Neonatal Thrombocytopenia & Platelet Transfusion – **An Update**

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Scope

1. How good is the **Definition** of Thrombocytopenia in neonates?
2. What are the **differences between neonatal and adult** thrombopoiesis?
3. What is the **Diagnostic Approach**?
4. What are the current **guidelines for Platelet Transfusion**?

A Case ……
Looks familiar?

- 36 weeks late preterm SGA 2.1 kg male infant born vigorous and roomed in with mother, noticed to be lethargic on day 3 and investigated:
- Haemogram: Hb: 15, PCV: 46, TLC: 9600, Platelet Count: 55,000
- CRP: Neg, Blood Culture: Sterile

How do we manage this baby?

Defining Thrombocytopenia ….

- A symptom of a variety of congenital or acquired conditions in the neonatal period

- **Platelet count <150,000 /uL**
  - Mild Thrombocytopenia:100-150,000
  - Moderate: 50-99,000
  - Severe: <50,000

- **Basis:**
  - Pl production starts in fetus @ 5 wks
  - Count reaches adult level by 22 wks

  Therefore traditionally, Neonatal value = Adult Value

Neonate = Adult ?

Challenging the Definition in Neonates ….

Recent large population study involving 47 291 neonates in 8 hospitals in US:

Lower limit of platelet

late preterm & term: **123,000**/uL

32 weeks': **104,000** /Ul

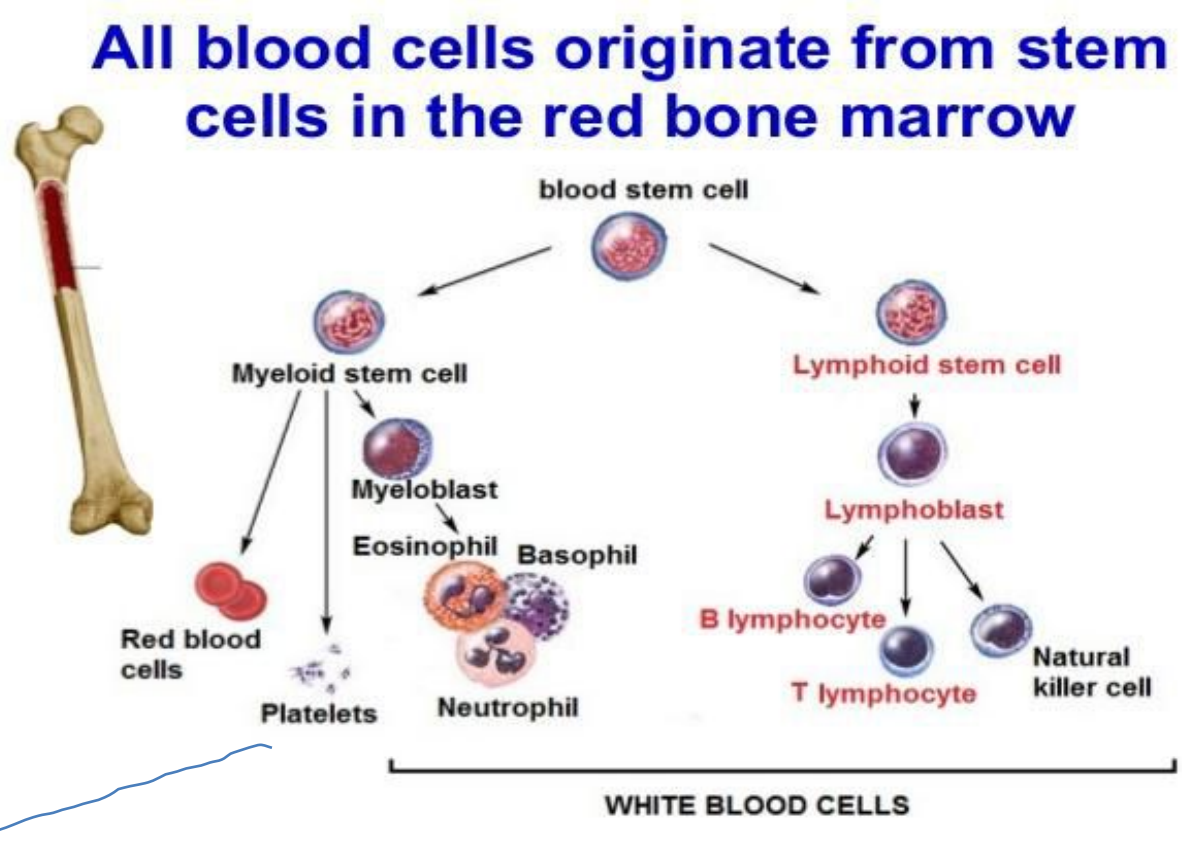
Significance ?

Wiedmeier SE et al,
Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system.
J Perinatol. 2009;29(2):130-136.

Magnitude of the Problem

- ~18-32% of infants admitted to NICU
- more preterm infants.
- Increased risk for
  - ICH,
  - mortality, and
  - long term neurodevelopmental disability.

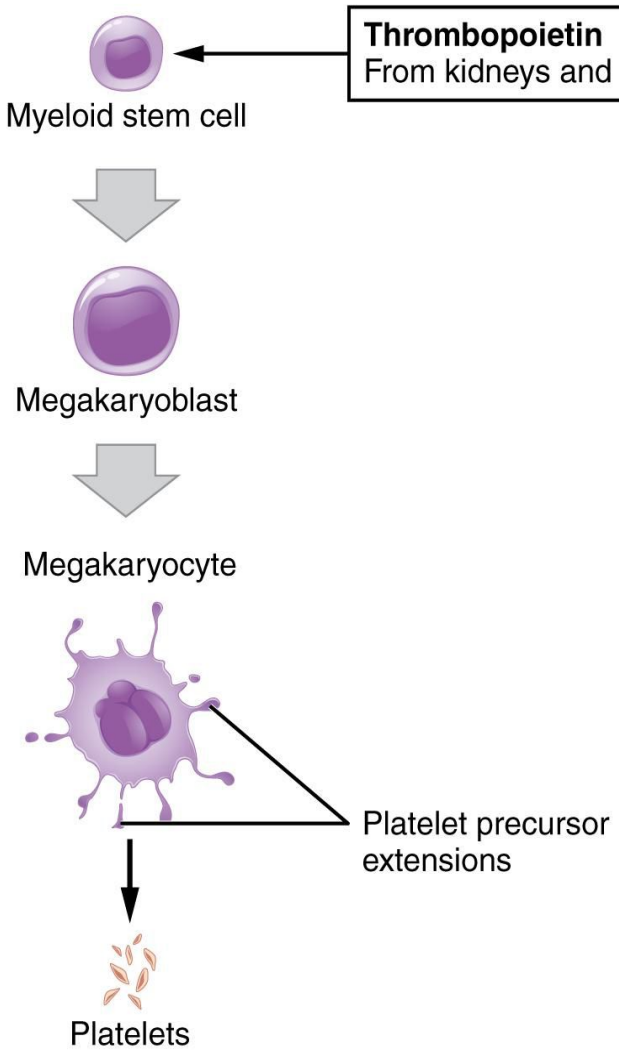
Platelet production:



Platelets: tiny cellular fragments produced by megakaryocytes

Short half life in circulation (7 - 10 days)

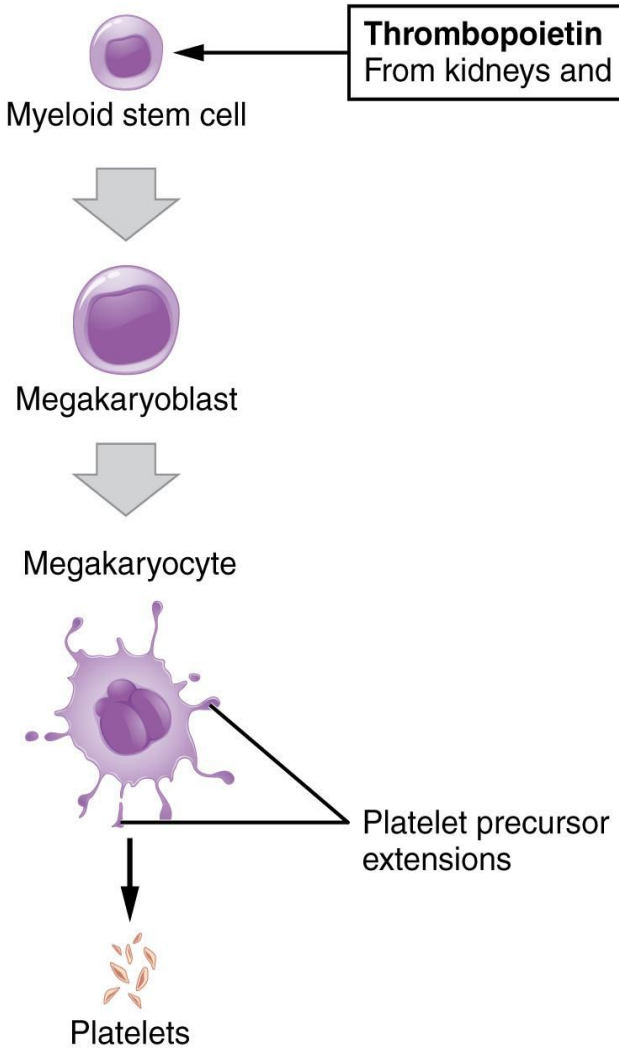
Mechanism of Platelet Production: 4 Steps



