Learning Goals

- Provide an overview of hyperbilirubinemia in the neonate
- Review the physiology of hyperbilirubinemia
- Review the physiology of hemolytic disease as a cause for hyperbilirubinemia
- Identify medical and nursing management strategies for treating hyperbilirubinemia in the NICU
NEONATAL HYPERBILIRUBINEMIA

- Newborns appear jaundiced when bilirubin > 7 mg/dL
- 25–50% of term newborns and higher percent of preterm infants develop clinical jaundice
- 9.1% of well term newborns have maximum serum bilirubin > 12.9 mg/dL
- Bilirubin level > 15 mg/dL found in 3% of normal term infants

PHYSIOLOGIC HYPERBILIRUBINEMIA

- Indirect bilirubin
  - does not exceed 5 mg/dL in the first 24 hours
  - 12 to 15 mg/dL in healthy full term infants during the first week of life
- Total bilirubin concentrations as high as 20 – 26 mg/dL can be explained only by physiologic jaundice of the newborn without any superimposed pathology
- Direct bilirubin levels should not exceed 1mg/dL
PHYSIOLOGIC HYPERBILIRUBINEMIA

Mechanisms involved:
- Increased bilirubin load on hepatocyte
- Defective hepatic uptake of bilirubin
- Defective bilirubin conjugation
- Defective bilirubin excretion

Non-Physiologic Hyperbilirubinemia

- Onset of jaundice before 24 hours of age
- Rise in bilirubin levels > 0.5 mg/dL/hour
- Signs of underlying illness in any infant
  - (vomiting, lethargy, poor feeding, excessive weight loss, tachypnea, temperature instability
- Jaundice persisting
  - > 8 days in a term infant or
  - > 14 days in a premature infant

History

- Family hx of jaundice
  - hereditary hemolytic anemia
- Family hx of liver disease
  - galactosemia, Gilbert’s, Crigler-Nijjar, or cystic fibrosis
- Sibling with jaundice
  - blood group incompatibility, breast milk jaundice
- Maternal illness
  - congenital viral or toxoplasmosis infection, IDM
- Hx of trauma during labor and delivery
  - extravascular hemolysis; delayed cord clamping
- Hx of delayed or infrequent stooling
Breast feeding vs. breast milk jaundice

- **Breast milk jaundice**
  - Late onset, may reach 20-30 mg/dL by 14 days of age. Levels stay elevated and then fall slowly at 2 weeks of age, returns to normal by 4 to 12 weeks of age
  - If breast feeding is stopped, bilirubin will fall rapidly in 48 hr, when breast feeding resumed only 2-4 mg/dL rebound
  - 70% recurrence rate in future pregnancies
  - Mechanism is unknown: interferes with bilirubin metabolism and enterohepatic circulation

- **Breast feeding jaundice**
  - Early onset of elevated bilirubin levels in the first 3 to 4 days of life
  - Etiology due to decreased intake of milk that leads to increased enterohepatic circulation

Clinical Laboratory Tests

- Total/direct serum bilirubin
- Blood type, Rh, direct Coombs test of the infant
- Blood type, Rh, maternal antibody screen
- Peripheral smear for RBC morphology and reticulocyte count
- CBC with differential
- Identification of antibody on infant’s RBCs (if Coombs’ is positive)
Bilirubin Toxicity

- Difficult to determine toxicity for different groups of infants: premature and low birth weight infants vs. healthy full term infants
- Bilirubin entry into the brain occurs as free bilirubin or bilirubin bound to albumin in presence of disrupted blood-brain barrier
  - 8.5 mg bilirubin will bind to 1 gm of albumin
  - FFA and drugs interfere with bilirubin binding to albumin
  - Acidosis affects bilirubin solubility and deposition into brain tissue
- Factors affecting blood-brain barrier: hyperosmolarity, anoxia, hypercarbia and more permeable blood brain barrier in premature infants

Management of Hyperbilirubinemia

- Infants <1000 gm
  - photRx started within 24 h
  - exchange Tx for bilirubin 10-12 mg/dL
- Infants 1000 – 1500 gm
  - photRx started for bilirubin 7-9 mg/dL
  - exchange Tx for bilirubin 12-15 mg/dL
- Infants 1500 – 2000 gm
  - photRx started for bilirubin 10-12 mg/dL
  - exchange Tx for bilirubin 15-18 mg/dL
- Infants 2000 – 2500 gm
  - photRx started for bilirubin 13-15 mg/dL
  - exchange Tx for bilirubin 18-20 mg/dL

Indications for phototherapy

- Used when the bilirubin level may be hazardous to the infant if it were to increase
- Prophylactic phototherapy may be indicated with extremely LBW infants or severely bruised infants or infants with hemolytic disease
- Contraindicated in infants with direct hyperbilirubinemia caused by liver disease or obstructive jaundice—may lead to “bronze baby” syndrome
- If both indirect and direct bilirubin are high, exchange transfusion is probably safer than phototherapy because it is unknown whether bronze pigment is toxic
Hemolytic Disease of the Newborn

What is hemolytic disease of the newborn?

