Hematology

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Ascension

I have no conflict of interest to disclose

Objectives

- At the conclusion of this presentation, participants will be able to:
  - Interpret common laboratory tests
  - Understand physiologic jaundice, direct hyperbilirubinemia, and indirect hyperbilirubinemia
  - Describe common hematologic problems including but not limited to: anemia, coagulopathies, polycythemia, and Rh/ABO incompatibility.

Interpretation of Laboratory Values

Hematology

Development of Blood Cells

Hematopoiesis is the formation, production, and maintenance of blood cells.

- Erythropoiesis is the production of erythrocytes or RBCs
- Regulated by erythropoietin (EPO), a hormone
- EPO is produced postnatally in the kidneys
- Prenatally, EPO is produced in extra renal sites (liver, submandibular glands)
- EPO levels increase in anemia and low oxygen availability/hypoperfusion

Hematology

Hemoglobin

- Iron containing component
- Carries oxygen from the lungs to the tissues
- At birth, RBCs contain 70-90% HbF
- Production of adult hemoglobin (HbA) begins at birth
- The switch from HbF to HbA is delayed in cases of hypoxia, growth restriction, or IDM. Fetal hemoglobin is replaced by adult by approximately 6 months of age.
- Hemoglobin binds with 2,3-diphosphoglycerate, releasing an oxygen molecule
  - HbF has less affinity for 2,3-DPG than does HbA, resulting in a greater affinity for oxygen. This gives the fetus access to oxygen from mother's bloodstream.

Hematology

Hemoglobin

- Values of hemoglobin depend on gestational age, volume of placental transfusion (ie: delayed cord clamping), and blood sampling site
- Capillary samples can be much higher than venous samples
- Peripheral vasoconstriction and stasis give the high capillary value
- Postnatal increase in PaO2 and HbA causes a decrease in EPO, leading to a gradual decline in hemoglobin

- Normal hemoglobin value: 12-18 g/dL

Hematology

Hematocrit

- Percentage of RBCs in a unit volume of blood
- Values depend on gestational age and volume of placental transfusion
- Capillary samples yield higher values than venous

- Normal hematocrit: 32-55%

Hematology

Red Blood Cell Count

- Number of circulating mature RBCs per cubic millimeter

- RBC life span
  - Adult: ~120 days
  - Term infant: ~70 days
  - Preterm infant: 35-50 days

- Normal value: 3.5 - 5.5 uL

White Blood Cell

- Mature in bone marrow and lymphatic tissue
- WBCs can leave circulation and enter extravascular tissues where they function as part of immune system in reaction to foreign proteins
- Granulocytes (basophils, eosinophils, and neutrophils), lymphocytes, and monocytes are all WBCS
  - Lymphocytes: 15-40% of WBCs; increase in response to viral infections
  - Monocytes: 2-8% of WBCs; increase in response to inflammation, infection

White Blood Cell

- Basophils
  - 0.5-1% of WBC count
  - Important in allergic reactions and inflammatory responses
- Eosinophils
  - 1-3% of WBC count
  - Also important in allergic and anaphylactic reactions. Most effective WBC for parasite destruction
  - Benign eosinophilia of prematurity (inversely proportional to gestational age) due to immature barrier in GI or respiratory tract
- Neutrophils
  - Function as phagocytes that ingest and destroy bacteria, protozoa, cells, debris
  - Stress can increase production of immature forms
  - Neutrophils are highest at birth and decrease during first week to reach % close to lymphocytes

