Out for Blood: Neonatal Hematology Review

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The speaker has signed a disclosure statement indicating that she has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary
This session will provide a general overview of neonatal hematology and common associated disorders to help participants prepare for certification exams.

Session Objectives
Upon completion of this presentation, the participant will be able to:

- Discuss components of blood cells and their importance in physiologic processes;
- Identify causes of anemia, polycythemia, hemorrhagic disease, DIC, thrombocytopenia, inherited bleeding disorders, and jaundice in the newborn;
- Describe common physical and lab findings related to the above disorders;
- Indicate appropriate management strategies for the above disorders.

Test Questions
1. The oxygen dissociation curve of Hgb F is shifted to the _____ to enhance oxygenation for the fetus in utero.
   a. Right
   b. Center
   c. Left

2. Treatment options for anemia include:
   a. Transfusion, iron supplementation and phototherapy
   b. Transfusion, EPO and minimizing phlebotomy losses
   c. Transfusion, lasix and minimizing phlebotomy losses

3. The following are causes of hemolytic anemia:
   a. Rh incompatibility, G6PD deficiency and physiologic nadir of Hgb
   b. ABO incompatibility, indirect hyperbilirubinemia and phlebotomy losses
   c. ABO incompatibility, Rh incompatibility and G6PD deficiency

4. Thrombocytopenia is defined as:
   a. A platelet count < 150,000
   b. A hemoglobin < 15 mg/dL
   c. A platelet count < 100,000
5. A 32 week A positive infant born to an O positive mother who is 36 hours old and has a rising bilirubin >5 mg/dL/day. The infant is NPO for treatment of a PDA with ibuprofen lysine and is receiving aminophylline. What are you concerned about?

   a. Nothing, this is physiologic jaundice
   b. Unbound bilirubin due to medications competing with albumin binding sites and ABO incompatibility
   c. Thrombocytopenia and kernicterus

References


How do blood cells develop?

- Hematopoiesis
  - Formation, production, maintenance
  - Pluripotent Stem Cells
    - All blood cells are made from these
  - Starts in the yolk sac during 3rd week of gestation
- Liver vs. Bone
  - Liver
    - Established by 9 weeks gestation
    - Peaks at 4-5 months gestation
    - Regresses as bone marrow production increases
  - Bone
    - Predominates from 22 weeks gestation forward
    - Hypoxia, bacterial infection, physiologic stress influence the rate of differentiation of pluripotent cells

How do blood cells develop?

- Erythropoiesis
  - Production of erythrocytes – aka Red Blood Cells
  - Erythropoietin
    - Hormone
    - Regulates erythropoiesis & hemoglobin synthesis
    - Produced by
      - Liver prenatally
      - Kidneys postnataally
    - Increased
      - Anemia
      - Low oxygen availability to tissues
      - Down Syndrome
      - Intrauterine Growth Restriction (IUGR)
      - Infants born to women with...diabetes or PIH
    - Decreased
      - Hypertransfusion

The Nuts and Bolts of Blood Cells

- Hemoglobin (Hgb)
  - Normal 14-20 g/dL in infants > 34 weeks, slightly lower in preterm infants
  - Major iron-containing component of RBC
  - Carries oxygen from the lungs to the tissue cells
  - HbF – fetal Hgb, begins ~14 days of life
    - RBCs contain 70%-90% HbF at birth
    - Has higher affinity for oxygen
  - HbA – adult Hgb, begins at end of fetal life
  - Value Factors
    - Gestation
    - Placental transfusion
  - Value Factors
    - Blood sampling site – capillary > central

The Nuts and Bolts of Blood Cells

- Hematocrit (Hct)
  - % of RBCs in a unit volume of blood
  - Value Factors
    - Gestation
    - Placental transfusion
    - Blood sampling site – capillary > central
The Nuts and Bolts of Blood Cells

- **Red Blood Cells (RBC)**
  - Reticulocyte – immature RBC
    - 1-2 days in the marrow and 1 more day in the circulation before full maturation - longer when stress present
  - Retic Count
    - The ↓ gestation the ↑ the count
    - Falls to < 2% by 7 days of life
    - ↑ count indicative of chronic blood loss or hemolysis
  - Function
    - Oxygen & carbon dioxide transport
    - Buffer

- **White Blood Cells (WBC)**
  - Aka leukocytes
  - Mature in the bone marrow & lymphatic tissues
  - React to foreign protein extravascular space
  - WBC count
    - # of circulating WBC/mm$^3$
    - Proportional to gestational age – premature have 30% to 50% less than term
  - 3 types of WBC
    1) Granulocytes
    2) Lymphocytes
    3) Monocytes

- **Granulocytes**
  - 3 types
    1) Basophils
      - Allergic and inflammatory responses
      - Least numerous – 0.5% to 1% of total WBC count
    2) Eosinophils
      - Similar to neutrophils in function but less effective in response
      - Prolonged survival in extravascular space
      - Allergic and anaphylactic responses, parasitic destruction
      - Elevated inversely to gestational age
      - 1-3% of total WBC count

- **Neutrophils**
  - Phagocytes – ingest & destroy small particles
  - Bacteria, protozoa, cells and their debris, colloids
  - Physiological stress can increase production and bone marrow release of immature forms
  - Bands, myelocytes, promyelocytes
  - May be increased at birth but decrease in the 1st week of life
The Nuts and Bolts of Blood Cells

- **Lymphocytes**
  - T-lymphocytes
    - Thymus derived
    - Graft vs. host disease, delayed hypersensitivity reactions
  - B-lymphocytes
    - Bone marrow derived
    - Production & secretion of immunoglobulins & antibodies

- **Monocytes**
  - Immature circulating macrophages
  - Mature in tissues
  - “The Cleaners” - clear old blood cells, cellular debris, opsonized bacteria, antigen-antibody complexes, activated clotting factors from the circulation

- **Platelets**
  - Small, nonnucleated, disk-shaped cells
  - Hemostasis, coagulation, thrombus formation
  - Response stimulated by disruption in the endothelium
  - Derived from megakaryocytes in bone marrow
  - Circulate in the blood 7-10 days before being removed by the spleen
  - Hypoactive in the first few days following birth
  - Platelet Count
    - Normal range 150K – 400K for all infants
    - < 150K considered abnormal requiring further investigation
    - SGA infants with 20%-25% lower counts

