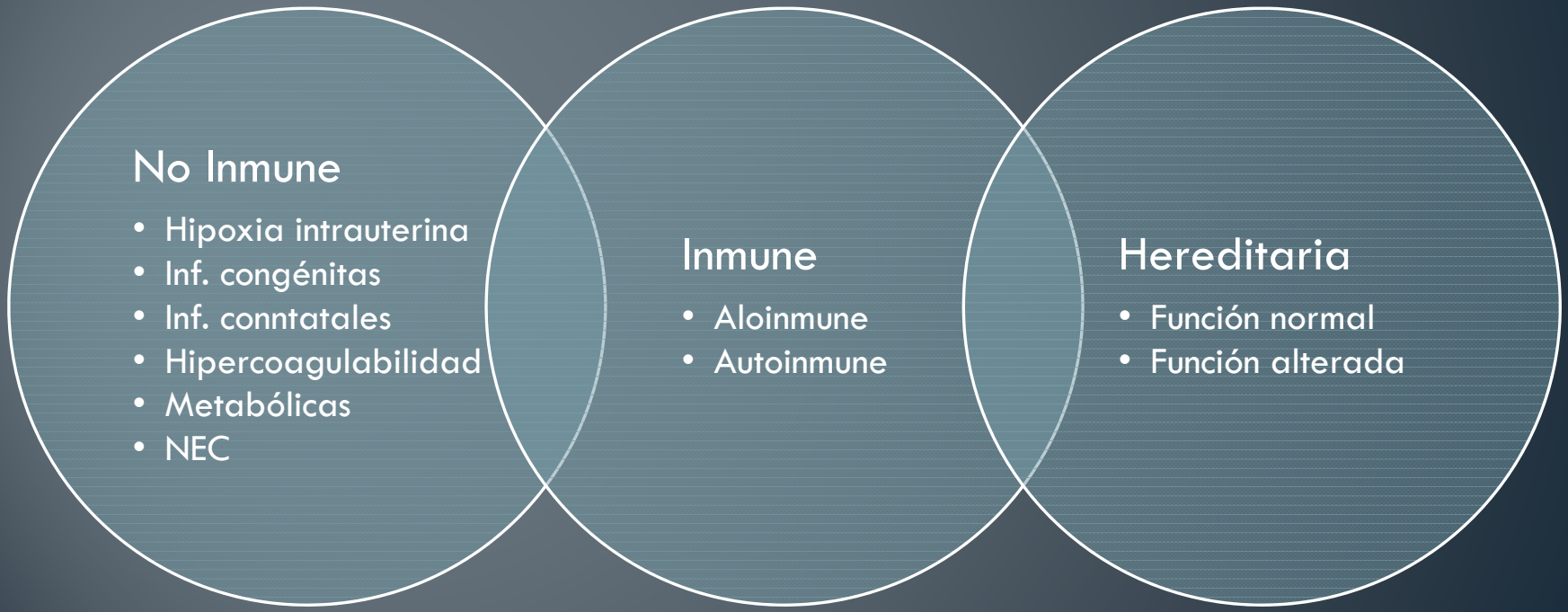
Subarna Chakravoty et al., How I manage the neonatal thrombocytopenia , British Journal of Haematology, 2011

Producción vs destrucción:

	Menor producción	Destrucción acelerada
Volumen plaquetario Medio	Normal (7,5-9,5 fL)	Aumentado (>12fL)
Reticulado	Bajo <2%	Alto >10%
TPO pl	Alta >500pg/mL	Normal (<250pg/mL)
MKC en medula ósea	Disminuidos	Aumentados

Fernanda Ferrer-Marin et al, Neonatal thrombocytopenia and megakariocytopoyesis , Semin Haematology, 2011