1. **Production of Thrombopoietin (Tpo):**

   Less in neonates

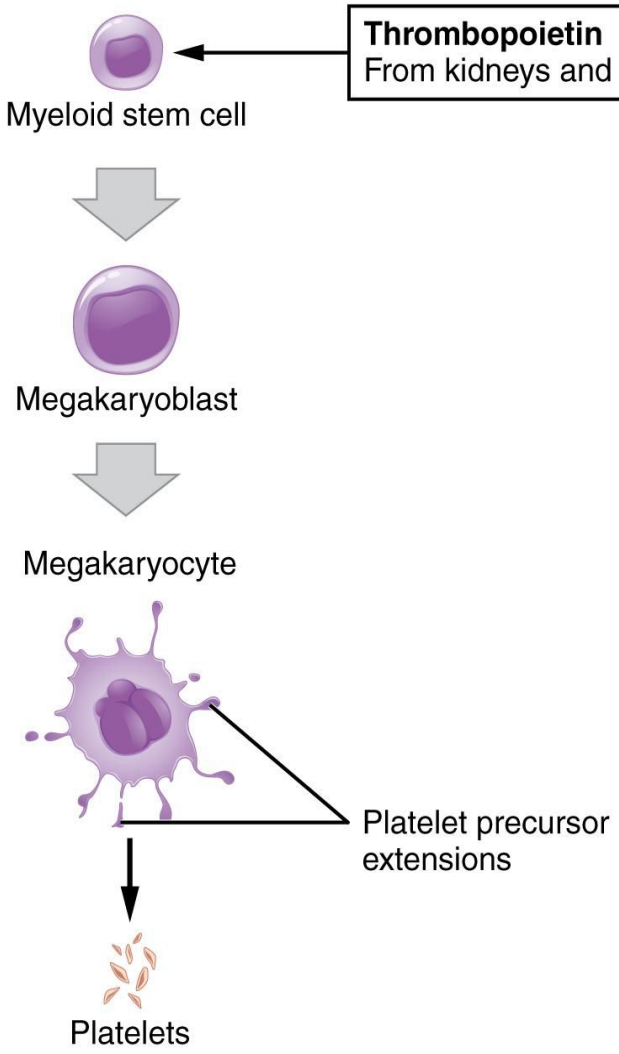
Mechanism of Platelet Production: 4 Steps



1. Production of Thrombopoietin (Tpo)

2. **Proliferation of megakaryoblasts**
   More sensitive to Tpo stimulation

Mechanism of Platelet Production: 4 Steps



1. Production of Thrombopoietin (Tpo)

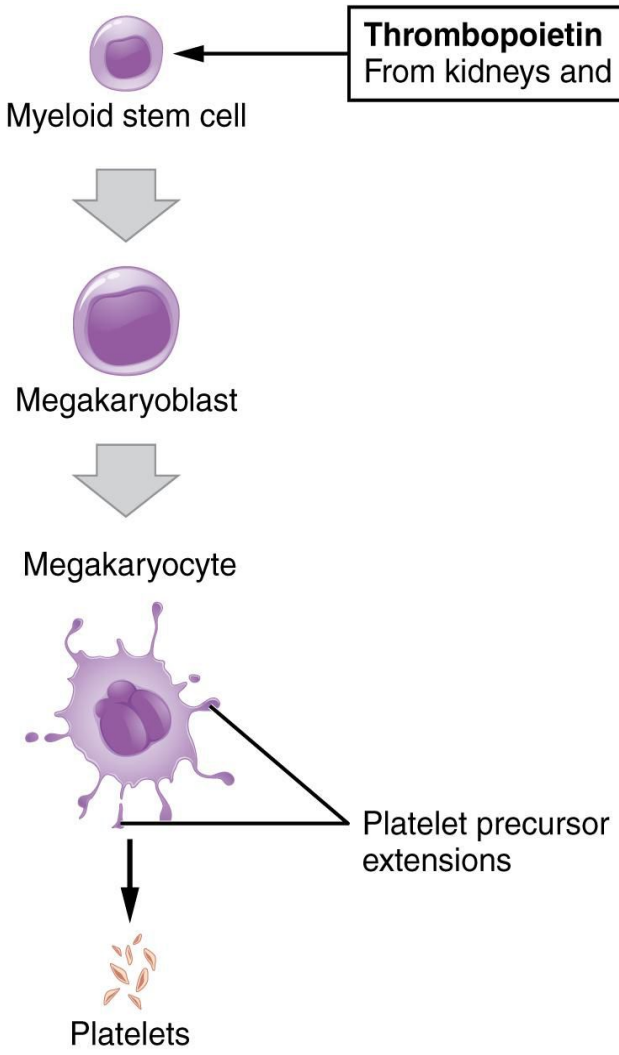
2. Proliferation of megakaryocytes progenitors

3. **Megakaryocyte maturation**

- Increase in nuclear ploidy (the number of sets of chromosomes in a given cell)
- Generation of large polyploid (8N–64N) megakaryocytes

➢ **more in number but**
➢ **smaller and**
➢ **have lower ploidy than adults**

Mechanism of Platelet Production: 4 Steps



1. Production of Thrombopoietin (Tpo)

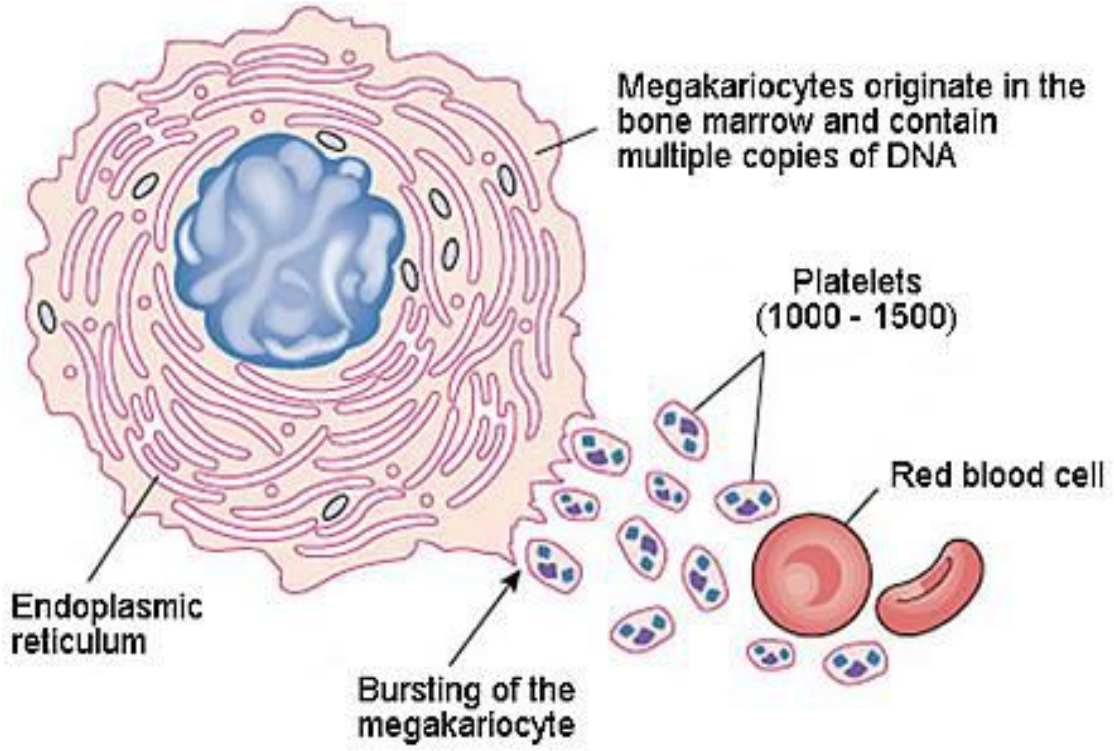
2. Proliferation of megakaryocytes progenitors