- Destruction of the RBCs of the fetus and newborn by antibodies produced by the mother
- Only IgG antibodies are involved because it can cross the placenta (not IgA or IgM)

Pathophysiology

- Although transfer of maternal antibodies is good, transfer of antibodies involved in this hemolysis are directed against antigens on fetal RBCs inherited by the father
- Most often involves antigens of the Rh and ABO blood group system, but can result from any blood group system
- Remember: The fetus is POSITIVE for an antigen and the mother is NEGATIVE for the same antigen
Pathophysiology

- Develops in utero
- Mother is sensitized to the foreign antigen present on her child’s RBCs usually through some seepage of fetal RBCs (fetomaternal hemorrhage) or a previous transfusion
- Hemolysis occurs when these antibodies cross the placenta and react with the fetal RBCs

ABO incompatibility

- ABO incompatibilities are the most common cause of hemolytic disease in the newborn but are less severe
  - About 1 in 5 pregnancies are ABO-incompatible
  - 65% of HDN are due to ABO incompatibility
- Usually, the mother is type O and the child has the A or B antigen...Why?
  - Group O individuals have a high titer of IgG anti-A,B in addition to having IgM anti-A and anti-B

ABO incompatibility

- ABO hemolytic disease can occur during the FIRST pregnancy b/c prior sensitization is not necessary
- ABO hemolytic disease is less severe than Rh hemolytic disease because there is less RBC destruction
  - Fetal RBCs are less developed at birth, so there is less destruction by maternal antibodies
  - When delivered, infants may present with mild anemia or normal hemoglobin levels
  - Most infants will have hyperbilirubinemia and jaundice within 12 to 48 hours after birth
Diagnosis of ABO incompatibility

- Infant presents with jaundice 12-48 hrs after birth
- Testing done after birth on cord blood samples:
  + ABO, Rh and DAT performed
  + Most cases will have a positive DAT
    - If DAT positive, perform elution to ID antibody

Treatment of ABO incompatibility

- Only about 10% require therapy
- Phototherapy is sufficient
- Rarely is exchange transfusion needed
- Phototherapy is exposure to artificial or sunlight to reduce jaundice
- Exchange transfusion involves removing newborn’s RBCs and replacing them with normal fresh donor cells

Rh Hemolytic Disease
What is Rh Hemolytic Disease?

- Mother is D negative (d/d) and child is D positive (D/d)
- Most severe form of HDN
- 33% of HDN is caused by Rh incompatibility
- Sensitization usually occurs very late in pregnancy, so the first Rh-positive child is not affected
  - Bleeds most often occur at delivery
  - Mother is sensitized
  - Subsequent offspring that are D-positive will be affected

FetoMaternal Hemorrhage

- Sensitization occurs as a result of seepage of fetal cells into maternal circulation as a result of a fetomaternal hemorrhage
  - Placental membrane rupture (7%)
  - Trauma to abdomen
  - Delivery (>50%)
  - Amniocentesis
  - Abortion
Risk

- Rh-negative women can be exposed to Rh-positive cells through transfusion or pregnancy
- Each individual varies in their immune response (depends on amount exposed to)
  - 85%* transfused with 200 mL Rh-positive cells will develop anti-D
  - There is only about a 9%* chance that Rh-negative mothers pregnant with an Rh-positive child will be stimulated to produce anti-D (without RhIg)


Pathogenesis

- Maternal IgG attaches to antigens on fetal cells
  - Sensitized cells are removed by macrophages in spleen
  - Destruction depends on antibody titer and number of antigen sites
  - IgG has half-life of 25 days, so the condition can range from days to weeks
  - RBC destruction and anemia cause bone marrow to release erythroblasts, hence the name *erythroblastosis fetalis*

Pathogenesis

- When erythroblasts are used up in the bone marrow, erythropoiesis in the spleen and liver are increased
  - Hepatosplenomegaly (enlarged liver & spleen)
  - Hypoproteinemia (from decreased liver function) leads to cardiac failure edema, etc called "Hydrops fetalis"
Bilirubin

- Hemoglobin is metabolized to bilirubin
  - Before birth, "indirect" bilirubin is transported across placenta and conjugated in maternal liver ("direct") where it is excreted
  - After birth, the newborn liver is unable to conjugate the bilirubin
  - Unconjugated ("indirect") bilirubin can reach toxic levels. This is called kernicterus and can lead to permanent brain damage

Diagnosis & Management

- Serologic Testing (mother & newborn)
- Amniocentesis and Cordocentesis
- Intrauterine Transfusion
- Early Delivery
- Phototherapy & Newborn Transfusions

Serologic testing on mother

- ABO and Rh testing
  - Test for D antigen (test for weak D if initially negative)
- Antibody Screen
  - To test detect for IgG alloantibodies that react at 37°C
  - If negative, repeat before RhIg therapy and/or if patient is transfused or has history of antibodies (3rd trimester)
- Antibody ID
  - Weakly reacting anti-D may be due to FMH or passively administered anti-G (RhIg)
  - If antibody is IgG, anti-D is most common followed by anti-K and other Rh antibodies
What to do?