The RBC “STUFF” at the end of a CBC

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Clinically Speaking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisocytosis</td>
<td>Severe anemia</td>
</tr>
<tr>
<td>Macrocytosis</td>
<td>Vitamin B12 &amp; folic acid deficiencies</td>
</tr>
<tr>
<td>Microcytosis</td>
<td>Iron deficiency, spherocytic &amp; hemolytic anemia</td>
</tr>
<tr>
<td>Poikilocytosis</td>
<td>Severe anemia</td>
</tr>
<tr>
<td>Spherocytosis</td>
<td>Congenital spherocytosis, hemolytic anemia, after transfusion of stored blood</td>
</tr>
<tr>
<td>Target Cells</td>
<td>Hemoglobinopathies, sickle cell disease, thalassemia, liver disease</td>
</tr>
<tr>
<td>Burr Cells</td>
<td>Hemolytic anemia, DIC, liver disease</td>
</tr>
<tr>
<td>Howell-Jolly Bodies</td>
<td>Aplasia, pernicious anemia</td>
</tr>
<tr>
<td>Nucleated RBCs</td>
<td>Chronic blood loss, significant hemolysis, chronic hypoxia, infection</td>
</tr>
</tbody>
</table>

A measure of it all...

Blood Volume
**A Measure of it all... Blood Volume**
- Measured in ml/kg of body weight
- Volume factors
  - Gestational age
    - Term: ~80-100 ml/kg
    - Preterm: ~90-105 ml/kg
  - Placental transfusion
    - Timing of cord clamping, infant position related to placenta (above or below), uterine contractions, cord compression, onset of respirations and decrease in PVR
  - Maternal → fetal or Fetal → maternal transfusion
  - Twin-twin transfusion
  - Placenta previa or abruptio placentae
  - Nuchal cord
  - Iatrogenic loss

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**So why is keeping track of blood volume losses so important?**

**SCENARIO**
- 2 kg 35 week infant with RDS & pneumonia on the vent with ABGs every 6 hours & daily lab draws
- On DOL 3 the flow sheet says that the baby is out 15 ml of blood...
- What % of the beginning blood volume is the baby out?
  - 8%...yikes! And that's if everyone has been keeping track accurately...

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**Anemia**
- Definition
  - Central venous Hgb of < 13 g/dL or capillary Hgb of < 14.5 g/dL
- Oxygen carrying capacity & level of oxygen available to the tissues reduced by...
  - Low Hgb concentration
  - Decreased # of RBCs
- Etiology
  - Hemorrhage
  - Hemolysis
  - Prematurity
  - Iatrogenic

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**Anemia – Causes of Hemorrhage**
- **Twin-to-Twin**
  - Monozygotic, monochorionic (single) placenta
  - 13%-33% of twin pregnancies
  - Hgb difference b/w twins > 5 g/dL
  - Often size discrepancy as well...> 20% difference with chronic hemorrhage
    - Larger Twin: recipient, polyhydramnios; at risk for congestive heart disease and/or systemic/pulmonary hypertension due to volume overload, hyperviscosity
    - Smaller Twin: donor, oligohydramnios; at risk for anemia with elevated retic count, at risk for IUGR and high output cardiac failure
  - High risk for long-term developmental delay

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**Anemia – Causes of Hemorrhage**
- **Placental/Cord**
  - Umbilical cord rupture
  - Cord or placental hematoma
  - Anomalous cord insertion
  - Rupture of anomalous vessels of cord or placenta
  - Accidental incision of cord or placenta
  - Placenta previa or abruptio placentae
    - Fetal-Maternal → Kleihauer-Betke test
      - Spontaneous
      - Traumatic amniocentesis
      - External cephalic version
Anemia – Causes of Hemorrhage

- **Internal**
  - Intracranial (subdural, subarachnoid, intraventricular), subgaleal
  - Organ rupture (liver, spleen, adrenal, kidney)
  - Pulmonary
- **External**
  - Phlebotomy
  - Iatrogenic

Anemia – Causes of Hemolysis

- **Rh Blood Group Incompatibilities**
  - Aka erythroblastosis fetalis
  - How does it happen?
    - Rh + fetal cells enter the bloodstream of an Rh – mother resulting in maternal antibody production to the Rh + fetal cells → SUBSEQUENT pregnancies will have destruction of fetal RBCs if the fetus is Rh +
  - Predisposing factors
    - Previous pregnancy or abortion
    - Fetal-maternal hemorrhage during pregnancy
    - Delivery (vaginal, breech, cesarean)
    - Amniocentesis, chorionic villus sampling
    - External version
    - Manual removal of placenta

- **ABO Blood Group Incompatibilities**
  - Occurs more frequently, but less severe than Rh incompatibility
  - Most commonly seen with O blood type mother carrying fetus with A or B blood type
  - How does it happen?
    - Can occur with 1st pregnancy due to maternal exposure to A & B antigens (food, bacteria, pollen) that results in production of anti-A & anti-B antibodies
    - Prevents Rh sensitization due to rapid destruction of fetal A/B cells

Potential ABO Incompatibilities

<table>
<thead>
<tr>
<th>Maternal Blood Group</th>
<th>Incompatible Fetal Blood Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>A or B</td>
</tr>
<tr>
<td>B</td>
<td>A or AB</td>
</tr>
<tr>
<td>A</td>
<td>B or AB</td>
</tr>
</tbody>
</table>

Adapted from Core Curriculum for Neonatal Intensive Care Nursing, 2004

- What to look for...ABO incompatibility
  - Mild hemolysis
  - Anemia
  - Reticulocytosis
  - Hyperbilirubinemia
Anemia – Causes of Hemolysis

○ How to Treat ABO and Rh Incompatibilities
  - RhGAM → Rh Negative ONLY
  - Prophylactic anti-D immune globulin
  - Blocks maternal antibody production by destroying fetal red cells in maternal circulation
  - Given at ~28 weeks, then again within 72 hours following delivery and anytime there may be fetal-maternal blood mixing in Rh – pregnant women
  - Phototherapy
  - Good hydration
  - IVIG (intravenous immunoglobulin) 1 g/kg over 4 hrs
  - Consider blood or exchange transfusion
  - Management of multisystem dysfunction