3. Megakaryocyte maturation

4. Development and release of new platelets.

✓ by bursting of megakaryocyte

Response to increased platelet demand:

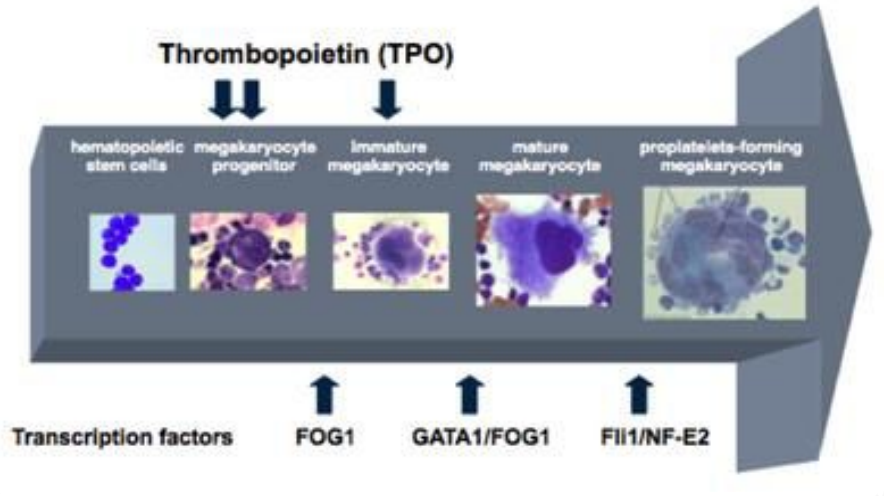


Adult BM: first increases the MK size and ploidy and then increases the MK number

Limitation in Neonates: can increase the number, but not the size of their MKs

Ma DC, Sun YH, Chang KZ, Zuo W.
Developmental change of megakaryocyte maturation and DNA ploidy in human fetus.
Eur J Haematol. 1996;57(2):121-127

Various Factors Influence Platelet Production:



Measures of platelet production like serum Tpo or reticulate platelet % (RP%)

- not reliable in the neonates!

How do I approach a neonate with thrombocytopenia?

Thrombocytopenia – 3 Periods of Presentation

Time of Onset	Type
Fetal	•**Immune: Alloimmune (NAIT) / Autoimmune** •Congenital Infections (TORCH, HIV) •Chromosomal (Aneuploidy)
Early (<72 hrs)	•All above •**Placental Insufficiency** (Eg: **IUGR**) •**Asphyxia** •**Sepsis (DIC)**
Variable (Early/Late)	•**Sepsis** Thrombosis •Vascular tumor •Metabolic (Proprionic acidemia, methylmalonic acidemia) •ECMO
Late (>72 hrs)	•**NEC** •**Drug** Induced (Penicillin and derivatives, vancomycin, metronidazole, Phenytoin, phenobarbital)

Early Onset <72 hrs

Well Baby:

- IUGR;
- Autoimmune thrombocytopenia
  - Mild to moderate thrombocytopenia
  - Nadir on postnatal day 4-5
  - Usually resolves by 7-10 days.

Sick Baby:

- Neonatal Alloimmune Thrombocytopenia (NAIT)

Variable (Sick / Well:

- Sepsis (Bacterial or viral), TORCH, DIC

Neonatal Autoimmune Thrombocytopenia

- Early onset
- Moderate severity
- Maternal history: +/-
  - Usually H/O ITP or autoimmune disease (2 in 1000 pregnancies)

  Any infant born to a mom with autoimmune disease should have a platelet count (10%).
  - Sometimes - Presenting sign of maternal autoimmune disease

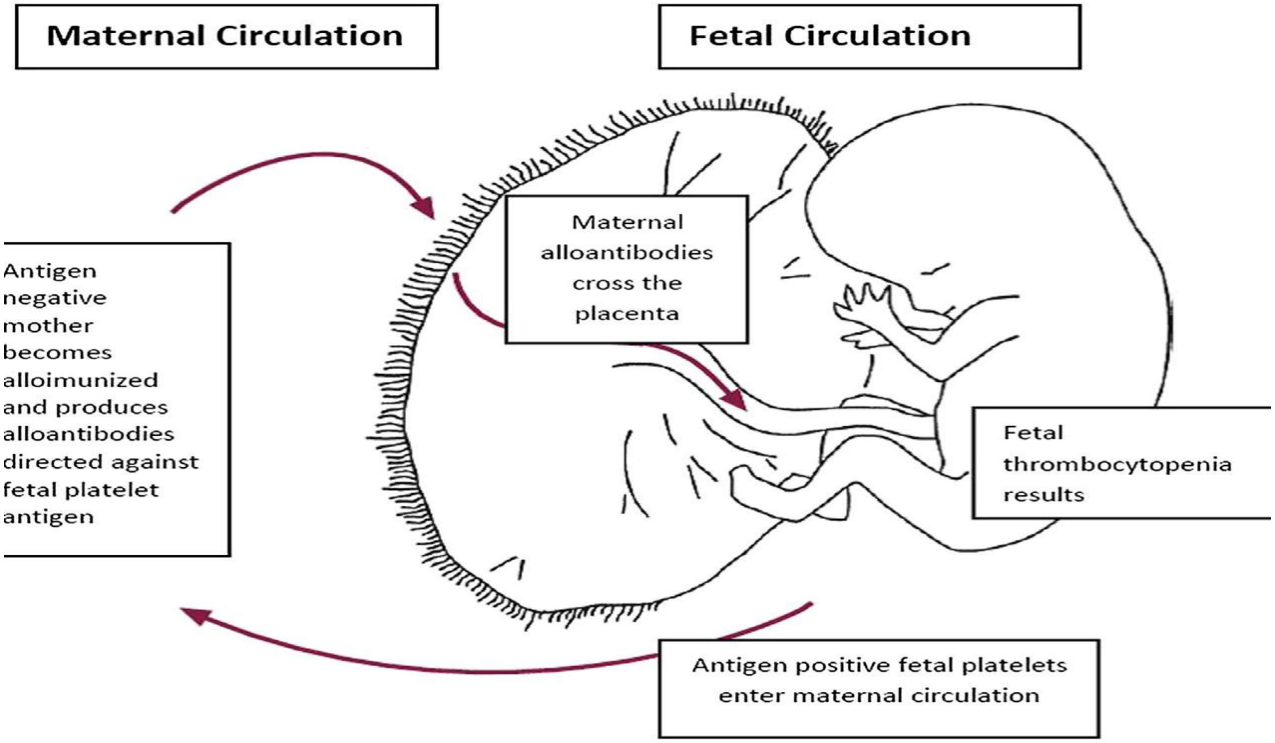
  Any mother having a neonate with thrombocytopenia should have a platelet count!

- Treatment: +/- (IVIG, Platelet transfusion)
- Evaluate for ICH (~1%).
- Lasts from days to months.

Neonatal Alloimmune Thrombocytopenia (NAIT)

- Severe (<50,000)
- Increased risk for ICH (8-22%)
- Antenatal Presentation: ICH, severe hydrocephalus, hydrops fetalis.
- Incidence 1 in 1500 pregnancies

Neonatal Alloimmune Thrombocytopenia (NAIT)



- Due to maternal Ab (to paternal Ag) present in fetal platelets
- Can occur in first pregnancy
- Testing of Mother and Father for Human Platelet antigen (HPA 1a, 5b, and 15b)
  - sixteen HPAs identified but only three cause 95% of the NAIT cases

Neonatal Alloimmune Thrombocytopenia (NAIT)

- Requires Transfusion
- Resolves within 2 weeks
- Platelet count: needs to be followed until normalized and stable.
- If persists longer may be a different diagnosis.
- Monitoring for future pregnancies and possibly treatment with maternal IVIG/steroids.

Late-Onset Thrombocytopenia

- Ill Appearing:
  - Sepsis (Viral & Fungal – Earlier)
  - NEC,
  - IEM (Propionic Acidemia, isovaleric acidemia, methylmalonic acidemia, Gaucher Disease)

- Well Appearing:
  - Drug induced,
  - thrombosis,
  - Fanconi's Anemia

The bleeding pattern

- Mucocutaneous.
- Petechiae, bruises, or bleeding from the mucous membranes

- Look out for: IVH / ICH!