Origen



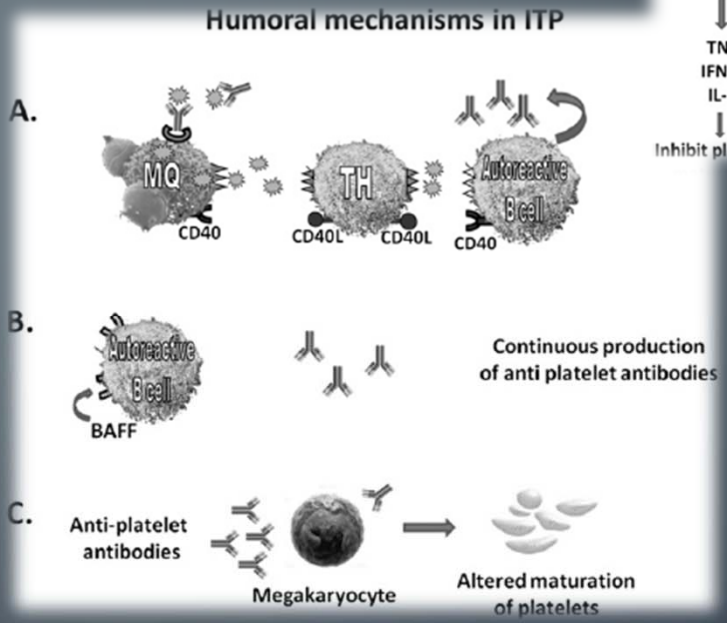
Subarna Chakravoty et al., How I manage the neonatal thrombocytopenia , British Journal of Haematology, 2011

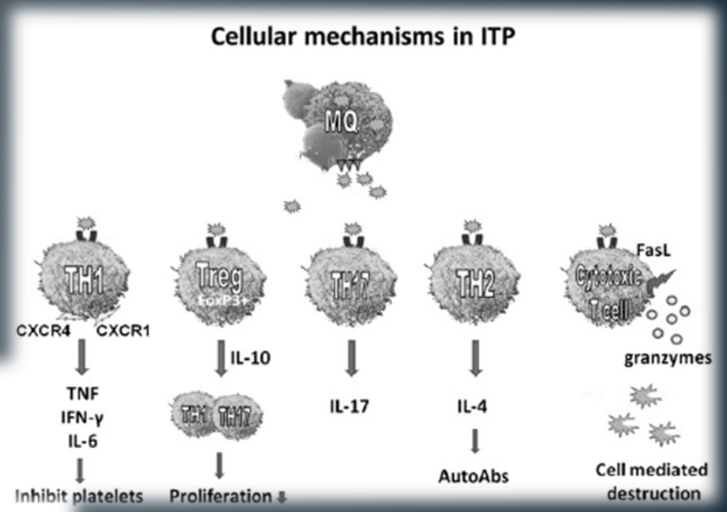
Trombocitopenia neonatal alloinmune (NAIT)

- Aspecto sano.
- 1/1000
- Plaquetas fetales:
  - Antígeno heredado del padre
  - RN con antígeno.
  - Madre lo carece
  - HPA (antígeno plaquetario humano).
    - HPA-1 (75%).
  - Clinica mucocutánea.
  - Duración: 1 a 4 sem.