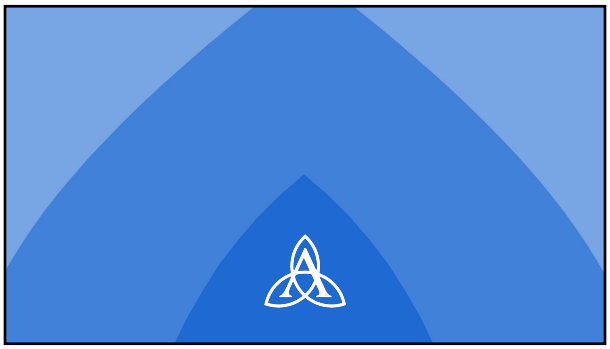
Antibody Tests

- Direct Antibody Test (DAT)
  - ie: direct Coombs test
  - Used to detect if antibodies have **attached** to RBC surface antigens
  - Test is positive in: hemolytic disease (Rh, ABO, anti-Kell, anti-duffy)
- Indirect Antibody Test
  - Detects **antibodies** against RBCs that are present in patient's serum (unbound or unattached)
  - Blood transfusion preparation / cross-matching blood
  - Antenatal antibody screening

Additional Tests

- Kleihauer Betke test
  - Blood test used to measure fetal hemoglobin in mother's blood stream
  - Used to detect fetal-to-maternal hemorrhage (trauma, blood incompatibilities)
  - Common indications for test:
    - Stillbirth or anemic newborn

- Apt test or Apt-Downey test
  - Test to differentiate between fetal or neonatal blood from maternal
  - Positive test indicates blood is fetal or neonatal (Negative indicates maternal)
  - Indications
    - Maternal bleeding late in pregnancy (to determine vasa previa)
    - Neonate with bloody stool or emesis following delivery



Bilirubin

Bilirubin

- Product of the breakdown of hemoglobin (heme + globin)
- Excreted via urine and stool
- Normal total bilirubin (indirect + direct) value: < 2 mg/dl

- Indirect or unconjugated bilirubin
  - Insoluble; not water soluble. Fat soluble
  - Travels to the liver, where it is changed into a soluble form (**direct** or conjugated)

- Direct or Conjugated bilirubin
  - Water soluble (dissolves in water)
  - Made by the liver from indirect bilirubin
  - Normal value: 0 – 0.3 mg/dl

Bilirubin

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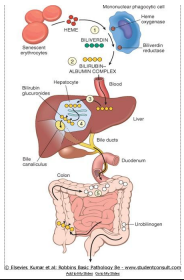
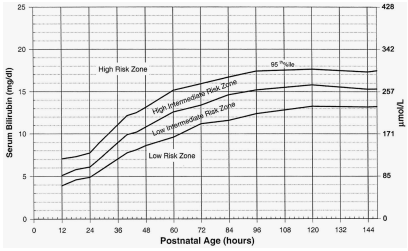


Hyperbilirubinemia

- Jaundice
  - Accumulation of bilirubin (yellow-orange pigment) in the skin and sclera
  - Occurs when rate of bilirubin production exceeds rate of elimination
  - Due to: increase RBC breakdown (shorter RBC lifespan), decreased albumin (what bilirubin binds to in bloodstream), impaired conjugation in liver, and increased enterohepatic circulation (reabsorption of bilirubin in the intestines)
  - Incidence: 60-70% of term infants and 80% in preterm
- Toxicity
  - Kernicterus; neurotoxicity (seizures, abnormal reflexes, encephalopathy)
  - Elevated levels of unconjugated bilirubin causing irreversible damage to the brain (basal ganglia)
- Treatment
  - Phototherapy (works via conjugating bilirubin so that it can be excreted)
  - Exchange Transfusion (patient's entire blood volume is replaced by new blood)

Hyperbilirubinemia



Hyperbilirubinemia

Suggested Use of Phototherapy and Exchange Transfusion - < 35 weeks

	Phototherapy	*Exchange transfusion*
Gestational age (week)	*Initiate phototherapy total serum bilirubin (mg dl^{-1})*	*Total serum bilirubin (mg dl^{-1})*
< 28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

Maisels MJ et al. J Perinatol 2012; 32:660

Indirect Hyperbilirubinemia

- Physiologic Jaundice
  - Occurs in first week of life
- Breast Milk Jaundice
  - Prolonged, beyond 2nd and 3rd week of life
  - May persists for 3 months
  - Unclear etiology – possibly due to substance in breast milk that inhibits conjugation of bilirubin
- Breastfeeding Jaundice
  - First week of life
  - Due to low volume intake, less stools resulting in increased intestinal reabsorption.

