Neonatal Leukopenia and Thrombocytopenia

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Objectives

- Summarize the differential diagnosis of leukopenia and/or thrombocytopenia in a neonate
- Describe the initial steps in the evaluation of a neonate with leukopenia and/or thrombocytopenia
- Review treatment options for leukopenia and/or thrombocytopenia in the NICU

Clinical Case 1

- One day old male infant admitted to the NICU for hypoglycemia and a sepsis rule out
- Born at 38 weeks EGA by SVD
- Birth weight 4 lbs 13 oz
- Exam shows a small cephalohematoma; no dysmorphic features
- PLT count 42K with an otherwise normal CBC

Definitions

- Normal WBC count 9-30K at birth
  - Mean 18K
- What is the ANC and ALC
  - <1000/mm^3 is abnormal
  - 6-8% of infants in the NICU
- Normal platelet count: 150-450,000/mm^3
  - Not age dependent
  - 22-35% of infants in the NICU have plts<150K

Neutropenia
Absolute neutrophil count <1500/mm^3

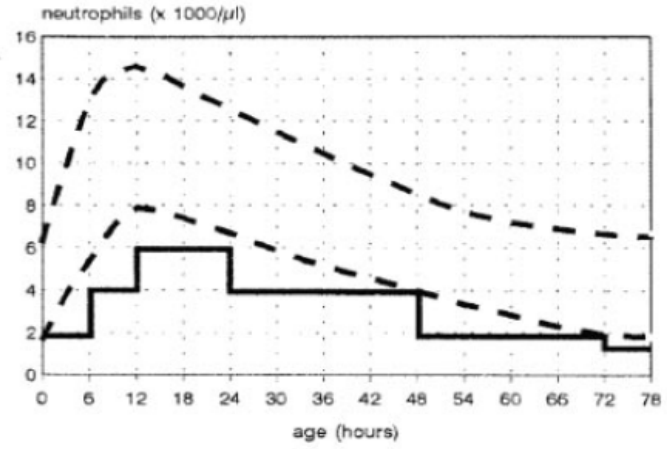
Category	ANC*	Infection risk
• Mild	1000-1500	None
• Moderate	500-1000	Minimal
• Severe	<500	Moderate to Severe (Highest if <200)

- Recurrent bacterial or fungal infections are the hallmark of symptomatic neutropenia!
- *ANC = WBC X % (PMNs + Bands) / 100

Definition of Neutropenia

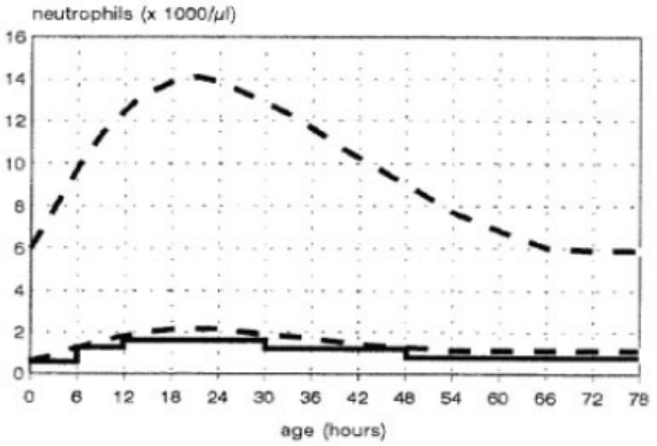
birthweight > 1500 g

age (hours)	neutropenia
0 - 6	<2000/μl
> 6 -12	<4000/μl
>12 -24	<6000/μl
>24 -48	<4000/μl
>48 -72	<2000/μl
>72	<1500/μl



birthweight ≤ 1500 g

age (hours)	neutropenia
0 - 6	<500/μl
> 6 -12	<1500/μl
>12 -30	<1800/μl
>30 -48	<1500/μl
>72	<1100/μl



Black and Maheshwari, Neoreviews 2009

How to Approach Cytopenias

- Normal vs. abnormal (consider severity)
- Malignant vs. non-malignant
- Congenital vs. acquired
- Is the patient symptomatic
- Transient, recurrent, cyclic, or persistent

How to Approach Cytopenias

- Adequate vs. decreased marrow reserve
- Decreased production vs. increased destruction/sequestration

Decreased neutrophil/platelet production

- Primary
  - Malignancy/leukemia/marrow infiltration
  - Aplastic anemia
  - Genetic disorders
- Secondary
  - Infectious
  - Drug-induced
  - Nutritional
    - B12, folate, copper