Trombocitopenia neonatal autoimmune

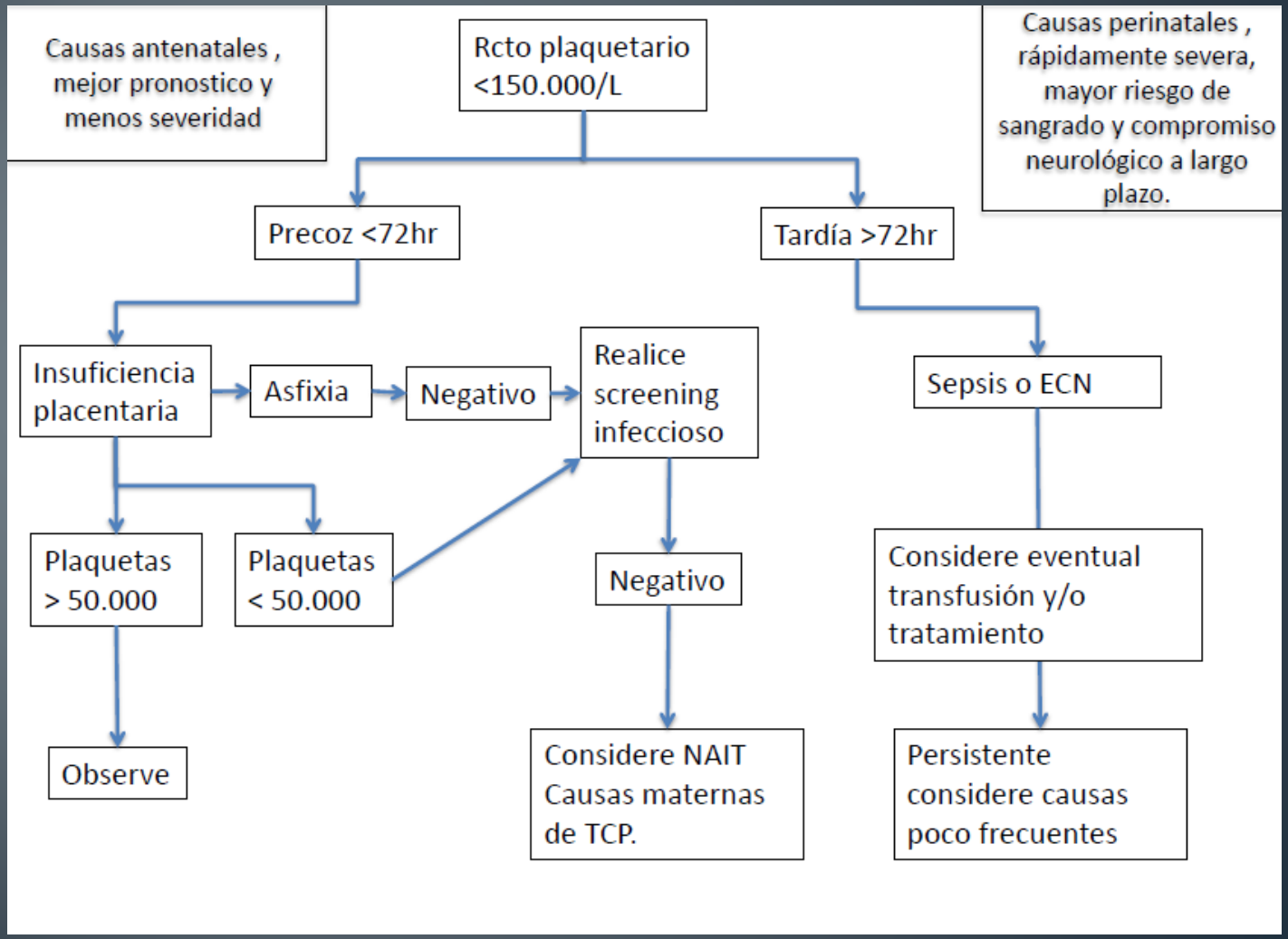
- Antígeno GPIIb-IIIa /GPIb-IX
- Anticuerpos maternos.
  - Madre
  - Feto
- PTI, Lupus.
- 2/1000.
- 10%.
- Semana.