○ Enzymatic Defect
  - G6PD (glucose-6-phosphate dehydrogenase) Deficiency
    - Most common inherited red cell disorder
      - Sex-linked, mainly male offspring, occasional female carriers
      - Most common in American black infants (10% to 15%), also Mediterranean, African, Asian decent
    - How does it happen?
      - Hemolysis & shortened erythrocyte life due to deficiency of red cell enzyme & exposure to antioxidant stress (drugs, infection)

○ Infection
  - Intrauterine
    - Congenital TORCH infections
      - Toxoplasmosis
      - Other (syphilis, hepatitis B, coxsackievirus, Epstein-Barr, varicella-zoster Virus, parvovirus)
    - Rubella
    - Cytomegalovirus
    - Herpes Simplex Virus
  - Postnatal
    - Bacterial infections
  - Both may cause...
    - Hemolysis, anemia, thrombocytopenia, DIC

Anemia of Prematurity

○ Considered physiologic
○ How does it happen?
  - Erythropoietin falls to minimal level d/t improved relative oxygenation after birth
  - Hgb falls by 1 g/dL/week in preterm infants, starting at ~2 weeks of age to an average nadir of 7-9 g/dL at 5 to 8 weeks of life
  - Smaller & more immature infants will reach lower nadir at an earlier age d/t shortened RBC life span
  - Transfusions result in a greater fall in Hgb d/t presence of HbA, will still undergo nadir
  - Premature infants have persistent hepatic pathway
  - The ensuing anemia triggers a hypoxic stimulus, thus increasing the presence erythropoietin and ultimately RBC production

No matter the antibody...

Hemolysis will continue until all antibody inhabited cells are destroyed...that can mean up to months depending on degree of antibody presence

Anemia of Prematurity

○ What to look for...
  - Symptoms of hypoxia
    - Poor feeding, poor weight gain, dyspnea, tachypnea, tachycardia, diminished activity, pallor, increased apnea/bradycardia events
  - Retic count
○ How to treat...
  - Minimizing blood losses
  - Iron supplementation
  - Transfusion
  - Recombinant Human Erythropoietin (EPO)
Iatrogenic Anemia

Caused by need for frequent blood sampling of critically ill infants...removal of > 20% of blood volume over 24-48 hours can produce anemia

What to look for...Anemia

- **Acute Blood Loss**
  - Pallor followed by cyanosis & desaturation
  - Shallow, rapid, irregular respirations
  - Tachycardia
  - Weak or absent peripheral pulses
  - Low or absent blood pressure
  - Acidosis
  - Hgb may be normal initially, then fall over 4-12 hours d/t hemodilution

- **Chronic Blood Loss**
  - Pallor w/o signs of acute distress
  - Normal blood pressure
  - Low Hgb level
  - Possible s/s of congestive heart failure w/ hepatomegaly

The Lab Low Down for Anemia

<table>
<thead>
<tr>
<th>Retic Count</th>
<th>Bilirubin Level</th>
<th>Coombs’ Test</th>
<th>RBC Morphology</th>
<th>Diagnostic Possibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or ↓</td>
<td>Normal</td>
<td>Negative</td>
<td>Normal</td>
<td>Physiologic anemia; Congenital hypoplastic anemia; Other causes of decreased production</td>
</tr>
<tr>
<td>Normal or ↑</td>
<td>Normal</td>
<td>Negative</td>
<td>Normal; Hypochromic microcytes</td>
<td>Acute hemorrhage; Chronic hemorrhage</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>Positive</td>
<td>Spherocytes</td>
<td>Immune hemolysis</td>
</tr>
<tr>
<td>Normal or ↑</td>
<td>↑</td>
<td>Negative</td>
<td>Variety of abnormal</td>
<td>Hereditary spherocytosis; Thalassemia; Pyruvate-kinase deficiency; DIC; G6PD; Infection; Enclosed hemorrhage</td>
</tr>
</tbody>
</table>

Adapted from Manual of Neonatal Care 5th edition, 2004

Polycythemia

Too much of a good thing!

Polycythemia...The Ins and Outs

- **Definition**
  - Hemoglobin > 22 g/dL or Hematocrit > 65% in the 1st week of life
  - Hyperviscosity
    - Blood viscosity increases with hematocrits > 60%
    - Leads to a reduction in organ blood flow

- **Causes**
  - Intrauterine hypoxia, placental insufficiency
    - Hypoxia stimulates erythropoiesis → increased RBC production
  - Preeclampsia, eclampsia, placenta previa, postmaturity syndrome, IUGR
  - Maternal-fetal, twin-to-twin transfusion
  - Placental hypertransfusion
  - Maternal diabetes
  - Congenital adrenal hyperplasia, Beckwith-Wiedemann syndrome
What to look for...Polycythemia

- On exam
  - Often asymptomatic
  - Plethora - common
  - Cyanosis
  - CNS abnormalities
    - Lethargy, jitteriness, seizures
  - Respiratory distress
    - Tachypnea, pulmonary edema, pulmonary hemorrhage
  - Tachycardia, congestive heart failure, PPHN
  - Hypoglycemia, calcemia, magnesemia
  - Poor feeding behaviors
    - Poor nipping, emesis

How to treat...Polycythemia

- The Labs
  - Hemoglobin...> 22 g/dL
  - Hematocrit...> 65%
  - Bilirubin...often elevated
  - Retic count...may be elevated
  - Platelet count...may be low

- Things to do...
  - Good hydration
    - May need normal saline boluses
  - Total fluids usually 100-120 ml/kg/day
  - Monitor CBC, bilirubin, retic & platelet counts
  - Partial exchange transfusion
    - Controversial when asymptomatic
    - Goal is to reduce hematocrit to < 60%
    - Can cause GI complications

Where it all begins...Bilirubin

They call me mellow yellow...

