Introduction: What is neonatal jaundice?

1. Neonatal jaundice is a common physiologic event (60% newborns)
    a. Jaundice is a physical exam finding that refers to yellow discoloration of skin and eyes (caused by bilirubin deposition)
    b. Hyperbilirubinemia is by definition a total serum bilirubin of greater than/equal to 95th percentile (less common—5% newborns)
        i. This definition can be used only for infants of gestational age greater/equal to 35 weeks (preterm infants have different standards)
        ii. Bilitool.org is website designed by AAP that allows one to plot the bilirubin level for age

What are the types of bilirubin? Why does the distinction matter?

1. Types of bilirubin:
    a. Indirect bilirubin = unconjugated
        i. Lipid soluble -> crosses blood brain barrier and if elevated can lead to kernicterus which is BAD!
        ii. We treat hyperbilirubinemia in neonatal period in order to prevent kernicterus (occurs with bilirubin greater than 20 mg/dL) and acute bilirubin encephalopathy (can manifest as lethargy, hypotonia, poor suck)
        iii. Kernicterus = chronic and permanent sequelae from bilirubin-induced neurologic dysfunction, which occurs when bilirubin crosses blood brain barrier (BBB) and deposits in brain tissue (especially basal ganglia)
            1. Called kernicterus because looks like yellow corn on gross pathology
    b. Direct bilirubin = conjugated (sugars attached to bilirubin by enzyme in liver)
        i. Water soluble -> does not cross blood brain barrier and so doesn't lead to kernicterus however ALL causes of elevated direct bilirubin are pathologic and so beyond scope of this presentation

Understanding bilirubin metabolism is helpful in understanding why neonatal jaundice occurs!

1. Bilirubin is a product of RBC breakdown
    a. Macrophages break down RBC into globin and heme
    b. Heme is further metabolized into unconjugated bilirubin which is water insoluble so is bound to albumin which carries it in bloodstream to the liver
2. Unconjugated bilirubin is taken up by liver hepatocytes where it is conjugated by enzyme UGT1A1 (uridine diphosphate glucuronosyltransferase) into a water soluble form (direct bilirubin) and is then excreted by hepatocytes into gallbladder and duodenum
3. Conjugated/direct bilirubin travels through intestinal tract
4. Intestinal bacteria convert direct bilirubin into series of molecules called urobilinoids *or urobilinogens*
    a. Most of the urobilinogen is excreted as feces *(fecal urobilinogen)*
    b. About half of urobilinogen is reabsorbed and taken up via portal vein to the liver to start the cycle all over again <u>(this process is called enterohepatic circulation)</u>
    c. A small amount of the urobilinogen does not get cleared by the liver and so enters general circulation where it is partly excreted in urine (hence why "urobilinogen" is part of urinalysis)

Three big categories for why newborns have elevated unconjugated bilirubin

1. <u>Increased production of bilirubin</u>

a. *Extravascular causes:*
    i. Birth trauma resulting in bruising or cephalohematomas leads to RBC breakdown which then leads to increased bilirubin
        1. Can use physical exam to determine this
b. *Intravascular causes:*
    i. Neonates born with higher hematocrits (60) = polycythemia of newborn. Risk factors include being large for gestational age, delayed cord clamping and being an infant of a diabetic mother.
    ii. Hemolysis due to antibodies (ABO incompatibility, Rh incompatibility)
        1. Blood type performed on all moms and if at risk will perform baby blood type and Coombs test
    iii. Hemolysis due to enzyme defects or defects of RBC membrane
        1. G6PD deficiency, pyruvate kinase deficiency, sickle cell disease, spherocytosis
            a. Can use CBC, reticulocyte count and G6PD level to help determine this. Take into account that G6PD level may not be interpretable during time of active hemolysis

2. <u>Impaired conjugation of bilirubin</u>
    a. All neonates have lower levels of UGT1A1 (therefore lower rates of conjugation)
    b. Diseases associated with mutated or deficient UGT1A1: Crigler Naijar or Gilbert disease
3. <u>Impaired excretion of bilirubin</u>:
    a. If bilirubin sits in intestinal tract for too long then there is conversion by intestinal bacteria back to unconjugated bilirubin and increased enterohepatic circulation instead of excretion as conjugated bilirubin
        i. This happens if infant is dehydrated which leads to lesser intestinal transit = **breast feeding jaundice**
            1. See this in first few days as maternal milk supply is coming in. Since less supply in first few days infants do not poop as much
        ii. **Breast milk jaundice:** seen after about 1 week of newborn life
            1. Exact mechanism unknown but theorized that is due to higher levels of beta-glucuronidase in milk compared to formula. This catalyzes the hydrolysis of beta-D-glucuronic acid which promotes increase in intestinal absorption of unconjugated bilirubin

References

"Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation." 2004. *Pediatrics* 114(1): 297 LP – 316. http://pediatrics.aappublications.org/content/114/1/297.abstract.