Indirect Hyperbilirubinemia

-Pathologic causes
  -Hemolytic disease (Rh and ABO incompatibility)
  -Hemoglobinopathies
  -Infection (due to hemolysis)
  -Polycythemia
  -Increased enterohepatic recirculation (intestinal absorption)
    -GI obstructions
  -Metabolic/Endocrine disorders
    -Galactosemia, Hypothyroidism
  -Disorders in bilirubin clearance
    -Crigler-Najjar Syndrome (absent enzyme that conjugates bilirubin)
    -Gilbert Syndrome (decreased enzyme activity that conjugates bilirubin)

Direct Hyperbilirubinemia

-Defined as a direct bilirubin level of >1 mg/dl
-Unlike indirect hyperbilirubinemia, which can be transient and physiologic, direct hyperbilirubinemia is always pathologic
-Incidence: ~1 in every 2500
-Risk factors: congenital infections, sepsis, hepatitis, ABO incompatibility, trisomy 21, and TPN use

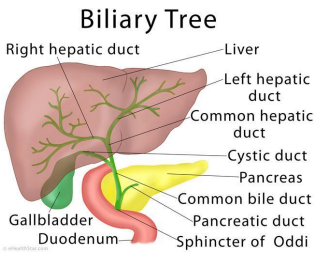
-Conjugation
  -Occurs inside the liver cells
  -Major enzyme involved is uridine diphosphoglucuronyl transferase (UDPGT)
  -Conjugated bilirubin is then water soluble and can be excreted into the urine, but most is rapidly excreted as bile into the intestine

Direct Hyperbilirubinemia

-Extrahepatic causes
  -Biliary atresia (one or more of the bile ducts are narrowed or absent)
  -Choledochal cyst (cyst within the biliary tree)
  -Bile duct stenosis
  -Bile duct perforation
  -Cholelithiasis (gallstones)
  -Neoplasms

-Intrahepatic causes
  -Alagille Syndrome, ie: Bile duct paucity (syndromic or nonsyndromic)
    -Altered embryogenesis where bile ducts are narrowed, malformed, and low in numbers
    -Other clinical findings: skeletal anomalies (butterfly vertebrae), CV anomalies (pulmonic stenosis), and abnormal facies
    -Cholestasis (progressive familial cholestasis – autosomal recessive)

Hyperbilirubinemia



Direct Hyperbilirubinemia

-Hepatocellular causes
- -Metabolic and Genetic
  - -Inborn errors of metabolism (galactosemia, tyrosinemia)
  - -Dubin-Johnson syndrome (autosomal recessive, defect in enzyme within hepatocyte to secrete conjugated bilirubin into bile)
  - -Rotor Syndrome (very similar to Dubin-Johnson, except liver cells are not pigmented under microscope)
- -Infections
  - -Viral (CMV, HSV, Adenovirus, Epstein-Barr)
  - -Bacterial (E. Coli, Group B Strep, Staph, Listeria, UTI)
- -TPN
  - -Lipid emulsion is damaging to liver (new studies using fish oil lipids instead of soy bean)
  - -Lack of feeds leads to slow flow of bile and biliary stasis

Direct Hyperbilirubinemia

-Hepatocellular causes, continued
- -Neonatal hepatitis
  - -Hepatitis A or B
  - -Alpha-1-antitrypsin deficiency (most common inherited cause of hepatitis)
    - *Alpha-1-antitrypsin inhibits destrictive proteins*
    - *Diagnose via blood test that shows low alpha-1-antitrypsin levels*
    - *Treatment: supportive or liver transplant if cirrhosis progresses*
- -Hemaochormatosis
  - -Excess iron that accumulates in the liver causing damage to cells