Shedding some light on jaundice

- Produced from the breakdown of heme-containing proteins
  - 75% from erythrocyte Hgb breakdown
  - 25% from breakdown of other proteins
- Excreted in bile, gives stool color
- Found in amniotic fluid 12-37 weeks
- Increased amounts concerning for hemolytic disease or intestinal obstruction below bile ducts
- Potent antioxidant
- Protection from oxygen free radicals?

What is Indirect Bilirubin?

- Unconjugated bilirubin
- Fat soluble → attracted to fatty tissues like subcutaneous tissue and brain tissue
- Binds to albumin → reversible
  - Metabolic Issues...hypoxia, acidosis
  - Hypothermia
  - Infection
  - Drugs...salicylates, sulfonamides, sodium benzoate, indomethacin, ampicillin
  - Free Fatty Acids...intralipids, starvation, hypothermia, hypoglycemia, anoxia
- Bound bilirubin typically nontoxic and does not cross blood/brain barrier
- Unbound bilirubin can cross blood/brain barrier → kernicterus

Fast Facts on Indirect Hyperbilirubinemia

- 50-60% of term and up to 80% of preterm infants will develop visible jaundice
- Progresses from head to toe as levels rise
  - Important to document level of jaundice on daily exam
- Visibly apparent when bilirubin levels > 5-7 mg/dL
- High levels during the first 24 hrs of life are NOT normal!
  - Must assess for...
    - Hemolytic Disease → Rh and ABO
    - Congenital Infection
    - Polycythemia
- AAP Guidelines
  - http://aappolicy.aappublications.org/cgi/content/full/pediatrictics;114/1/297
Risk Factors for *Indirect* Hyperbilirubinemia

- **Ethnicity**
  - Chinese, Japanese, Korean, Native American, Greek, Hispanic
- **Perinatal Events**
  - ↑ Delayed cord clamping
  - ↑ Breech, vacuum or forceps
  - ↑ Oxytocin or epidural bupivacaine
  - ↑ Asphyxia
  - ↑ Maternal diabetes
  - ↓ Early feeding
- **Other Factors**
  - Sibling with history of jaundice
  - Male
  - Exclusive breast feeding
  - Late preterm infant (≤ 37 weeks)
  - Maternal age ≥ 25 years
  - Early discharge from hospital (36-48 hrs of age)

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Controversial Terminology

**Physiologic vs. Pathologic Jaundice**

### Indirect Hyperbilirubinemia

#### The 2 Old School Types

**Physiologic**
- Normal in 1st week of life
- Multifactorial
  - ↑ bilirubin load to liver
  - ↓ hepatic uptake
  - Defective conjugation
  - ↓ excretion of bilirubin
- Peaks DOL 3 in term and DOL 5-6 in preterm

**Pathologic**
- Defined by any of the following...
  - Appears in 1st 24 hrs of life
  - ↑ level > 5 mg/dL/day
  - Level > 12.9 mg/dL in term or > 15 mg/dL in preterm
  - Lasting > 1 week in term or > 2 weeks in preterm
- Etiology
  - Hemolysis
  - Extravasation of blood
  - Swallowed blood
  - ↑ enterohepatic circulation
  - ↓ hepatic function/perfusion
  - Hypothyroidism
  - Hypopituitarism
  - Inborn errors of metabolism

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When to see the light...

Treatment of Indirect Hyperbilirubinemia

Treatment based upon...
- Age → gestation and hours of age
- Method of feeding → EBM vs. formula
- Ethnicity → be on the watch for G6PD
- Hydration → ESSENTIAL
- Rate of rise
- AAP Guidelines

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Options for Treatment

**Indirect Hyperbilirubinemia**

*Treatment of choice based upon etiology and AAP recommendations*

- Observation and monitoring of serial bilirubin levels
- Early initiation of feeds
- Phototherapy
- Exchange transfusion
- IVIG administration
- Early follow-up after discharge
  - The rule of 2’s – 2 days, 2 weeks

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AAP Guidelines for Phototherapy

- *See AAP guidelines for further details.*
Breast Milk vs. Breast Feeding Jaundice

**Breast Milk**
- Late, DOL 4-7
- Incidence 10-30% from 2-6 weeks of life
- Levels 12-20 mg% for up to 8 weeks
- Caused by ingredients in breast milk

**Breast Feeding**
- Early, DOL 2-4
- Caused by inadequate frequency and/or intake of milk → decreased fluid/caloric intake, dehydration
- Prevention with frequent breast feeding 8-12 times/day until milk supply established

Treatment of Breast Milk/Feeding Jaundice

**Acceptable Options from the AAP**

- Interruption of breast feeding not encouraged in HEALTHY infants...
- Observe
- Breast feed with phototherapy
- Bottle feeding supplementation with breast feeding, phototherapy optional
- Suspend breast feeding and bottle feed
- Suspend breast feeding, bottle feed and phototherapy

Levels should decrease by 72 hours...
if not must look for other causes


Bilirubin Gone Bad...Kernicterus

- Rare acute encephalopathy
  - Bilirubin staining of neurons and neuronal injury, especially in basal ganglia, caused by unbound bilirubin crossing blood/brain barrier
  - Increased risk with decreased albumin/bilirubin binding and/or altered integrity of blood/brain barrier
  - Hypoproteinemia
  - Drugs that compete with albumin binding
  - Sepsis, acidosis, hypoxia

- Treatment is prevention
  - Early follow-up is key...The rule of 2’s
  - See AAP Guidelines
  - Litigation Landmine...Almost always preventable!

- The Late Preterm Infant
  - The Greatest Risk...Why?
    - Increased risk of feeding difficulties
    - Decreased blood/brain barrier
    - Discharged “early” at 36-48 hours of age vs. further monitoring in hospital

Clinical Findings

- Initial Phase
  - Slight stupor/lethargy, hypotonia, paucity of movement, poor suck, high pitched cry
- Intermediate Phase
  - Moderate stupor, irritability, hypertonia, reverse C-shaped arching (retrocollis or opisthotonos), fever
- Advanced Phase
  - Deep stupor to coma, pronounced retrocollis or opisthotonos, no feeding
- Chronic Findings
  - Hearing loss, cerebral palsy, gaze abnormalities, intellectual deficits

MRI Findings

Kernicterus...

What is direct hyperbilirubinemia?
Always pathologic!