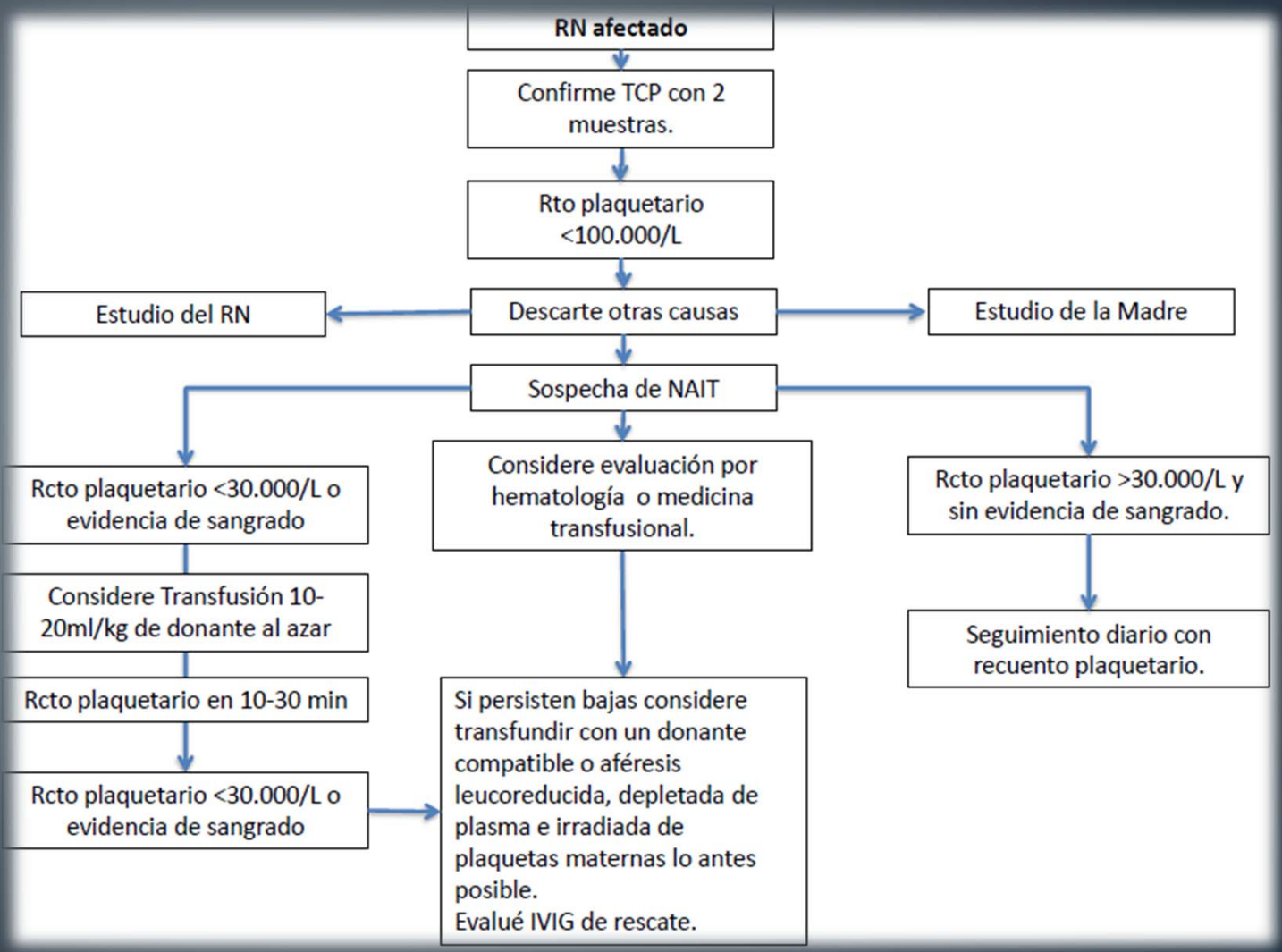
Dana Yehudai and Col, Autoimmunity and Novel Therapies in Immune-Mediated Thrombocytopenia, Semin Hematol 50:S100–S108

Tratamiento



(3) Subarna Chakravoty et al., How I manage the neonatal thrombocytopenia , British Journal of Haematology, 2011

Tratamiento:



Amanda Symington, Am Journal of Perinatology 28: 137-144 ; 2011

Transfusiones:

Profiláctica

Tratamiento

Fernanda Ferrer-Marin et al, Neonatal thrombocytopenia and megakariocytopoyesis , Semin Haematology, 2011
RD: Christensen Congreso SIBEN, 2011