Treatment of Direct Hyperbilirubinemia

-Special formula
  -with medium chain triglyceride due to absorption without bile acids
  - ie: Enfaport and Pregestimil
-Vitamin Supplementation
  -DEAK – fat soluble vitamins
-Ursodiol (Actigall)
  -A naturally occurring bile acid to help cholestasis
  -Stimulates bile flow
-Phenobarbital
  -Enhance bile acid synthesis, increases bile flow
-Surgical
  -Kasai procedure (small intestine connected directly to liver, bypassing biliary tree)
  -Transplant

Specific Hematologic Problems

Anemia

- Defined as
  - hemoglobin < 12 mg/dl
  - hematocrit <30%
- Reticulocyte count
  - Reticulocytes are immature RBCs, they live in the blood for 2-3 days before becoming mature RBCs
  - Test measures production of RBCs
  - Normal value: 3-7%
- Causes
  - Destruction (increase loss of RBCs)
  - Underproduction

Anemia

- Physiologic Anemia
  - Hemoglobin remains unchanged until ~3rd week of life
  - Reaches nadir at 6-10 weeks
  - Decline is more profound in premature infants
    - Due to: decrease mass of RBCs, increased loss via blood sampling, shorter RBC life span, inadequate production, and rapid growth
    - Lower nadir
    - Nadir is reached earlier, ~4-6 weeks

Anemia

- Hemorrhagic Anemia
  - Antepartum
    - *Placental abruption, previa, anomalies of umbilical cord, twin-to-twin transfusion*
  - Intrapartum
    - *Fetomaternal hemorrhage, c-section, trauma*
  - Neonatal
    - *Caput succedaneum, cephalhematoma, subgaleal hemorrhage, intracranial*
  - Defects in hemostasis
    - *Coagulation factor deficiency, consumption coagulopathy (DIC, sepsis), deficiency in vitamin K, thrombocytopenia*

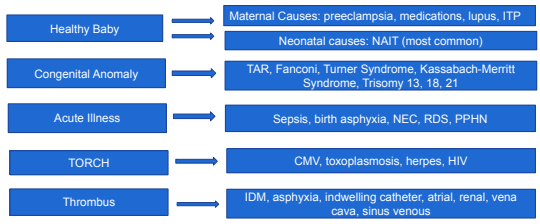
Anemia

- Hemolytic Anemia (destruction)
  - Immune
    - Rh incompatibility
    - Autoimmune hemolytic anemia
  - Nonimmune
    - Sepsis
    - TORCH infection
  - Congenital RBC defect
    - Enzyme deficiency (G6PD, Pyuvate kinase)
    - Thalassemia
    - Hemoglobinopathy (spherocytosis, elliptocytosis, Sickle Cell)

Thrombocytopenia

- Defined as a platelet count < 150,000
  - Mild 100-149,000
  - Moderate 50-99,000
  - Severe <50,000
- Most common hematologic abnormality in sick newborns

Thrombocytopenia



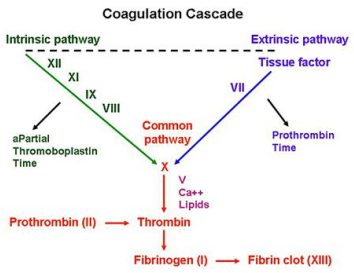
Thrombocytopenia

- Maternal Causes
  - Chronic hypoxia (most common, placental insufficiency, diabetes, hypertension)
  - Preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
  - Drug use (aspirin, heparin, thiazide diuretics)
  - Infections (TORCH)
  - Placental disorders (abruption, vascular thrombo)
  - Immune thrombocytopenia
    - Idiopathic thrombocytopenic purpura (ITP)
      - *Antibodies against platelets*
      - *Occurs after an acute or chronic infection*