Physical Exam

Keeping in Mind:

1. **Time of onset:** early & late

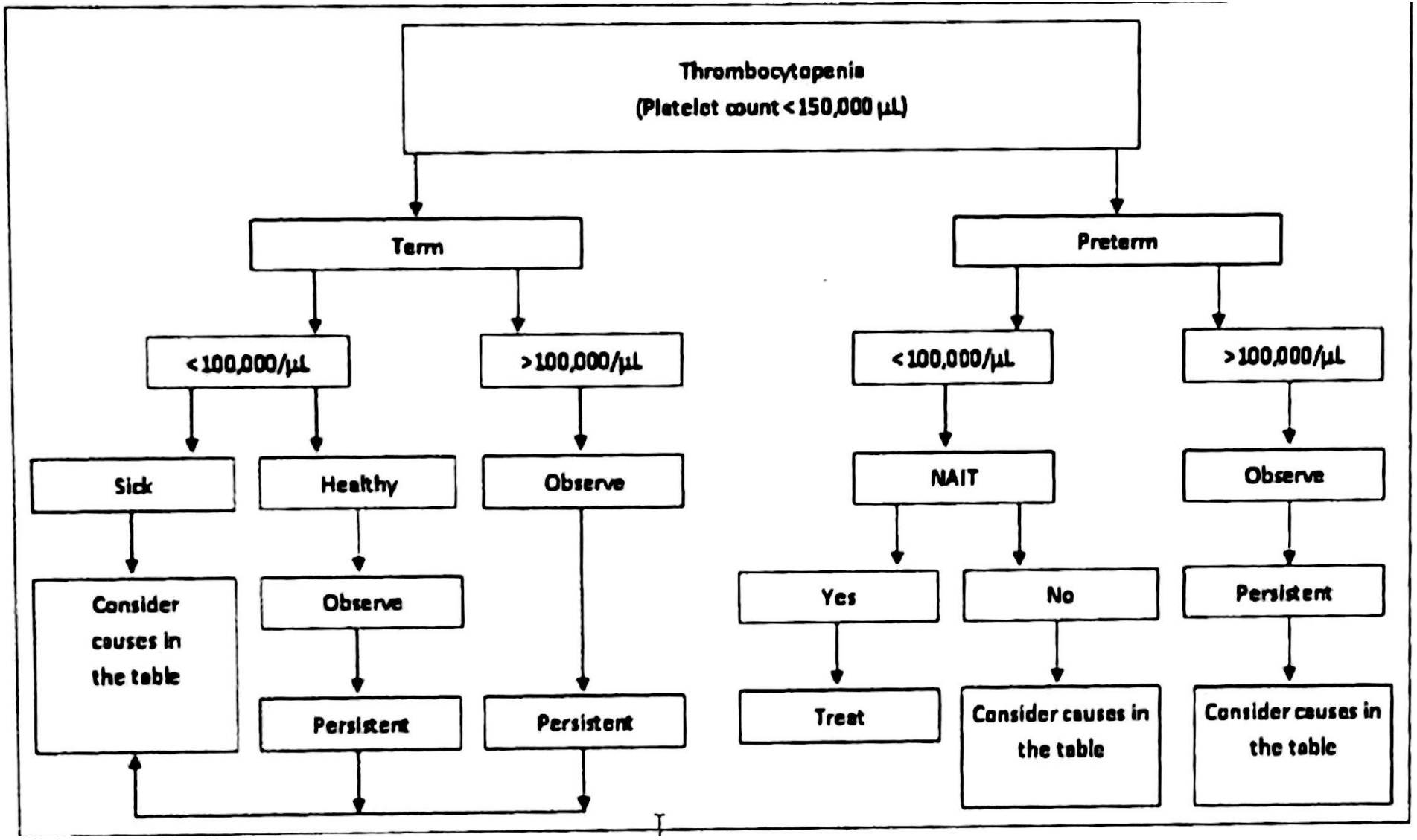
2. **Gestational age**: Term Vs preterm

3. **Possible underlying mechanism** (consumption, increased destruction, decreased production), Due to maternal or infant factors or individualized to the particular infant.

- Ill or Well
- Petechia, bruising
- Fontonelle
- Liver size
- Abdominal masses (renal vein thrombosis)
- Dysmorphic features
- Forearm or thumb abnormalities (TAR syndrome or Fanconi anemia)

When do we need to treat?

Diagnostic approach



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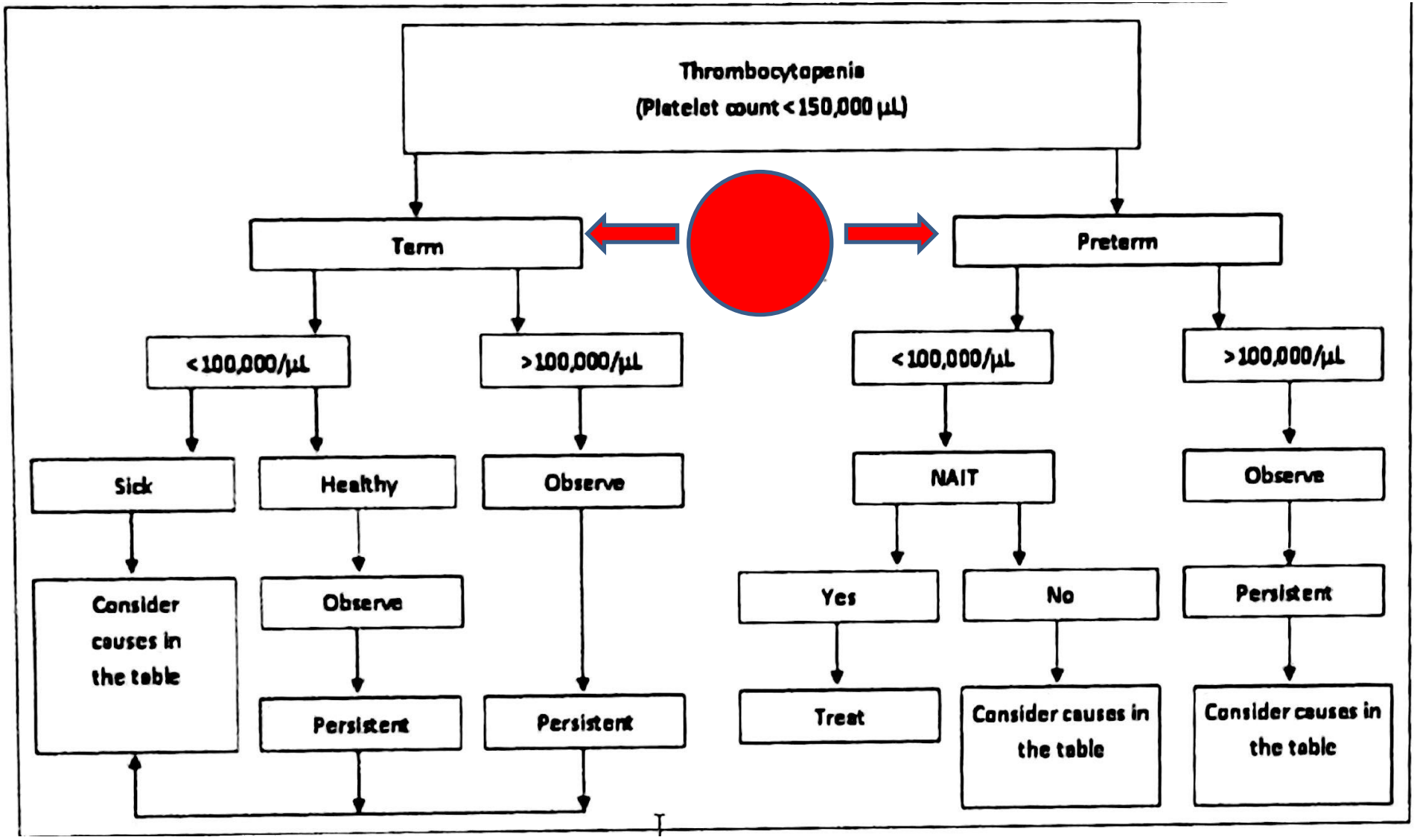
Diagnostic approach