- Direct component > 1-2 mg/dL
- Causes
  - Liver Cell Injury
    - TPN cholestasis, infection (viral, bacterial, parasitic), hepatitis, drugs
  - Bile Flow Obstruction
    - Biliary atresia (clay colored stools), extrahepatic obstruction (choledochal cyst, Trisomy 13/18, polysplenia), intrahepatic obstruction (choledochal cyst, bile duct stenosis, bile duct rupture, tumors, CF)
  - Excessive Bilirubin Load
  - Maternal/Fetal Blood Group Incompatibility
    - ABO, Rh

Direct Hyperbilirubinemia

- Exam → hepatosplenomegaly, petechiae, chorioretinitis, microcephaly, IUGR
- Labs/Studies → AST, ALT, GGT, alpha-1-antitrypsine, hepatitis panel, PT, PTT, serum albumin level, type and screen, viral and TORCH studies, septic workup, abdominal ultrasound
- Treatment and prognosis based upon cause...consider Pediatric GI consult
  - Time to heal, getting off of TPN and onto goal feeds (may need medium chain TG formula), drugs typically started when > 2 mg/dL (ADEK, phenobarbital, ursodiol), surgery including liver biopsy

Sticking together...
A Closer Look at the Coagulation Process

- Deficiencies in Clotting
  - Transient decrease in platelet function
    - Drugs and bugs
    - Transient decrease in clotting factors
      - II, VII, IX, X, XI, XII
    - Causes – immaturity of hepatic enzymes, transient deficiency of vitamin K (needed for II, VII, IX, X)
    - Concentration proportional to gestational age
  - Hemostasis
    - Reactions produced...
      - Vascular – vessel contraction
      - Intravascular – platelet plug formation
      - Extravascular – compression by surrounding tissue, release of thromboplastin

Sticking together...Coagulation

- The Process
  - Cascade of cellular & plasma reactions whose product is a fibrin-based clot
    - Calcium, iron, & phospholipids are key components
    - Endothelial and tissue injury cascades result in the activation of Factor X ultimately leading to the formation of a stable fibrin clot
  - Clotting is balanced by concurrent fibrinolysis

The Coagulation Process
Sticking together…Coagulation

- The Labs
  - Platelet count – platelet #
  - Prothrombin time (PT) – extrinsic & common portions of the coagulation cascade
  - Partial thromboplastin time (PTT) – intrinsic & common portions of the coagulation cascade
  - Fibrinogen – circulating level of this protein substrate, required for clot formation
  - FDP/FSP – fibrinolytic activity
  - D-Dimer – fibrin degradation product

Hemorrhagic Disease

Hemorrhagic tendency caused by vitamin K deficiency AND decreased activity of factors II, VII, IX, X

Hemorrhagic Disease…Etiology

- Primary vitamin K deficiency
- Vitamin K is required for...
  - Activation of clotting factors II, VII, IX, X
  - Activation of proteins C & S after liver synthesis
- Vitamin K is affected by...
  - Lack of bacterial presence
    - Intestinal flora is needed for vitamin K synthesis
    - Intestinal tract is virtually free of bacteria until feedings initiated
    - Antibiotics can alter intestinal colonization
  - May result in intraventricular/intracranial hemorrhage

3 Types → Early, Classic, Late

- Early
  - Least common
  - Bleeding within 1st 24 hrs of life
  - Typically associated with maternal anticonvulsant therapy
  - Cannot be prevented with administration of vitamin K
  - Therapy = treatment of mother with large doses of vitamin K >/= 10 days prior to delivery

- Classic
  - 2-5 days of life
  - Generalized and occasional dramatic bleeding (GI, umbilicus, circ site, skin, internal organs)
  - Typically breast fed infant who has not received prophylactic vitamin K and is not taking adequate amounts of EBM
  - At Risk → late preterm, near term, post c/section

- Late
  - After 7 days
  - More devastating d/t increased incidence of intracranial hemorrhage (~60%), permanent sequelae (~25%), mortality rate (~15%)
  - Associated with chronic diseases that interfere with fat absorption or performance of intestinal flora
Hemorrhagic Disease

- **What to look for...**
  - **Bleeding**
    - Begins 24-72 hours after delivery
    - Rare life threatening
    - Late onset possible at 2-3 weeks of age
  - **Oozing**
    - Localized typically to the GI system
    - May also be noted from umbilical cord, circumcision, puncture sites
  - **On exam...**
    - Diffuse ecchymosis, petechiae, abdominal distention, jaundice
  - **The labs...**
    - Prolonged PT/PTT, low vitamin K dependent clotting factors

- **How to treat...**
  - Prophylactic vitamin K administration immediately following delivery
    - 0.5 – 1 mg IM, may be given IV in ELBW
  - Has virtually eliminated the disease
  - May need transfusion in presence of significant bleeding
  - Preterm Infants
    - May have persistent bleeding
      - FFP to replace clotting factors
      - Repeat doses of Vitamin K

Disseminated Intravascular Coagulation

An acquired hemorrhagic disorder associated with an underlying disease manifested as uncontrolled activation of coagulation & fibrinolysis

Heading down the road to DIC...

Precipitating Factors

- **Maternal**
  - Preeclampsia, eclampsia, placental abruption
  - Placental abnormalities
- **Intrapartal**
  - Fetal distress with hypoxia & acidosis
  - Dead twin fetus
  - Traumatic delivery
- **Neonatal**
  - Infection of any type
  - Conditions causing hypoxia, acidosis, shock
  - Severe Rh incompatibility
  - Thrombocytopenia
  - Tissue injury (birth trauma, breech crush injury)

The DIC Cascade

- **The warning signs...**
  - Hemorrhage, Ischemia, Anemia (Hi-Ya)
    - Depleted clotting factors & platelets
    - Blood loss & red cell fragmentation
    - Microvascular thrombi lead to ischemia & necrosis of any organ...kidneys are a favorite
- **On exam...**
  - Prolonged oozing from puncture sites or umbilicus
  - Petechiae, purpura, ecchymosis
  - Pulmonary, cerebral, GI hemorrhage
  - Localized necrosis & gangrene
  - **SHOCK**
How to treat...DIC

- The Labs
  - Platelet count...low
  - PT/PTT...prolonged
  - Fibrinogen level...low
  - D-dimer...sensitive, detects mild DIC
  - Factors VIII & II, proteins C & S, antithrombin III...decreased
  - Peripheral blood smear

- Things to do...
  - Aggressively treat underlying disease
  - Transfusion of blood, platelets, FFP, cryoprecipitate, Antithrombin III
  - Heparin therapy...controversial
  - Exchange transfusion...poor tolerance, more of a last ditch therapy d/t complication risks

Thrombocytopenia

A platelet count of < 150K

The most common newborn bleeding disorder

Where did all my platelets go?!?