Thrombocytopenia

-Neonatal causes
 -Alloimmune thrombocytopenia (NAIT)
  -Most common cause of severe thrombocytopenia
  -Seen in <72 hrs of age
  -Human platelet antigen (HPA) negative mother and HPA positive fetus
 -Decreased production
  -TAR syndrome (absent radius syndrome, normal thumb)
  -Fanconi anemia (pancytopenia, hypoplastic/aplastic thumb)
  -Trisomies (13, 18, 21)
  -Congenital amegakarocytic thrombocytopenia
 -Increased destruction
  -Illness (RDS, sepsis, PPHN, birth asphyxia, NEC…etc)
  -Congenital infections (TORCH, especially CMV)
  -Thrombus, DIC
  -Kasabach-Merritt Syndrome (platelet destruction via giant hemangioma)

Coagulation



Coagulopathy

-Hemophilia (sex-linked, X chromosome, recessive)
 -Hemophilia A (1 in every 5000 males) – deficiency of factor VIII (8)
 -Hemophilia B (1 in every 25000 males) – deficiency of factor IX (9)
 -Treatment for both is replacement of the missing factor

-Von Willebrand Disease
 -Rarely presents in neonatal period
 -VW factor is an essential clotting protein

Coagulopathy

-Disseminated Intravascular Coagulation
- -Excessive and inappropriate activation of clotting cascade
- -Small clots form in vessels causing end-organ damage
- -Also consumes platelets, causing bleeding
- -Causes: sepsis, severe RDS, asphyxia, or NEC
- -Diagnosis: sick neonate with thrombocytopenia, elevated PT, PTT, and low fibrinogen (protein that helps in formation of clots)
- -Treatment
  - -Most important thing: treat underlying cause
  - -Fresh frozen plasma (blood product made from liquid portion of whole blood)
  - -Replaces clotting factors and proteins

Coagulopathy

- Hemorrhagic Disease of Newborn (ie: Vitamin K Deficiency)
- -Rare in the US with administration of Vitamin K
- -Vitamin K is a precursor for coagulation proteins needed for clotting
- -Newborns are at risk due to:
  - -poor placental transfer, insufficient production, and inadequate intake in diet
- -Classic disease presents between day of life 1 and 7 with GI bleeding, intracranial bleeding, skin bruising and bleeding (esp following circumcision)
- -Late disease presents between 2 and 12 weeks. Most commonly in breast fed babies who do not receive none or only one oral dose of Vitamin K.
- -1 mg Vitamin K IM single dose prevents both classic and late disease
- -2 mg Vitamin K can be given orally following birth but must be followed by 1 mg dose weekly for 3 months. Efficacy not well known.

Rh Incompatibility

-Isoimmune hemolytic anemia
- -Rh negative mother who was previously exposed to an Rh-positive fetus
- -Rh negative mothers do not have exposure to the Rh antigen
- -Placental transfer of blood between Rh-negative mother and a Rh-positive fetus exposes mom to the antigen and her body begins making IgG antibodies against the antigen
- -First born is at <1% risk
- -Subsequent pregnancies are at greatest risk due to presence of antibodies

- Prevention
- -Verify Rh status at first pregnancy visit
- -If Rh-antibody is detected, must perform maternal titers. If titers reach a critical value, this warrants fetal monitoring via amniocentesis and ultrasound
- -RhoGAM – an immunoglobulin given to mother that is composed of Rh antibodies (given at 28 weeks gestation, following any feto-maternal hemorrhage, and following delivery)