Increased destruction/sequestration

- Immune-mediated
- Drug-induced
- Consumption → Hypersplenism vs. Vascular
- Necrotizing enterocolitis
- Pseudo-neutropenia
- Pseudo-thrombocytopenia (in vitro finding)

Fetomaternal Disorders

Table 1 Disorders of the Fetomaternal Unit Resulting in Hematological Manifestations in the Fetus/Neonate

- Placental insufficiency
  - PIH-spectrum disorders (preeclampsia, eclampsia, HELLP syndrome)
  - Maternal diabetes
  - Transplacentally acquired infections (such as CMV)
  - Systemic conditions (malignancies, cardiac disease, thyroid disease, SLE, and other autoimmune disorders etc.)
- Immune-mediated disorders
  - Hemolytic disease of the newborn
  - Alloimmune neonatal neutropenia
  - Neonatal alloimmune thrombocytopenia
  - Autoimmune hemolytic anemia
  - Neonatal autoimmune neutropenia
  - Neonatal autoimmune thrombocytopenia
- Transplacentally acquired infections
  - Toxoplasmosis
  - Syphilis
  - Viral infections
    - Cytomegalovirus (CMV)
    - Rubella
    - Human immunodeficiency virus (HIV)
    - Parvovirus B19
    - Echovirus
    - Coxsackie B virus
  - Tuberculosis
  - Malaria

Black and Maheshwari, Seminars in Perinatology 2009

Outpatient Neonatal Hematology

- Bone Marrow Failure Syndromes
  - Severe and symptomatic
- Immune-mediated disorders
  - Severe and asymptomatic
  - Usually resolves by 2 months of age
  - May have implications for future children
- Other fetomaternal disorders
  - Placental insufficiency
- Other causes usually resolve before discharge

Bone Marrow Failure Syndromes

- Genetic disorders of hematopoiesis that affects one or more cell lines and may lead to complete marrow failure or malignant transformation (i.e. MDS/AML)
- Most are inherited, though spontaneous mutations are possible

BMFS: common clinical features

- Bone marrow failure
  - Can be complete aplasia or isolated to a single cell line
  - Can be progressive
  - Hypoproliferative cytopenias, marrow aplasia, macrocytosis (elevated MCV)
  - AA, MDS, or leukemia may be the first hematologic manifestation
- Congenital abnormalities (not always)
- Cancer predisposition
  - Family history is essential (also consider other end organ damage)
- May present in adulthood

Severe Congenital Neutropenia

- Clinical features: severe, persistent neutropenia and recurrent infections
  - Also FTT, periodontal disease
- Also known as Kostmann's syndrome
- Genetics: AD, AR, and sporadic mutations
- ELA-2/ELANE, HAX-1, and others
- Treatment: Surveillance for MDS/AML (about 2%/year), oral care, prompt treatment for suspected infections, G-CSF, HSCT

Cyclic Neutropenia

- AD or sporadic inheritance
- Neutrophil elastase gene
  - leading to apoptosis of myeloid precursors
- Prevalence: 1 per million
- Really cyclic hematopoiesis
- Cycles 14-28 days (average 21 days)
- Neutropenia lasts 3-5 days
- 10% patients develop life-threatening infections
- No increased risk of malignancies

Shwachman-Diamond Syndrome

- Clinical features: triad of neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities
  - May also have neutrophil dysfunction
- Genetics: AR mutations in the SBDS gene (90% of patients)
- Testing: Skeletal survey, evaluation for malabsorption
  - Low serum trypsinogen and pancreatic isoamylase (values are age-dependent)
  - Low fecal elastase
  - Fatty pancreas on CT scan
  - Pancreatic stimulation testing by pediatric GI
- Treatment: surveillance for MDS/AML, supportive care, pancreatic enzyme replacement, ADEK vitamin supplementation, HSCT