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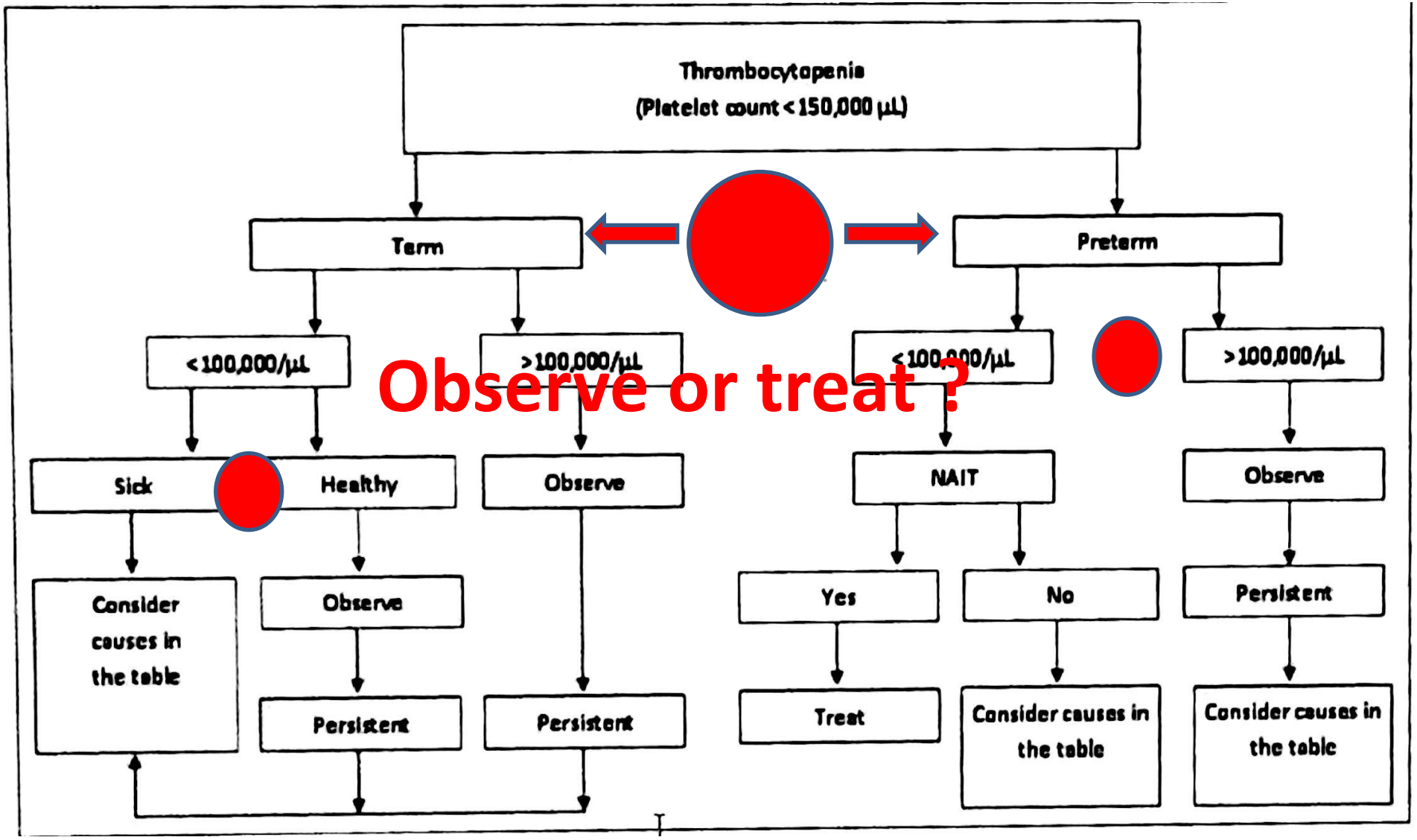
Diagnostic approach



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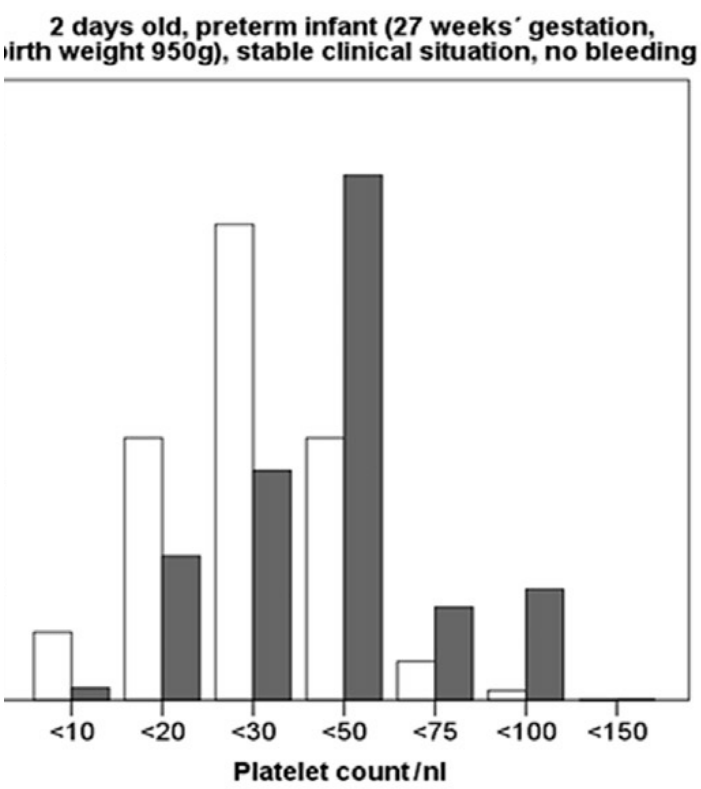
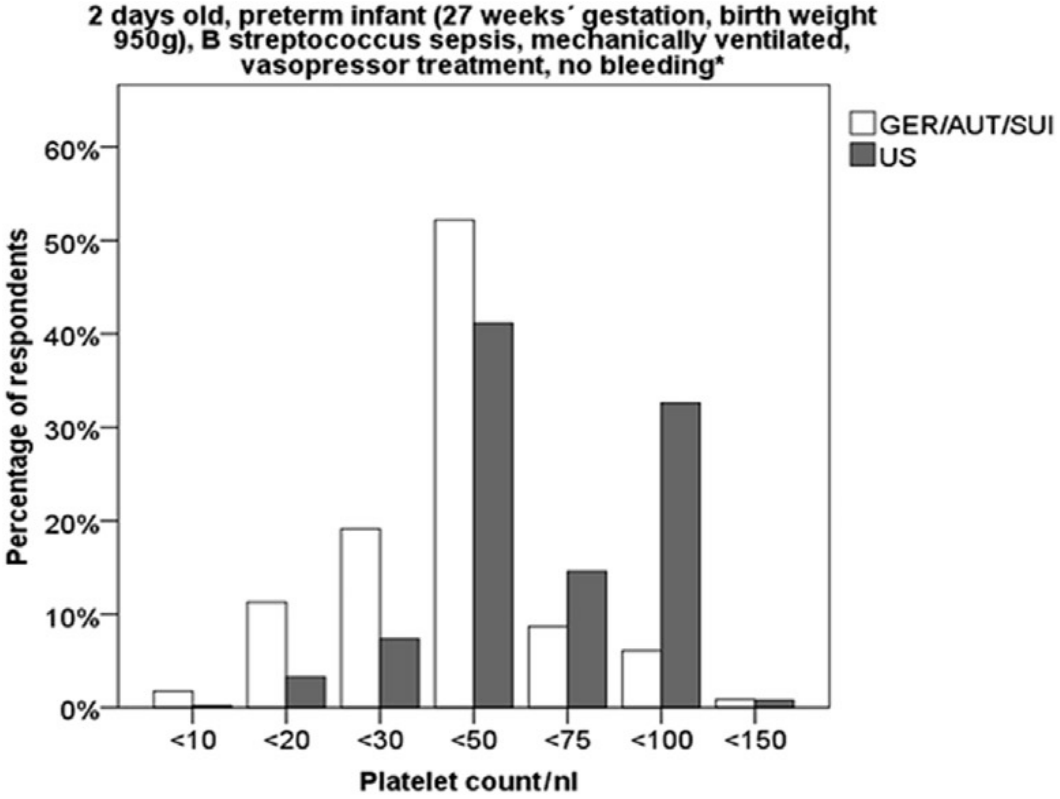
When is the right time to transfuse Platelets?





Platelet transfusion thresholds selected by neonatologists in German-speaking European countries versus U.S. neonatologists in 2 different clinical scenarios!

Transfusion 2011;51:2636–7

When is the right time ???

Various prospective, observational trials strongly suggest that factors other than the platelet count determine the risk for major ICH!!