Transfusiones vs muerte

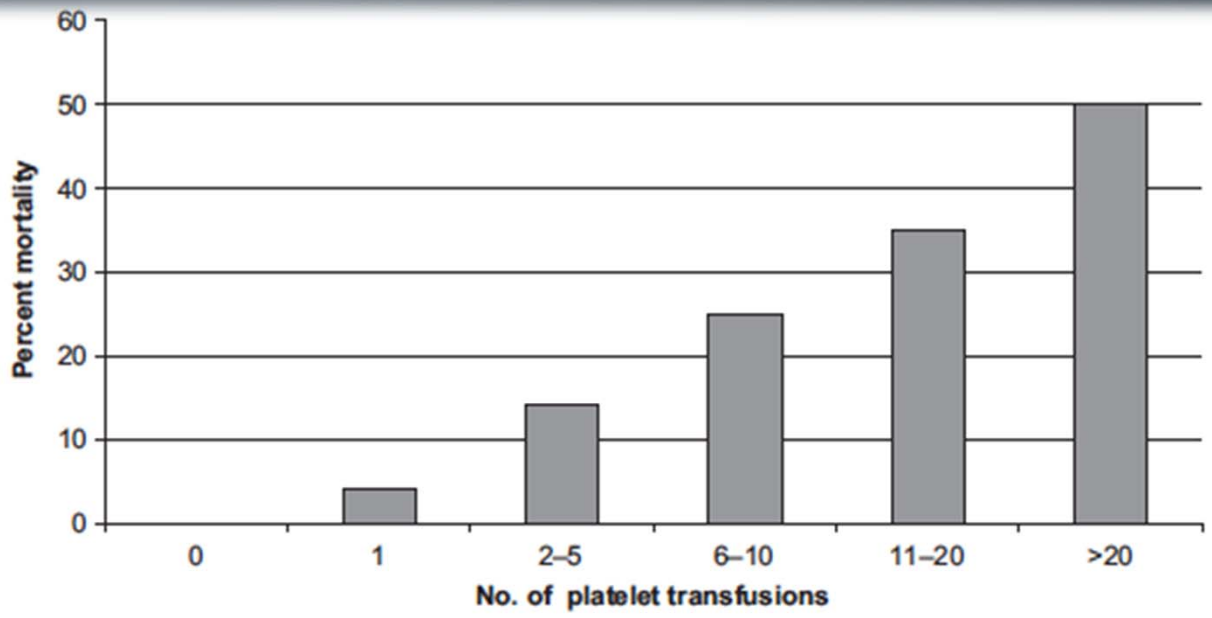


FIGURE 3
Mortality rate of NICU patients with severe thrombocytopenia, displayed according to the number of platelet transfusions received.

Baer v.L. Severe thrombocytopenia in NICU, Pediatrics ,124 , 1095-1100; 2009

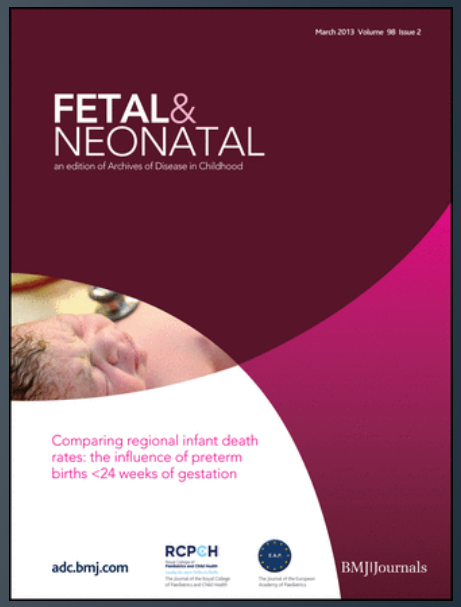
Indicaciones

Rcto plaquetario	Indicación
<20.000	Todos los RN
<30.000	RN < 7 días RN < 1 kg Inestabilidad clínica Antec. de sangrado mayor Sangrado menor actual Coagulopatía Necesidad de cirugía o exanguineo transfusión
<50.000	Sangrado mayor

Gibson 2004 , Indications for neonatal platelet tranfusion.

¿Menor cantidad de hemorragias?

- Estudio multicéntrico prospectivo
- 169 RN
- 27 sem
- <60000.
- 91% sin HIC.
- Recuento plaquetas vs Edad
- ECN.