TABLE I. Spectrum of Clinical Problems in SDS

System	Manifestation
Hematologic	
Peripheral blood counts	Neutropenia
	Intermittent or persistent
	Anemia
	Thrombocytopenia
Bone marrow	Decreased cellularity
	Aplastic anemia
	Myelodysplasia
	AML
	ALL
	Cytogenetic abnormalities
Gastrointestinal (GI)	
Exocrine pancreas	Steatorrhea[a]
	Impaired enzyme output[a]
	Low serum trypsinogen[a]
	Low serum pancreatic isoamylase[a]
	Abnormal imaging
Liver	Elevated transaminases[a]
	Fibrosis, steatosis
Cardiovascular	Myocardial fibrosis
Musculoskeletal	Rib cage abnormalities
	Metaphyseal chondrodysplasia
	Hip dysplasia
Immune	Increased infections
	B and T cell abnormalities
	Decreased number of NK cells
	Impaired neutrophil chemotaxis
Growth and development	Short stature
	Delayed puberty
	Developmental delays
	Learning problems
	Low IQ
Other	Renal abnormalities
	Dental abnormalities

Black et al, Pediatr Blood Cancer 2008

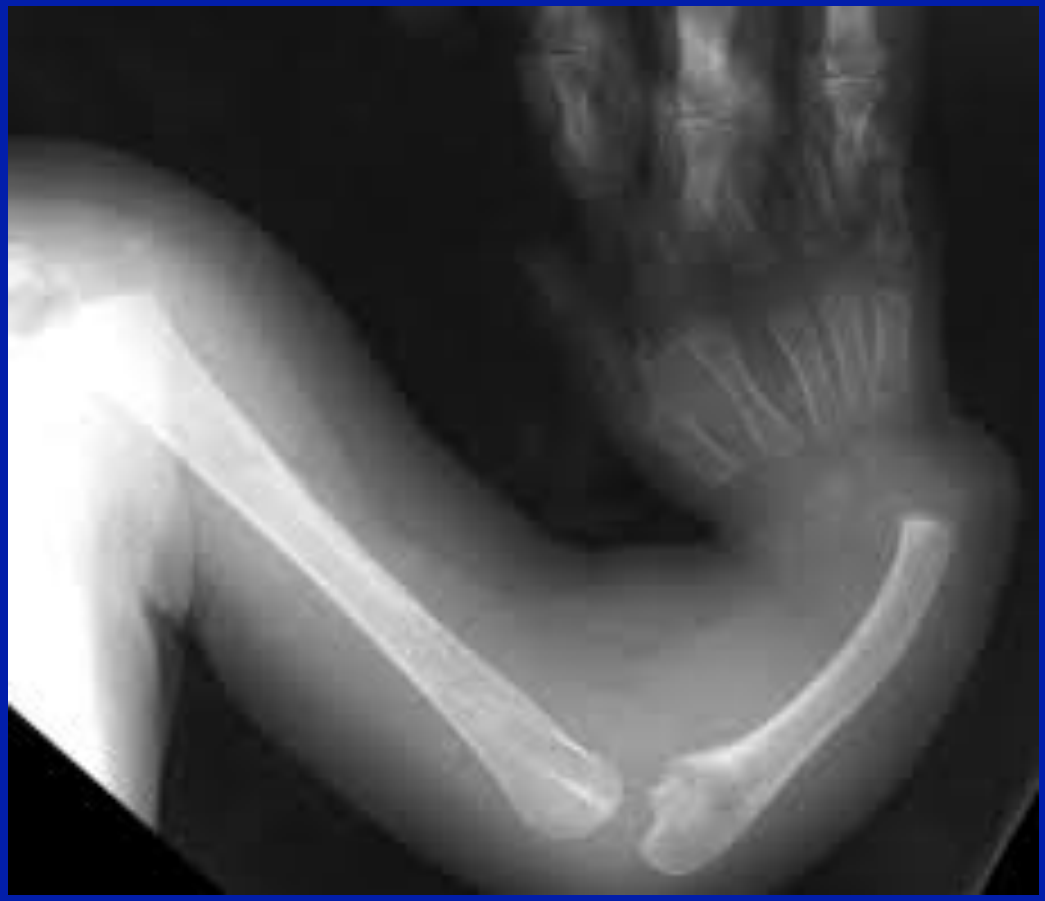
Congenital Amegakaryocytic Thrombocytopenia

- Clinical features: severe thrombocytopenia and bleeding
  - Rare congenital anomalies, median age at presentation 7 days
- Genetics: AR, c-MPL (TPO receptor)
  - 2 clinical groups characterized by early (80%) or late progression (20%) to aplastic anemia
  - 8% of patients develop MDS/AML
- Testing: exclusion of immune-mediated causes
- Treatment: transfusions, HSCT (even if alternative donor sources are required)