Platelet Count and Risk of Bleeding (US)

Risk:

- 100,000 – 20,000/uL: Minimal or mild risk of bleeding
- **20,000** – 5,000/uL: Moderate Risk
- <5,000/ Ul: severe Risk

Transfusion Threshold:

- Lower for **preterm** (Higer incidence IVH & “immaturity of the hemostatic system”) - **50,000**/uL ?
- When platelets < **30,000**/Ul: Trauma & stress of birth can precipitate ICH

Formulating a Guideline: NeoReviews Vol.14 No.2 February 2013

Defining Threshold for Transfusion: (UK)

- < 150000 vs <50,000 no differences in freq or severity of ICH (Andrew et al 1993)
- Transfuse platelets: (volume reduction not necessary)
  - <100,000: Any infant if ICH or signs of active bleeding.
  - <50,000: Ill term / preterm (<33weeks) in 1st week of age.
  - <30,000: stable term / preterm > 1 week of age

    (Murray et al 2002: no major hemorrhage in infants if platelets >30,000)

Chakravorty S, Roberts I. How I manage neonatal thrombocytopenia. Br J Haematol. 2012;156(2):155–162

NAIT: Management Guidelines:

- If platelets <50,000- Suggest **cerebral imaging** (US, MRI)
- **Transfuse platelets:**
  - trial of random donor platelets first.
  - If ineffective: **Antigen negative platelets** should be used (maternal platelets or known PL A1 or PL A5 negative platelets)
- Consider **IVIG** 1g/kg q 24hrs x 2 doses (+/- in combination with random donor transfusions)
- Consider **methylprednisolone** (1mg/kg q 8hrs) with IVIG.

Before deciding to transfuse ……

- Any doubt - repeat sample
  - Errors from improper collection or unrecognized platelet clumping
- Blood culture +/- antibiotics depending on history, clinical picture and severity.
- Review peripheral smear and MPV
  - (Jacobsen and Fechtner syndromes present with large platelets and Wiskott-Aldrich syndrome and X-linked thrombocytopenia present with small platelets)

Remember when you Transfuse ……

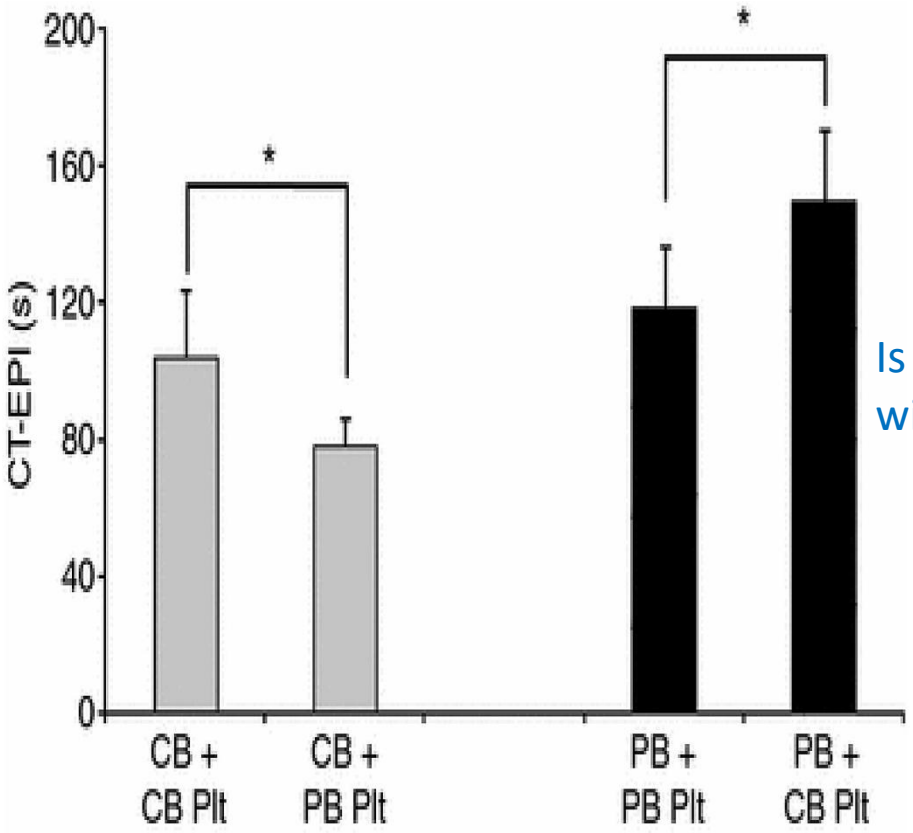
- **Dose: 10-15ml/kg** random-donor platelets
  - Either CMV neg or leukoreduced
  - Irradiation to reduce GVHD

- **Adv Effects:** Platelet transfusions associated with **TRALI (Transfusion Related Acute Lung Injury)** and increased mortality ??

- **Multiple Transfusion Requirement:**
  - on a weekly basis - decreased platelet production (congenital amegakaryocytic thrombocytopenia)
  - every 1-2 days - increased platelet consumption.

Unanswered Questions !!

Which is more suitable platelet for transfusion in neonates?



Adult Vs Neonatal Platelets:
Effects of platelet transfusions on neonatal primary hemostasis

Is there a developmental mismatch associated with platelet transfusions?

Closure times after stimulation with CT-EPI (closure time epinephrine) –

Significantly shorter in neonatal blood "transfused" in vitro with adult platelets compared with blood "transfused" with neonatal platelets.

*P < 05.

Ferrer-Marin F, Chavda C, Lampa M, Michelson AD, Frelinger Iii AL, Sola-Visner M. Effects of in-vitro adult platelet transfusions on neonatal hemostasis. *J Thromb Haemost.* 2011;9(5):1020-1028.

Current Research:

PlaNet-2 study

Ongoing RCT comparing two different platelet transfusion thresholds and aims to establish whether a lower platelet transfusion threshold is as good as a higher threshold in preterm infants < 34 weeks POG

Randomisations to date = 532 / 660

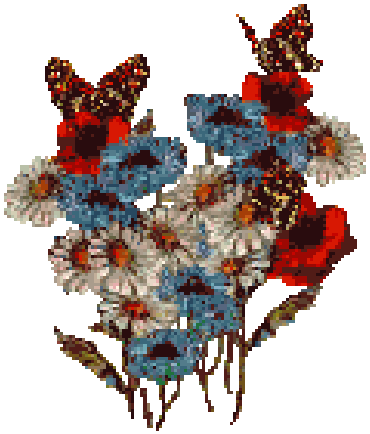
Platelet transfusion cut off: **Arm A : < 25; Arm B < 50**

Primary Outcome: Death or severe IVH in 1ST 28 days

Dr Simon Stanworth, et al, University of Cambridge.

Thank you!