Destruction vs. Impaired Production

Destruction of Platelets

- Autoimmune ~ 80%
  - Maternal autoantibody condition
    - Idiopathic thrombocytopenic purpura, systemic lupus erythematosus
    - Seek & Destroy...maternal IgG antibodies cross the placenta & destroy fetal platelets
      - Nadir occurs on DOL 2
      - Counts depressed as long as antibodies are present, typically as long as 4 months
    - Maternal platelet count LOW
    - Treat supportively
    - No evidence of severe IVH
    - Mortality rate 1% - 10%

- Alloimmune ~ 20%
  - Analogous to Rh incompatibility
    - Affects 33% - 50% of 1st pregnancies
    - 1 in 2000 - 5000 live births
    - Maternal production of antibodies to fetal platelets in maternal circulation resulting in destruction of fetal platelets...paternal inheritance
      - Nadir occurs in 1st few days, normal by 1 month of age
    - Maternal platelet count NORMAL
    - Treat with transfusion of maternal platelets
      - 15% - 25% have intracranial hemorrhage with ~10% - 15% occurring in utero, most b/w 30 – 35 weeks gestation
      - Mortality rate 10% - 15% due to more severe bleeding

- Infection
  - Bacterial, TORCH
    - Can cause DIC d/t increased consumption
    - Increased platelet sequestration
    - May form antigen/antibody relationship with the bug

- Thrombotic Disorders
  - Large-vessel disease...renal vein thrombosis
  - Microvascular disease...NEC, RDS, PPHN
  - DIC...platelet consumption

- Birth Depression – Apgar score < 7
  - Fetal megakaryocytes with increased sensitivity to hypoxic injury

- Giant Hemangiomas
  - Consumption, mechanical destruction & sequestration

- Exchange Transfusion
  - Shortened platelet survival

- Destruction of Platelets

- Birth Depression
  - Apgar score < 7
  - Fetal megakaryocytes with increased sensitivity to hypoxic injury

- Giant Hemangiomas
  - Consumption, mechanical destruction & sequestration

- Exchange Transfusion
  - Shortened platelet survival
Impaired Production of Platelets

- **RARE (< 5%)**
- Associated with congenital malformations
  - **Trisomy 13, 18**
  - Bone marrow hypoplasia can cause decreased megakaryocyte production
- **TAR syndrome**
  - Thrombocytopenia w/ Absent Radii
  - Megakaryocyte progenitor cell defective
  - Present at birth, improvement follows
  - Anomalies of the radius only, thumb okay
- **Fanconi anemia**
  - Rarely presents in the neonatal period, worsens w/ time
  - Thumb, skeletal, renal, CNS anomalies w/ café-au-lait spots
- **Rare syndromes**
  - Unusually small or large platelets

Platelet Interference…Last but Not Least

- Caused by maternal drug ingestion
  - Interferes with platelet aggregation
- Associated drugs
  - Demerol (meperidine)
  - Phenergan (promethazine)
    - Maternal history of hyperemesis
  - Acetylsalicylic acid
  - Sulfonamides
  - Quinidine
  - Quinine
  - Thiazides

What to look for…Thrombocytopenia

- On exam
  - Signs of bleeding, jaundice, IUGR, microcephaly, hepatosplenomegaly with infectious etiology, anomalies associated with syndromes

How to treat…Thrombocytopenia

- The Labs
  - Platelet count…low
  - PT/PTT…normal
  - Bleeding time…prolonged
  - Peripheral blood smear
  - Maternal studies
    - Platelet count
    - HPA (Human Platelet Antigen) type
    - Platelet specific antibody
  - Severe cases – platelet typing of parents & infant
How to treat...Thrombocytopenia

- Things to do...
  - Supportive care
  - Treatment of underlying disease
    - Most often secondary to other diseases
  - Platelet transfusion
    - Donor or maternal
  - Screening cranial ultrasound
  - IVIG
  - Exchange transfusion
    - Life threatening hemorrhage or hyperbilirubinemia only
  - Steroids

Neonatal Thrombosis
Clotting Gone Wrong

- Platelet transfusion
  - Donor or maternal
  - Screening cranial ultrasound
  - IVIG
  - Exchange transfusion
    - Life threatening hemorrhage or hyperbilirubinemia only
  - Steroids

Thrombosis...Clotting Gone Wrong

- Neonates at greater risk d/t diminished fibrinolysis r/t decreased plasminogen levels
- Increased risk associated with...
  - Umbilical vessel catheters (most significant)
  - Asphyxia
  - Sepsis
  - Polycythemia or Hyperviscosity
    - Dehydration, IDN, IUGR, congenital heart disease
  - Shock
  - Deficiencies in protein C, S, ATIII, factor V Leiden
- Treatment
  - Antithrombotic therapy typically reserved for massive and/or life threatening occurrences
  - tPA, heparin, LMW heparin

Thrombosis...What to look for and How to diagnose

- Clinical Presentations
  - Renal Vein Thrombosis (most common, often LGA)
    - Symptoms: flank mass/enlarged kidney, hematuria, hypertension, renal failure, proteinuria, thrombocytopenia, depletion of coagulation factors
    - More likely with hypercoaguable states
  - Renal Artery Thrombosis
    - Symptoms: flank mass/enlarged kidney, hematuria, renal failure; may have hypertension
    - Often indwelling umbilical arterial catheter (> 90%)
  - Stroke
    - Symptoms: seizures, thrombocytopenia
    - Also found in inferior vena cava, aorta, portal vein, hepatic veins, adrenal veins
- Diagnosis
  - Renal ultrasound with doppler studies
  - Abdominal ultrasound with doppler studies
  - Echocardiogram
  - MRI of brain