Thrombocytopenia Absent Radius Syndrome

- Clinical features: the same says it all!!!!
  - Platelet count <50K at birth
  - Other anomalies may be present
- Genetics: ?1q21.1
- Therapy and outcome
  - Platelet count increases to >100K by one year of age (usually)
  - Few cases of ALL/AML have been reported
  - HSCT in platelet-refractory patients

TAR Syndrome



TAR vs. FA

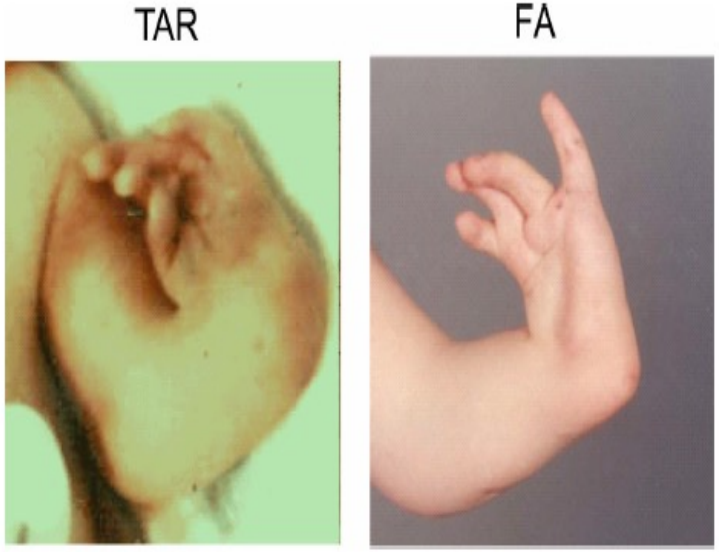


Figure 13.
Comparison of radial ray anomalies in TAR and FA. Left, TAR. Right, FA. TAR patient has absent radii, but thumbs are present, albeit not normal in shape or position. FA patient has an absent radius, but the thumb is also absent, and the fingers are abnormal.[64,153]

Shimamura, Blood Reviews 2010

Wiskott-Aldrich Syndrome

- Clinical features: triad of thrombocytopenia, eczema, and recurrent infections
  - T and B cell deficits, inability to form antibodies
- Pay attention to the MPV
- Increased risk of leukemia/lymphoma
- Genetics: X-linked disorder in the WASP gene
- Treatment: platelet transfusions, IVIG, Amicar, HSCT

Immune-mediated Disorders

- Neonatal alloimmune neutropenia/NAIT
- Neonatal autoimmune neutropenia/ thrombocytopenia (i.e. maternal ITP)
- Autoimmune neutropenia of infancy/ITP (i.e. baby has ITP) – less common in the NICU

Neonatal Alloimmune Thrombocytopenia

- Most common cause of early, severe thrombocytopenia
- Most common cause of ICH in term neonates
- True incidence is unknown
  - Generally quoted to be 1:1,000-1:5,000
- Screening is recommended when PLTs<50K at birth (based on data from HPA-1a incompatibility)
- Worsens with subsequent pregnancies
- Platelet count usually stabilizes within 2 weeks

Lymphopenia

- Absolute lymphocyte count (ALC) = WBC X % (lymphocytes)/100
- Normal values are age dependent
  - Adults have a mean ALC of 1,800/mm^3
  - Higher ALCs in infants (mean 6,700/mm^3)
- Generally, less than 1,000/mm^3 is abnormal
  - ALC <1,000-2,000/mm^3 in an infant <2 months of age is highly abnormal → consider SCID

Diagnostic Considerations

- Severity of cytopenias
- Duration of cytopenias
- Is the patient symptomatic?
- Is the patient sick?
  - Evidence of infection, NEC, or DIC
- Timing: Onset<72 hours vs. >72 hours
- Evidence of placental insufficiency
  - Birthweight
  - Maternal hypertension
  - Apgar scores