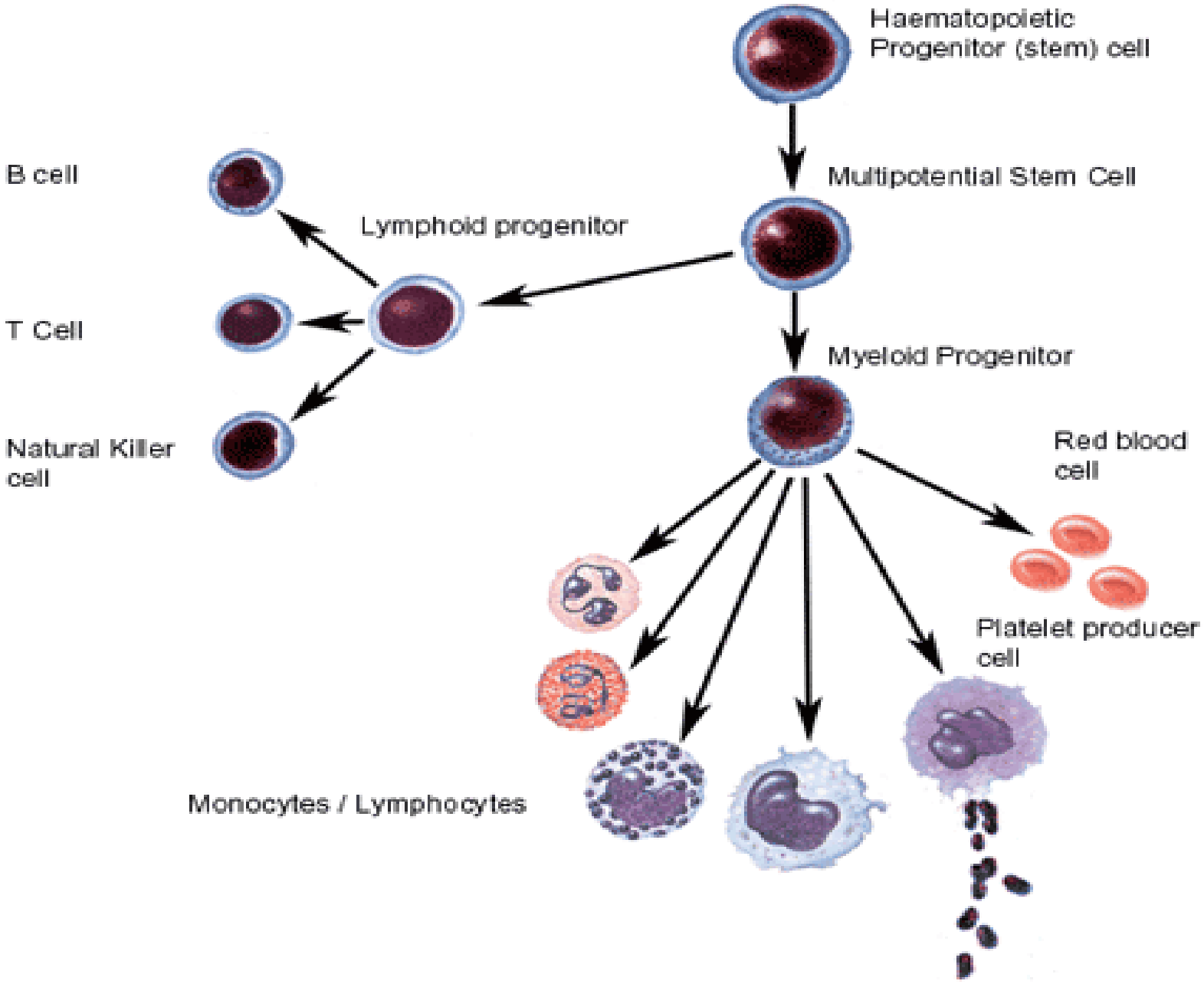
jubileenicu@gmail.com,

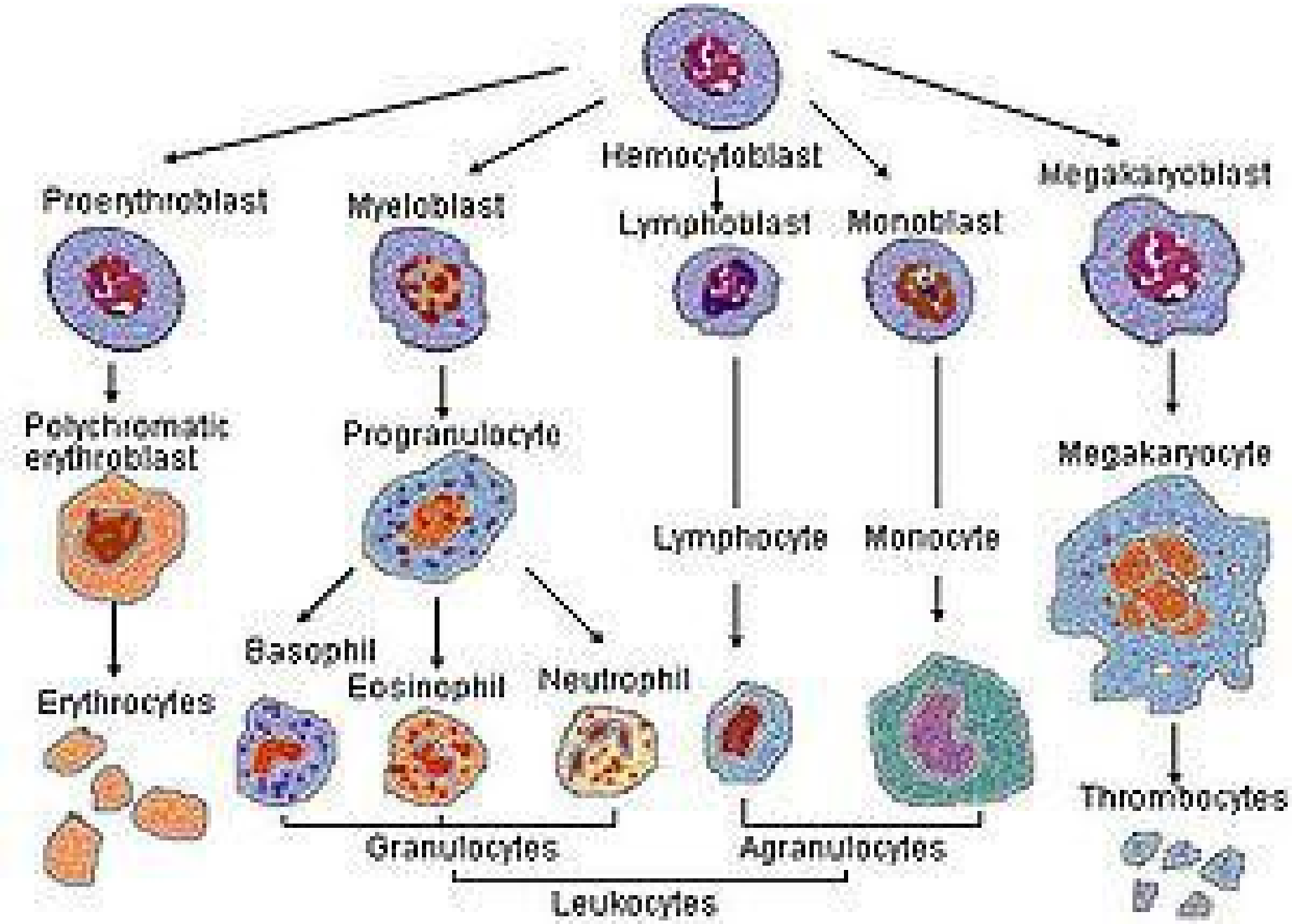


Genetic Disorders Associated With Thrombocytopenia

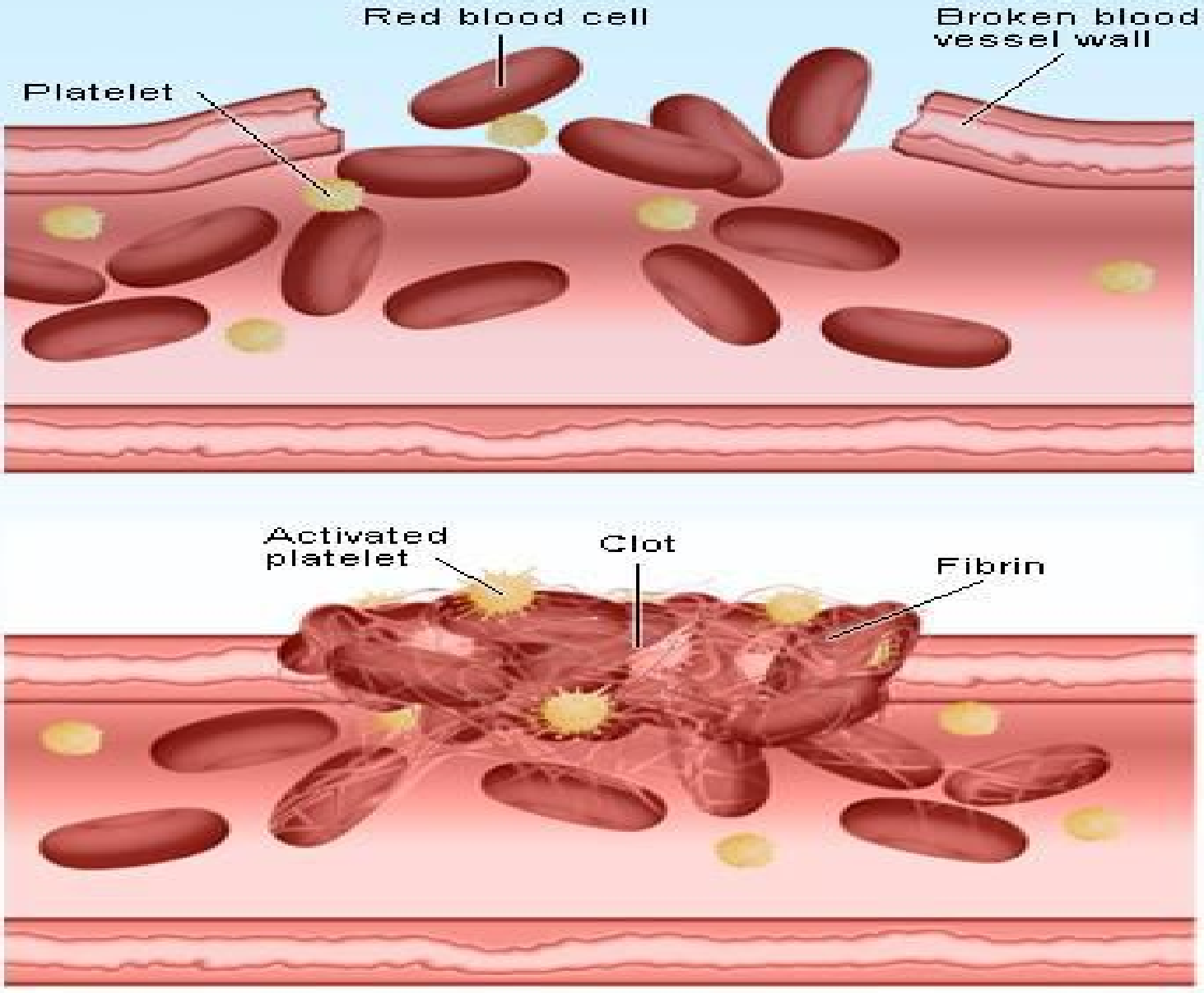
Chromosomal: Trisomy 13	Aplasia cutis, CHD, cleft lip and palate, polydactyly
Trisomy 18	IUGR, CHD, rocker-bottom feet, overlapping digits, hypertelorism, small mouth, clinodactyly
Trisomy 21	CHD, single palmar crease, hypotonia, short neck, w/ redundant posterior folds
Turner syndrome	CHD, cubitus valgus, webbed posterior neck, broad chest , with wide-spaced nipples,lower extremity edema
11 q terminal disorder (Jacobsen syndrome)	CHD, GU anomalies, facial anomalies, abnl brain imaging, limb anomalies
Familial : May-Hegglin anomaly (Sebastian syndrome)	Giant platelets, neutrophilic inclusions
Fechtner syndrome	Giant platelets, sensorineural hearing loss, cataracts, nephritis, neutrophilic inclusions
Bernard-Soulier syndrome	Anemia, genitourinary abnormalities (cryptorchidism)
Congenital amegakaryocytic thrombocytopenia	Abnl head size and shape, developmental delay, CHD, cleft and high-arched palate, abnormal kidneys, optic atrophy, valgus and varus deformities, vertebral anomalies,coloboma, scoliosis, absent bone marrow megakaryocytes
Wiscott-Aldrich syndrome	Immunodeficiency, small platelets, eczema
Amegakaryocytic **thrombocytopenia**	Restricted forearm pronation, proximal radioulnar synostosis in forearm, and radioulnar synostosis absent bone marrow megakaryocytes
Fanconi anemia	Hypopigmented and hyperpigmented skin lesions, urinary tract abnormalities, microcephaly, upper extremity radial-side abnormalities involving the thumb, pancytopenia (usually with onset in childhood)