Thrombosis...Inherited Thrombophilias

- Congenital
  - Family history, early age of onset, recurrent disease, unusual/multiple locations of thrombosis
  - Deficiencies of protein C, protein S, antithrombin, activated protein C resistance (factor V Leiden and prothrombin G20210A mutations), MTHFR deficiency
- Acquired
  - Coagulation factor deficiency r/t placental transfer of maternal anti-phospholipid antibodies (example: maternal lupus)
  - Both may present with purpura fulminans

Your brain...
Inherited Bleeding Disorders

The Rare, The Random, The Severe

Hemophilia
- 90%
  - Classic hemophilia ~70% (hemophilia A, factor VIII deficiency, ~10% present in neonatal period with bleeding r/t blood draws, circumcision, ICH)
  - Christmas disease ~30% (hemophilia B, factor IX deficiency, similar to Classic)
- Treatment → replacement of missing factor
- Symptoms directly r/t plasma factor levels
- X-linked recessive inheritance
  - Gene on X chromosome
  - Females are carriers only due to XX
  - Males are affected due to XY – no normal X counterbalance
  - 25% chance of occurrence with each pregnancy with 50% of male offspring affected
  - 75% with family history of male bleeding disorders

von Willebrand disease
- Component of factor VIII functioning as ligand b/w platelet and vessel
- Autosomal dominant or recessive inheritance
  - Males and females equally affected
  - Each pregnancy with 50% chance of occurrence
  - Vertical transmission – seen in successive generations
  - Family history may be unremarkable
- Rares presents in neonatal period → mucous membrane bleeding
- Diagnose with ristocetin factor
- Treatment
  - Cryoprecipitate; factor VIII with vWF, desmopressin acetate
- Autosomal recessive inheritance
  - Parents phenotypically normal carriers
  - Males and females equally affected
  - With each pregnancy
    - 25% of offspring will be affected
    - 50% will be carriers
    - 25% will be normal
  - Horizontal expression
    - Deficiency seen in siblings
    - Skips a generation
  - Symptoms → prolonged bleeding from umbilical stump or several days after circumcision, ICH, wound dehiscence
  - Treatment
    - Cryoprecipitate, factor XIII concentrate

What to look for...
Inherited Bleeding Disorders
- On exam
  - Rarely presents in newborns
    - Except for factor XIII deficiency
  - Well infant with prolonged bleeding
    - Umbilical cord (> 80% with factor XIII)
    - Circumcision oozing
  - Rare intracranial hemorrhage
  - Family History...it may be the key

How to treat...
Inherited Bleeding Disorders
- The Labs
  - PT/PTT...typically normal
  - Platelet count...typically normal
  - Fibrinogen level...typically normal
  - Factor assays
    - Factor VIII...should be = to adult levels
    - Factor IX...< 2% activity
  - Things to do...
    - Transfuse with FFP
    - Contains all clotting factors but factor VIII
    - Transfuse with cryoprecipitate
    - Contains factor VIII, use if FFP not effective
    - Diagnosis & replacement of specific factor
A sticky mess…
Quickly Assessing the Bleeding Infant

<table>
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<th>Platelets</th>
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<th>PTT</th>
<th>Fibrinogen</th>
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<td>Vitamin K Deficiency</td>
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<td>N ↓</td>
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<td>N ↑</td>
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Get ready to rumble!

An Overview of the Neutrophil

The Neutrophil…
The most sensitive indicator of sepsis
- Significant variance in count in 1st few days of life…lower in preterm infants
- Mature and Immature forms
  - Mature = polymorphonuclear (PMNs)
  - Immature = promyelocytes, myelocytes, metamyelocytes and bands
- Absolute Neutrophil Count (ANC)
  - WBC x (% immature neutrophils + % mature neutrophils)
  - Example
    - WBC count 5.25 (use 5250 for calculation)
    - 23% neutrophils, 2% bands, 3% metamyelocytes, 3% myelocytes (use .29 for calculation)
    - ANC = 1523
- Immature/Total Neutrophil (I/T) Ratio
  - Increase in I/T ratio is a “Left Shift”
  - Ratio > 0.20 is suggestive of infection, sensitivity 90%
  - % immature forms / % mature + % immature forms

Spotlight on the Neutrophil

Neutropenia
- Definition ANC < 1500
- Most accurate predictor of infection
- Clinical Findings
  - Maternal hypertension
  - Periventricular hemorrhage
  - Severe asphyxia
  - Reticulocytosis after 14 days of age

Neutrophilia
- Less predictive, but still associated with infection
- Normal at birth (up to 26K) /r birth stress, increased production/rate of release
- Clinical Findings
  - Hemolytic disease
  - Asymptomatic hypoglycemia
  - Trisomy 21
  - Oxytocin during labor
  - Maternal fever
  - Perinatal stress
  - Exogenous steroids
  - Pneumothorax
  - Meconium aspiration
  - Seizures
  - Stress – including prolonged crying and surgery

Replenishing what you’ve lost…
The Ins and Outs of Transfusions and
A Closer Look at Other Treatment Options

Informed Consent – Right of Choice
Be proactive…
Discuss before you must
### Informed Consent – The Risks

- **Infection**
  - Blood products screened for HIV, HBV, HCV, HTLV, syphilis...occasionally CMV
  - NICU donors maybe more thoroughly screened...repeated test negative over time
- **Transfusion reactions**
  - Fever – most common
  - Allergic reactions – rare in the neonate
  - Hemolytic reactions – type, screen, crossmatch, use of donor blood vs. parental blood
- **Graft versus host disease**
  - Occurs after transfusion...within 100 days
  - Foreign lymphocytes not rejected d/t immature immune function \(\rightarrow\) infection & neutropenia
  - Rash, diarrhea, hepatic dysfunction, pancytopenia \(\rightarrow\) bone marrow suppression
  - Irradiation of blood products