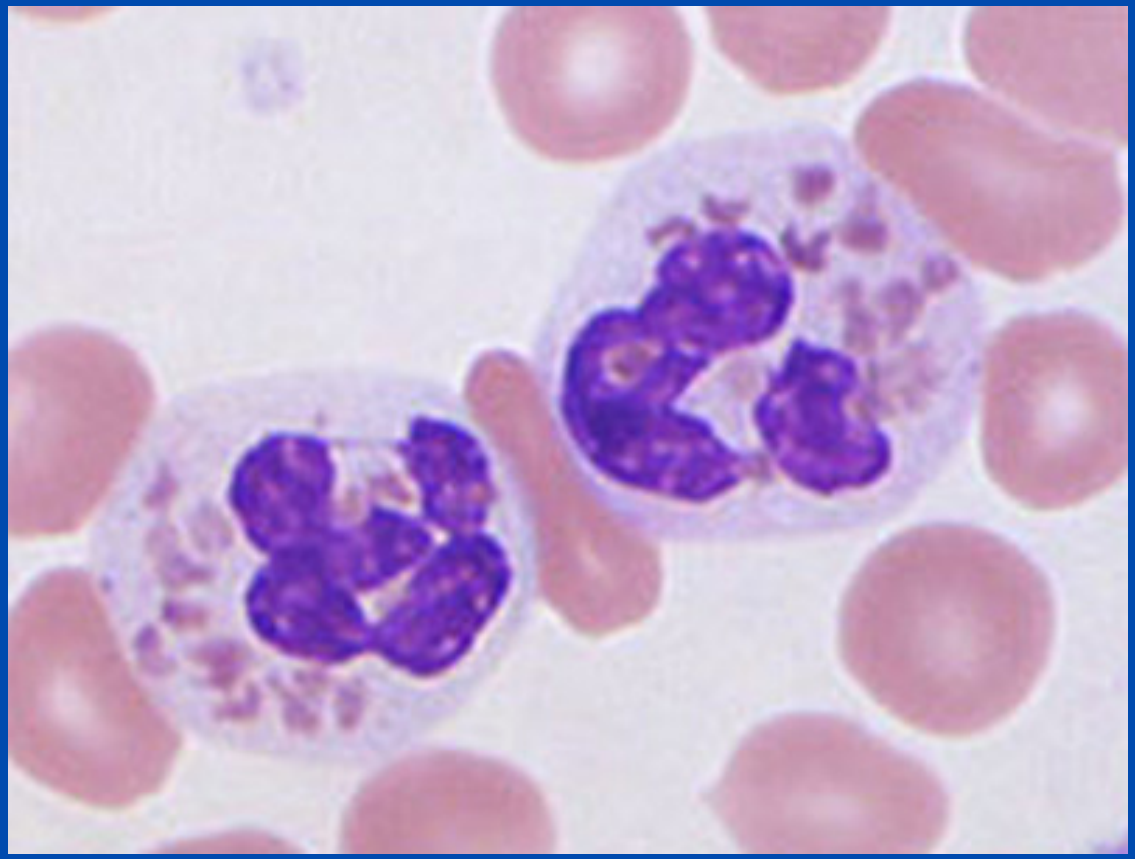
Diagnostic Considerations

- Maternal labs
- Family history
- Associated Findings (e.g. Barth syndrome)
- Careful physical exam
  - Dysmorphic features, esp. radial or thumb abnormalities
  - Hepatosplenomegaly → TORCH, GSD
  - Skin/hair/pigment abnormalities → Chediak-Higashi
  - Hemangiomas → Kasabach-Merritt syndrome

Laboratory Evaluation

- CBC with differential
  - Note other cell lines
  - Don't forget about the MCV
- CMP
- Peripheral blood smear
- If thrombocytopenic, assess for consumption
  - PT, PTT, fibrinogen
- Anti-neutrophil antibody screen if neutropenic
  - Does not rule out immune-mediated neutropenia