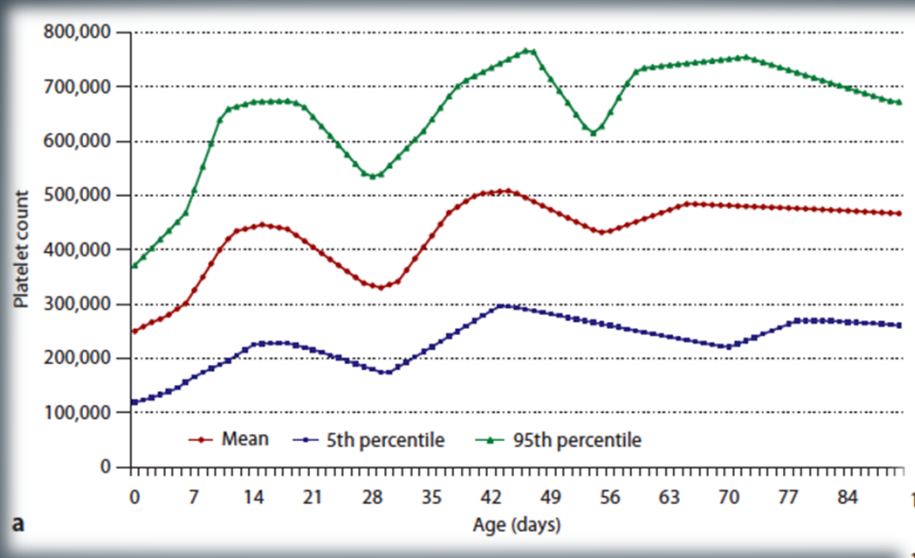
Vidheya Venkatesh, Do we know when to treat neonatal thrombocytopaenia? Arch Dis Child Fetal Neonatal Ed September 2013 Vol 98 No 5

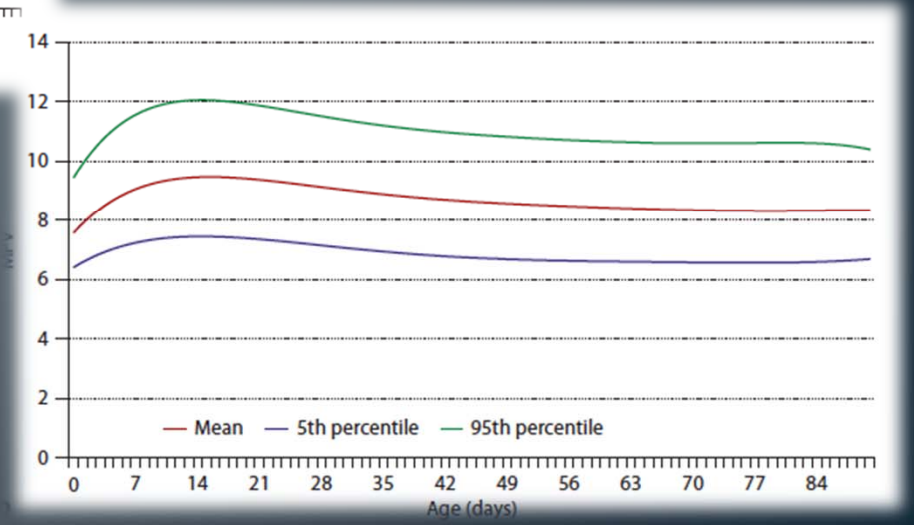
¿Qué es lo que importa?

¿Cuándo transfundir?

¿Qué parámetros ocupo?

Volumen plaquetario medio





Christensen RD, Platlet tranfusion in the neonatal intensive care unit, benefits, risk, alternatives , 100: 311-318.

Masa plaquetaria

- < 17% de transfusiones.

TABLE 1. PLT transfusion guidelines during the period where PLT count–based guidelines were used (Period 1) and in the period where PLT mass–based guidelines were used (Period 2)

Risk group	Period 1: PLT count–based guidelines ($\times 10^9$/L)	Period 2: PLT mass*–based guidelines (fL/nL)
Group 1: ECMO, bleeding, pre- or postoperative	PLT count <100	PLT mass <800
Group 2: unstable†	PLT count <50	PLT mass <400
Group 3: stable	PLT count <20	PLT mass <160

* PLT mass is calculated by multiplying the PLT count by the MPV (example: PLT count 100×10^9/L, MPV 8.0 fL. Thus, $100 \times 8 = 800$ fL/nL). Taking an average MPV of 8 fL for these calculations was done in accordance with our previous studies.[19]

† "Unstable" refers to neonates less than 1500 g birth weight in the first week of life or patients on mechanical ventilators or receiving continuous vasopressors.