ABO Incompatibility

- Isoimmune hemolytic anemia
  - Occurs in mothers with O type blood and infants with A or B type blood
  - In utero, there is placental transfusion of blood between mother and baby
  - Mother's exposed to "foreign" blood type begin making IgG antibodies against the A or B antigen on the surface of RBC
  - Maternal IgG antibodies cross the placental and cause mild hemolytic anemia in infants
  - ABO blood group system is a well known surface antigen system, expressed on a multitude cells
  - Anti-A or anti-B antibodies that enter the fetal circulation from the mother find A (or B) antigens on many different fetal cell types, leaving fewer antibodies available for binding onto fetal red blood cells (why ABO incompatibility causes only mild clinical symptoms)

Hydrops Fetalis

- Accumulation of fluid in at least 2 fetal compartments
  - Ascites, pleural effusion, pericardial effusion, subcutaneous tissue
- Usually caused by some type of anemia, causing the heart to have to pump harder (Rh disease at one time being the most common cause)
- Increased risk of fetal death, still birth, and intolerance of labor
- Improved outcomes with antenatal monitoring and transfusions
- Complications:
  - Pulmonary edema, severe RDS, heart failure, hypotension, cardiac rhythm defects, severe anemia, hypoxia, acidosis
- Extensive resuscitation
  - Blood, fluid resuscitation, blood gas and electrolyte management, positive pressure ventilation, thoracentesis/paracentesis

Polycythemia and Hyperviscosity

- Polycythemia
  - Central hematocrit of >65%
  - Occurs in 2-4%

- Hyperviscosity
  - Cause of clinical symptoms in infants symptomatic from polycythemia
  - Can have hyperviscosity without polycythemia and vise versa
  - Hyperviscosity without polycythemia occurs in 1%
  - 25% of polycythemic babies will have hyperviscosity

- Complications:
  - Tissue hypoxia, acidosis, microthrombi in circulation

Polycythemia and Hyperviscosity

-Causes:
- -Fetal hypoxia (enhances erythropoiesis)
  - -Placental insufficiency
  - -Post-dates
  - -Congenital Heart disease
  - -IUGR
  - -Maternal drug or smoking
- -Endocrine
  - -Infant of a diabetic mother
  - -Congenital adrenal hyperplasia
  - -Beckwith-Wiedemann syndrome (hyperinsulinism)
- -Hyperperfusion
  - -Delayed cord clamping
  - -Twin-twin transfusion

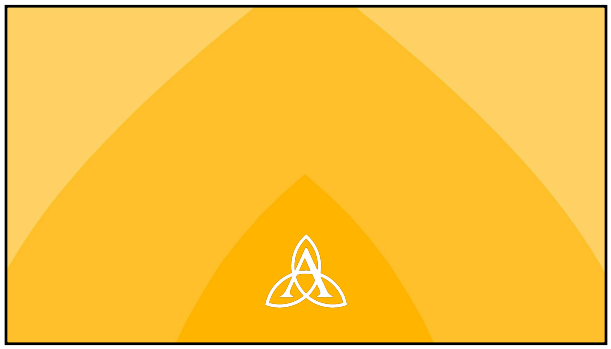
Administering Blood Products

Administering Blood Products

- RBCs
  - Universal donor: O negative
  - 10-20 ml/kg over 1-3 hours
- Type and Screen
  - Initial ABO and Rh type determination
- Type and Cross
  - Testing done prior to a transfusion to assure donor's blood is compatible with recipient's
- Platelets
  - 10-20 ml/kg should raise by 60,000-100,000
  - In severe causes of NAIT, HPA negative platelets are necessary

Administering Blood Products

- Transfusion reactions
  - Acute hemolysis (incompatible blood products)
  - Bacterial contamination
  - Hypothermia (if blood is not warmed)
  - Hyperkalemia
    - In large RBCs transfusions or ECMO
  - Allergic reactions
    - Extremely rare in neonates
    - Caused by antibodies
  - Transfusion-associated acute lung injury
    - Usually due to large transfusions of FFP or platelets
    - Caused by antibodies
  - Nonhemolytic febrile reactions
    - Usually mild, caused by cytokine release from WBCs



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