Thrombocytopenia and absent radii	Shortened/absent radii bilaterally, nml thumbs, ulnar and hand abnormalities, abnormalities of the humerus, CHD, eosinophilia, leukemoid reaction
Neonatal primary hemophagocytic lymphohistiocytosis	Fever, HSM, hyperferritemia, hypertriglyceridemia, hypofibrinogenemia
Metabolic:	
Propionic acidemia, methylmalonic acidemia	FTT, developmental delay, ketoacidosis, hyperglycinemia, hyperammonemia
Isovaleric acidemia	Odor of sweaty feet, poor feeding, hypotonia, hyperammonemia, metabolic acidosis
Gaucher disease	Hepatosplenomegaly, Gaucher cells in bone marrow

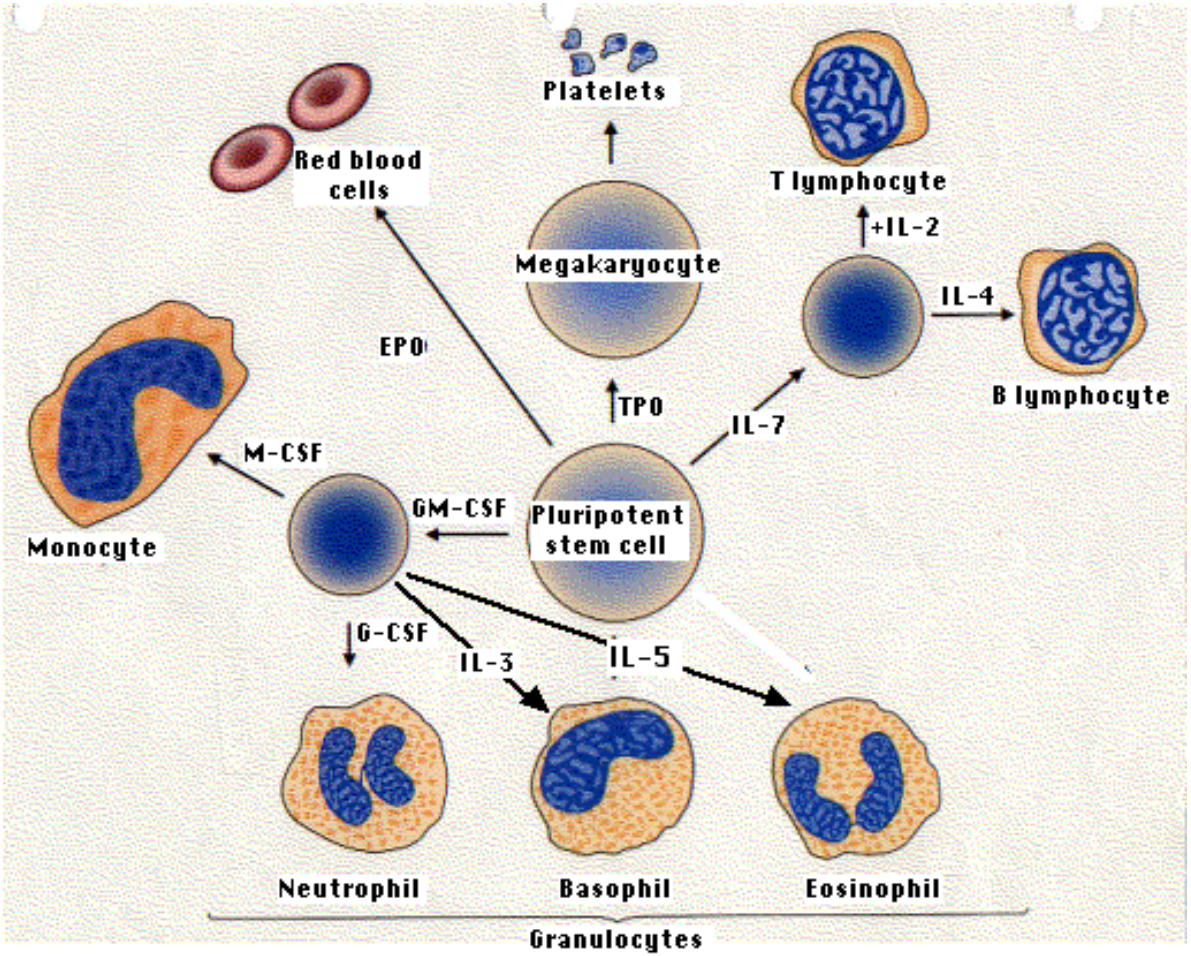
Neoreviews 2009


Haematopoietic
Progenitor (stem) cell
Multipotential Stem Cell
Lymphoid progenitor
B cell
T Cell
Natural Killer
cell
Myeloid Progenitor
Red blood
cell
Platelet producer
cell
Monocytes / Lymphocytes


Hemocytoblast
Proerythroblast
Myeloblast
Lymphoblast
Monoblast
Megakaryoblast
Polychromatic erythroblast
Progranulocyte
Megakaryocyte
Lymphocyte
Monocyte
Basophil
Eosinophil
Neutrophil
Erythrocytes
Thrombocytes
Granulocytes
Agranulocytes
Leukocytes

Blood Clot




Platelets
Red blood cells
T lymphocyte
+IL-2
Megakaryocyte
IL-4
B lymphocyte
EPO
TPO
IL-7
M-CSF
GM-CSF
Pluripotent stem cell
Monocyte
G-CSF
IL-3
IL-5
Neutrophil
Basophil
Eosinophil
Granulocytes

Specific Illnesses and Patterns Associated With Neonatal Thrombocytopenia

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*	Variable	Early*
	Metabolic	Propionic 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