Gerday E. Et al. , Testing platelet mass vrsus platelet count to guide platelet transfusion in neonatal intensive care unit, Transfusion, Volume 49, 2009

TABLE 3. PLT transfusions administered during the period where PLT count–based transfusion guidelines were used (Period 1) compared with the period where PLT mass–based guidelines were used (Period 2)

Period	Percentage of NICU patients receiving one or more PLT transfusions	PLT transfusions per transfused patient, median (range)	Percentage of PLT transfusions that were given prophylactically*	Percentage of NICU patients receiving one or more prophylactic PLT transfusions	Percentage of PLT transfusions compliant with guidelines
Period 1: PLT count	3.6	2.0 (1-23)	91.3	3.3	54
Period 2: PLT mass	1.9	2.0 (1-17)	75.0	1.4	72
p Value	<0.002	>0.40	<0.01	<0.001	0.03

* Percentage of PLT transfusions that were given prophylactically, meaning that the patient had no bleeding observed, and the purpose of the PLT transfusion was to prevent bleeding.

TABLE 4. Percentage of NICU patients with various bleeding-related issues recorded during the period where PLT count–based transfusion guidelines were used (Period 1) compared with the period where PLT mass–based guidelines were used (Period 2)

Period	IVH all grades (%)	IVH Grades III and IV (%)	IVH Grades III and IV among those weighing <1500 g at birth (%)	IVH Grades III and IV among those weighting <1000 g at birth (%)	Pulmonary hemorrhage (%)	Gastrointestinal hemorrhage (%)	Cutaneous hemorrhage (%)
Period 1: PLT count	5.0	1.8	9.9	18.8	0.6	2.0	6.2
Period 2: PLT mass	4.5	0.4	3.1	4.8	0.7	1.4	5.3
p Value	0.36	0.01	0.06	0.10	0.52	0.27	0.02

Gerday E. Et al. , Testing platelet mass vrsus platelet count to guide platelet transfusion in neonatal intensive care unit, Transfusion, Volume 49, 2009

THE JOURNAL OF PEDIATRICS • www.jpeds.com Vol. 164, No. 1

Primary Hemostasis in Neonates with Thrombocytopenia

Emoke Deschmann, MD[1,2], Martha Sola-Visner, MD[1], and Matthew A. Saxonhouse, MD[3,4]

Objective To evaluate the relationship between platelet counts and the platelet function analyzer-100 closure times (CTs) in neonates with thrombocytopenia, and to determine what other factors significantly affect CTs.

Study design In a single institution prospective cross-sectional study, blood samples from neonates with platelet counts $<150 \times 10^9$/L were tested on the platelet function analyzer-100 with CT-collagen/epinephrine (CT-Epi) and CT-collagen/adenosine diphosphate (CT-ADP) cartridges.

Results The mean platelet count was $95 \pm 28 \times 10^9$/L for 48 infants with a mean gestational age 30.9 ± 5.3 weeks and median postnatal age of 5 (3-18) days. No association was evident between CT-Epi and platelet count. However, the CT-ADP was prolonged in many (but not all) infants with platelet counts $<90 \times 10^9$/L. Among infants <32 weeks gestational age, we found a moderate negative correlation between CT-ADP and platelet count ($r = -0.54$, $P = .0045$). The negative correlation was strongest in infants <32 weeks and <10 days old ($r = -0.8$, $P = .0017$). Other variables examined (hematocrit, infection, Score of Neonatal Acute Physiology II) did not have a significant effect on CT-ADP in a linear regression model.

Conclusions Platelet counts $<90 \times 10^9$/L are associated with prolonged CT-ADP times in some but not all infants. Gestational and postnatal age-related differences in platelet function account for some of this variability. The predictive value of CT-ADP on neonatal bleeding risk remains to be studied. *(J Pediatr 2014;164:167-72)*.