- Intrauterine transfusion is done if:
  - Cord blood sample has hemoglobin <10 g/dL
  - Hydrops is noticed on ultrasound
- Removes bilirubin
- Removes sensitized RBCs
- Removes antibody

Prevention

- RhIg (RhoGAM®) is given to the mother to prevent immunization to the D antigen
  - “Fools” mom into thinking she has the antibody
  - RhIg (1 dose) is given at 28 weeks’ gestation
  - RhIg attaches to fetal RBCs in maternal circulation and are removed in maternal spleen; this prevents alloimmunization by mother
  - May cause a positive DAT in newborn (check history)

Postpartum administration of Rhogam

- Another dose of Rhogam should be given to the mother within 72 hours of delivery (even if stillborn)
  - Mother should be D negative
  - Newborn should be D positive or weak D
  - About 10% of the original dose will be present at birth, so it’s important to give another dose to prevent immunization
Kleihauer-Betke test

- **Quantitates** the number of fetal cells in circulation
  - Fetal hemoglobin is resistant to acid and retain their hemoglobin (appear bright pink)
  - Adult hemoglobin is susceptible to acid and leaches hemoglobin into buffer (“ghost” cells)

Exchange Transfusion

- Removes partially hemolyzed and antibodycoated RBCs as well as unattached antibodies and replaces them with donor RBCs lacking the sensitizing antigen
- As bilirubin is removed from the plasma, extravascular bilirubin will rapidly equilibrate and bind to the albumin in the exchanged blood.
- Within ½ hour of exchange, bilirubin levels return to 60% of their pre-exchange levels

Indications for Exchange Transfusion

- When phototherapy fails to prevent rise in bilirubin to toxic levels
- Correct anemia and improve congestive heart failure in hydropic infants with hemolytic disease
- Stop hemolysis and bilirubin production by removing antibody and sensitized RBC’s
Indications for Exchange Transfusion

- Exchange transfusion should be considered:
  - Cord bilirubin > 4.5 mg/dL and cord Hb < 11 gm/dL
  - Bilirubin rising > 1 mg/dL/hour
  - Bilirubin level > 20 mg/dL
  - Progression of anemia; in spite of adequate control of bilirubin
- Repeat exchanges are done for the same reasons

What type of blood is used for the baby?

- CMV negative
- Irradiated
- Fresh Whole Blood (to avoid $\text{Ca}^{++}$)
- Maternal blood if possible
- Leukoreduced

Case Study #1

- A 25 year old primagravida mother, blood type O+, presents with SPROM at 39 wks gestation. The patient is then given oxytocin to augment the labor. 24 h after admission, she is completely effaced and 10 cm dilated but develops fever to 101°. A male infant is delivered by forceps with Apgars 71 and 95. The infant has a large cephalohematoma and facial bruising. The infant does well for 24 h, but is feeding poorly at 36 h, appears lethargic and icteric. The infant’s total bilirubin is 15 mg/dL, blood type A+ and Coombs positive serology.
List the factors that might be responsible for the elevated bilirubin level in this infant

Answers:

- ABO
- Sepsis
- Race
- Oxytocin
- bruising

Case Study #2

A 20 y.o. G2P0 Ab1 white female presents at 34 wks gestation with abdominal pain and vaginal bleeding. She delivers precipitously a 2,200 g female infant with Apgars 31 and 85. Infant has acrocyanosis, nasal flaring, grunting and tachypnea. Because of persistent acidosis and hypoxia, the infant is intubated and placed on mechanical ventilation and improves during the next 2 days. At 72 h, the infant has total bilirubin of 15 mg/dL. Phototherapy is begun. On day 4 of life, the infant has a total bilirubin of 19 mg/dL.
1. What are some of the factors in preterm infants that predispose them to bilirubin toxicity?

2. When should an exchange transfusion be considered in this infant?

**Answers:**

1. they exhibit ability to conjugate bilirubin
2. experience higher levels of bilirubin
3. they have serum albumin concentrations
4. blood-brain barrier more prone to disruption
5. likelihood of hypothermia and hypoglycemia
6. likelihood of sepsis

**WHEN SHOULD AN EXCHANGE TRANSFUSION BE CONSIDERED IN THIS INFANT?**

Perform an exchange transfusion at a serum bilirubin of 15 - 20 mg/dL. A more precise answer would depend on whether other risk factors for kernicterus exist (e.g., acid-base status, albumin level, degree of illness)