### Informed Consent – The Benefits

- **Whole Blood** - Hematocrit ~35%
  - Replacement of blood volume
- **PRBC** - Hematocrit ~60% - 90%
  - Oxygenation – carrying capacity, tissues
- **Platelets**
  - Improved coagulation
  - Hemorrhage d/t thrombocytopenia or platelet dysfunction
- **FFP**
  - Replacement of clotting factor deficiency
- **Albumin**
  - Volume expansion, improved oncotic pressure
  - Hypovolemia, 3rd space losses

### Informed Consent – The Alternatives

- **Family & Friend Donations**
  - Donate with compatible blood type
  - Blood must be irradiated to prevent graft versus host disease
  - No evidence of increased safety
- **Parental Donation**
  - Maternal
    - Plasma not usable due to risk for antibody presence
    - Platelets & RBC can be washed
  - Paternal
    - Risky due to risk of paternal antigen inheritance
- **Recombinant Human Erythropoietin (EPO)**
  - Prophylaxis & treatment of anemia
  - Variable results – investigating dosage & interval

### Turning up the volume...

- **PRBC**
  - Increments of 5 – 15 ml/kg to prevent volume overload
- **Partial Exchange**
  - Normal saline – polycythemia
    - Blood volume x (Measured Hct – Desired Hct) / Measured Hct
  - PRBC – hydrops fetalis
    - Blood volume x (Desired Hct – Measured Hct) / PRBC Hct – Measured Hct

### Turning up the volume...

- **Complete Exchange**
  - Removes 70% - 85% of infant blood
  - Use blood < 5 days old to decrease risk of hyperkalemia
  - Indications - hyperbilirubinemia, DIC, autoimmune thrombocytopenia
  - May cause hypo…glycemia, calcemia, magnesemia
- **Platelets**
  - 1 unit = ~40 ml \(\rightarrow\) 10 – 20 ml/kg
  - Count increase dependent on age of platelets
    - Typical rise 75K – 100K
  - Lack of rise indicative of destruction
  - Concentrating volume not indicated
Turning up the volume…
- **FFP**
  - Increments of 10 ml/kg to prevent volume overload
  - Plasma obtained from whole blood & frozen within 6 hours of collection
- **Cryoprecipitate**
  - Usually 1 unit/kg (1 unit = ~15 ml)
  - Fibrinogen, factor VIII, factor XIII
- **Albumin**
  - Volume expansion 5% in increments of 10 ml/kg
  - Oncotic pressure 25% in increments of 4 ml/kg

Pharmacologic Treatment Options…
- **Erythropoetin**
  - Used for treatment of anemia of prematurity
  - Dose
    - 500-1400 units/kg/week given single or divided, SC or IV
  - Mechanism of Action
    - Colony-stimulating factor
    - Stimulates RBC production and induces the release of reticulocytes from the bone marrow
  - Need to be on iron supplement to support increased erythropoiesis
  - Minimize phlebotomy losses and restrict transfusions

Pharmacologic Treatment Options…
- **Ferrous Sulfate**
  - Prophylaxis for and/or treatment of anemia of prematurity
  - May also be used in older infants with significant anemia
  - **Dose**
    - 2-5 mg/kg/day elemental iron given daily with a feeding for total of 4-6 mg/kg/day
    - Iron fortified formula can provide up to 2 mg/kg/day
  - **Mechanism of Action**
    - Essential mineral
    - ↑ iron stores

Pharmacologic Treatment Options…
- **Heparin Sodium**
  - Uses
    - Anticoagulant typically used for heparin locks and to maintain patency of central catheters; controversial use for treatment of DIC; during treatment with ECMO; treatment of thrombosis
  - Dose
    - Heparin Lock → 1-2 ml of 10 unit/ml solution every 4-6 hrs and PRN
    - Continuous Infusion for Central Line → 0.5-1 unit/ml in infusion fluid
    - Continuous Infusion for Thrombosis → dedicated line if possible, initial bolus 75 units/kg followed by continuous infusion 28 units/kg/hour, titrate down for lower gestations
  - **Laboratory Monitoring**
    - Heparin Activity Level (anti-factor Xa level) 0.3-0.7 units/ml and/or PTT, CBC to assess for thrombocytopenia

Antidote
- Termination of therapy
- Protamine Sulfate IV → dose dependent on heparin dose
- **Mechanism of Action**
  - Inhibits the intrinsic clotting cascade and prevents fibrin formation
- **Precautions**
  - Platelet count < 50K, suspected ICH, GI bleeding, shock, severe hypotension, uncontrolled bleeding
Pharmacologic Treatment Options…

- **Enoxaparin (Lovenox)**
  - Low molecular weight heparin
  - Advantages over standard heparin
    - Predictable pharmacokinetics, decreased need for laboratory monitoring, subcutaneous dosing, reduced risk of thrombocytopenia, possible reduced risk of bleeding
  - **Dose**
    - 0.5-1.5 mg/kg/dose SQ BID
  - **Laboratory Monitoring**
    - Target anti-factor Xa level 0.5-1 unit/ml obtained 4-6 hrs after injection, CBC to assess for thrombocytopenia
  - **Antidote**
    - Termination of injections
    - Protamine Sulfate 1 mg/1 mg LMW heparin given in last injection

- **Tissue Plasminogen Activator (tPA)**
  - Minimal data for safety and efficacy
  - Agent of choice due to...
    - Allergic reactions associated with streptokinase
    - Availability of urokinase
    - Shortest half-life
    - Less stimulation of systemic prolytic state d/t poor binding of circulating plasminogen and maximal impact on fibrin bound plasminogen
  - **Indications**
    - Arterial thrombosis, massive thrombosis with evidence of organ dysfunction or compromised limb viability, life threatening thrombosis
  - **Dosing**
    - 0.1-0.5 mg/kg/hr for 6-12 hrs → lysis continues after infusion stops
  - **Laboratory Monitoring/Imaging**
    - Prior to Therapy → CBC, PT, PTT, fibrinogen; consider evaluation for ICH
    - PT, PTT, fibrinogen every 4 hrs initially then every 12-24 hrs
    - CBC every 12-24 hrs
    - Imaging of thrombosis every 6-24 hrs
  - **Management**
    - Maintain fibrinogen > 100 mg/dL and platelet count 50K-100K

Marathon…

- a: an endurance contest
- b: something (as an event, activity, or session) characterized by great length or concentrated effort

No butts about it...we’re done!