Table. Baseline patient characteristics

Number of patients	48
Sex, male, n (%)	33 (68.7%)
Gestational age in wk, mean ± SD	30.9 ± 5.3
Weight in g, mean ± SD	1744 ± 931
Postnatal age in d, median (IQR)	5 (3-18)
Postconceptional age in wk, mean ± SD	32.5 ± 4.6
SNAP II score, median (IQR)	5 (4-10)
Hematocrit in %, mean ± SD	42 ± 9
Platelet count $\times 10^9$/L, mean ± SD	95 ± 28
Mean platelet volume in fl, mean ± SD	10.4 ± 2.7
Platelet mass in μL, mean ± SD	1025 ± 366
CT-ADP in s, median (IQR)	79 (67.5-97.5)
CT-Epi in s, median (IQR)	123 (97-229)

Values for categorical variables are presented as n (%); values for continues variables are presented as mean ± SD if normally distributed, and as median (25%-75% IQR) if skewed.

Emoke Deschmann, MD and Col, Primary Hemostasis in Neonates with Thrombocytopenia, THE JOURNAL OF PEDIATRICS, Vol. 164, No. 1

GOBIERNO DE CHILE Hospital PUERTO MONTT SERVICIO DE SALUD RELONCAVI	BANCO DE SANGRE	Código: BSang01 Edición: 04 Fecha: Noviembre 2010 Página: 1 de 13 Vigencia: 2010 – 2014

PROTOCOLO

TRANSFUSIONES EN PEDIATRIA Y NEONATOLOGIA HOSPITAL DE PUERTO MONTT

AÑO: 2010 - 2014

Hospital de Puerto Montt

- < 5.000 plaquetas/mm3.
- No demuestra beneficios con administración profiláctica.
  - <20.000 plaquetas/mm3

- RN < 37 semanas:
  - < 30.000 x mm3 en prematuro estable.
  - < 50.000 x mm3 en prematuro enfermo (
    - Asfixia perinatal.
    - Ventilación asistida con FiO2 > 40%.
    - Sepsis.

- Falla de Producción:
  - Plaquetas < 5.000 x mm3
  - Plaquetas < 10.000 x mm3 con sangramiento, fiebre o infección.
  - Plaquetas < 50.000 x mm3 con sangramiento activo o necesidad procedimiento invasivo.
- En CIVD u otra alteración de coagulación:
  - Plaquetas < 100.000 x mm3 ,
  - Con sangramiento activo o
  - Necesidad de procedimiento invasivo.
- Defecto cualitativo de la plaqueta y prolongación del tiempo de sangría:
  - en caso de sangramiento, independiente del recuento de plaquetas.

- Recomendaciones:
  - Volumen transfusional: 10 ml/Kg.
  - Rendimiento: 1 unidad de concentrado plaquetario aumenta en 5.000 plaq./mm3
  - Goteo y duración de transfusión: lo más rápido posible pues vida media de plaquetas es de minutos.

TABLE 1. PLT transfusion guidelines during the period where PLT count–based guidelines were used (Period 1) and in the period where PLT mass–based guidelines were used (Period 2)

Risk group	Period 1: PLT count–based guidelines ($\times 10^9$/L)	Period 2: PLT mass*–based guidelines (fL/nL)
Group 1: ECMO, bleeding, pre- or postoperative	PLT count <100	PLT mass <800
Group 2: unstable†	PLT count <50	PLT mass <400
Group 3: stable	PLT count <20	PLT mass <160

* PLT mass is calculated by multiplying the PLT count by the MPV (example: PLT count 100×10^9/L, MPV 8.0 fL. Thus, $100 \times 8 = 800$ fL/nL). Taking an average MPV of 8 fL for these calculations was done in accordance with our previous studies.[19]

† "Unstable" refers to neonates less than 1500 g birth weight in the first week of life or patients on mechanical ventilators or receiving continuous vasopressors.

Gerday E. Et al. , Testing platelet mass vrsus platelet count to guide platelet transfusion in neonatal intensive care unit, Transfusion, Volume 49, 2009

...Gracias