Case 2



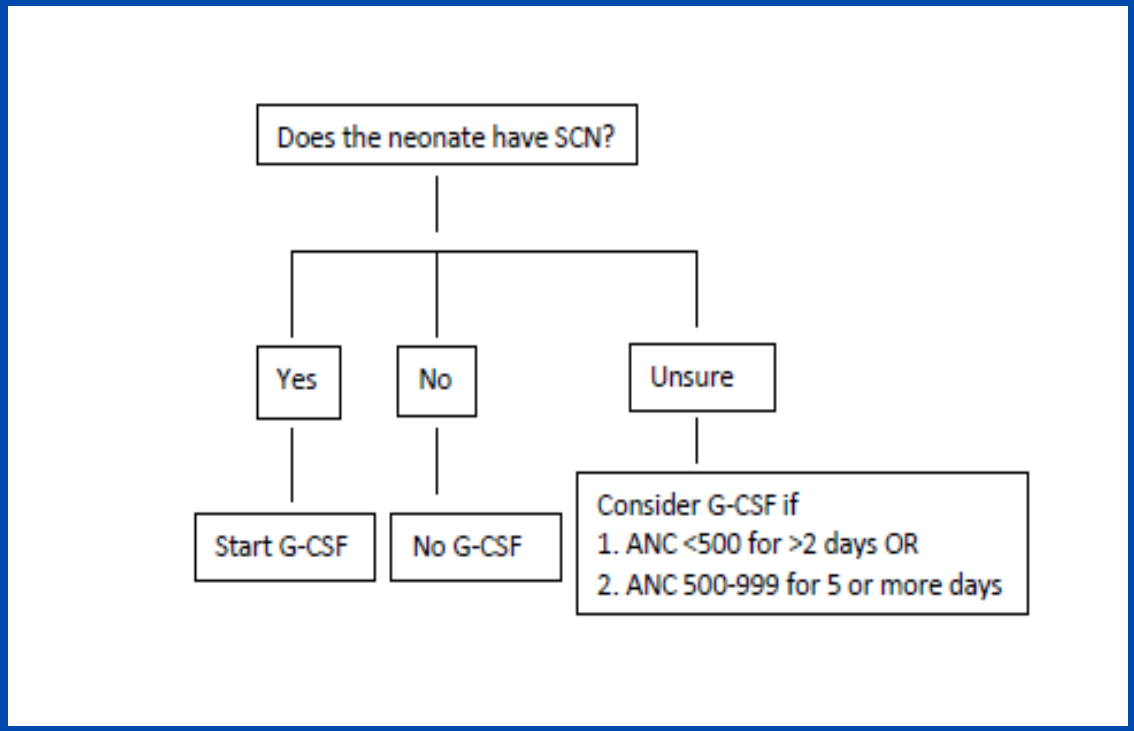
Additional Tests

- Imaging: skeletal survey, abdominal US
- Immune-mediated testing to specialized laboratories
  - Usually Blood Center of Wisconsin or Red Cross Neutrophil laboratory
  - Maternal sample required
- Bone marrow aspirate/biopsy may be helpful in the appropriate setting
- Gene testing for BMF syndromes

Treatment: Neutropenia

- Supportive care/antimicrobials
- G-CSF is the mainstay of treatment
  - Starting dose 5-10 mcg/kg daily SQ or IV
- Adjunctive therapies may be considered in immune-mediated neutropenias
  - IVIG 0.5-1 gm/kg → some response in about 50% of cases, but repeat doses are often required
  - Variable results with corticosteroids

When to Start G-CSF*



*Modified from RD Christensen In: *Hematology, Immunology, and Infectious Diseases,* 2nd Ed.

Treatment: Thrombocytopenia

- Platelet transfusions are the mainstay of treatment in symptomatic or severe thrombocytopenia
- Obtain a head US to rule out ICH
- Consider IVIG and/or steroids if thrombocytopenia is present at birth

NAIT Treatment

- Treatment is generally indicated for platelet counts <30K (<50K if high risk for ICH)
  - Goal >100K in cases of ICH
- IVIG 1 gm/kg x 2 days
- +/- steroids (e.g. Methylprednisolone 1mg IV every 8 hours on the days IVIG is given)
  - Typical dose is 1-4 mg/kg/day
  - Consider risk of fungal infections in the neonatal period

Platelet Transfusions

- Thresholds for transfusion remain controversial and to some degree must be individualized based on the bleeding risk
- Usual dose of 10-15 mls/kg of a CMV-safe product (pheresed or random donor)
- PLTs should be leukoreduced
- Irradiation is indicated for suspected T-cell deficiency/dysfunction (DiGeorge, WAS) or BW<1500 gms

Platelet Transfusions and NAIT

- Maternal platelets – must be irradiated and plasma reduced or washed
- Random donor platelets that are crossmatch compatible or negative for the identified antigen (e.g. HPA-1a negative platelets)
- Random donor platelets with IVIG +/- steroids (most common unless in utero diagnosis has been made)

Summary

- Leukopenia and thrombocytopenia are common findings in the NICU
- Most cases are mild-moderate in severity and transient
- Consider immune-mediated causes and BMF syndromes in cases that are severe and/or persistent

Summary

- Don’t forget about the mother → fetomaternal disorders are an important consideration
- Many potential confounders in a sick neonate
- The two most important labs are often the platelet count (or ANC) at birth and mom’s platelet count (or ANC)
- The answer is not always immediate

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