The jaundiced infant

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- Jaundice: an increase in serum bilirubin

From whence cometh bilirubin?

- 80% daily bilirubin product from the catabolism of hemoglobin
- Heme dissociates from globin
- Heme oxygenase in RE cells, macrophages, parenchymal cells
- Catalyzes the cleavage of the tetrabpyrrole ring at the methene bridge
- Releases biliverdin, Fe, CO
- Biliverdin reduced to bilirubin IX-a by biliverdin reductase
- Major catabolic product but...insoluble

How to excrete bilirubin?
First solubilize it !!!

- Conjugation with glucuronic acid
  - One both propionic acid side chains
  - UDP-glucuronyl transferase
  - dip-glucuronide > 90% of bilirubin conjugates in normal human bile
- Photoisomerization
  - Exposure to light 425 - 475 nm
  - Changes the configuration of the double bonds adjacent to the outer pyrrole rings
  - Discovered incidentally
  - Phototherapy

Let it flow in bile....

- Conjugation
- Bile Secretion
- Bile Excretion

NB: once bilirubin is conjugated, it requires bile flow for excretion into the gut

If you are jaundiced....stay calm - you have one of two problems:

1. Handling the unconjugated bilirubin load
2. Excreting the conjugated bilirubin in bile

The cardinal first step in evaluation

unconjugated    conjugated

Let it flow in bile....
The Jaundiced Infant

Unconjugated hyperbilirubinemia
- Increased bilirubin load
  - RBC load - polycythemia
    - ABO, Rh
    - RBC membrane, pyruvate kinase
  - Male hemi, Female homo
  - Drugs
  - Breast milk

Unconjugated hyperbilirubinemia
- Decreased conjugation
  - Physiologic
    - UDP-GT:1A1 mutations

Physiologic jaundice of infancy
- Immaturity - UDP-glucuronosyl transferase (UDP-GT:1A1)
  - 0.1% - 17-30 wks, 1% - 30-40 wks, 100% - 14 wks post-natal
  - Induction after birth irrespective of gestational age
- Common
  - Peaks at day 3
  - Bilirubin level 10-12
  - Danger - kernicterus
    - Risk
      - Low birth weight
      - Asphyxia neonatorum
      - Septicemia
      - Hypobilirubinemia, drugs
      - Basal ganglia, deafness, mental retardation

Physiologic jaundice of infancy - therapy
- Action taken depends on risk factors
- IV hydration
- Phototherapy
  - Photosomerizaion - bilirubin solubilization - excretion
- Exchange transfusion

Conjugation defects - UDP-GT1A1 mutations
- Crigler-Najjar I, II
  - I - activity 0%, AR, 1:1000, bil > 20, kernicterus +++, any exon
  - II (Arias) - activity <10%, AR/AD, 1:1000, bil 15-20, kernicterus low
  - UGT 1A1 only, inducable by phenobarbital
- Gilbert's syndrome
  - Mild, chronic, recurrent, activity 30%, fasting, illness
  - 9 % of population homozygous, 47 % heterozygous
  - extra TA in promoter - (TA)?

Breast milk jaundice
- 2 weeks of life
- Etiology unknown
  - ? Increased enterohepatic circulation of bilirubin
  - Inadequate breast milk, dehydration
  - Off breast for 48 h
  - Pump milk
  - Document drop in bilirubin - 2 points
  - Restart breast feeding
  - Not a reason to discontinue
Conjugated hyperbilirubinemia
- Occurs later in life - 3-4 weeks
- Serious etiologies - chronic disease
- Anything that impairs bile flow
- Clinical consequences result from impaired bile flow

How and why does bile flow
- Synthesized from cholesterol - hepatocyte
- 7, and 12α-hydroxylation
- Conjugated, actively secreted into canniliculus
- Pulls water
- Essential property - amphiphilic - sits comfortably at lipid/water interface
- Forms micelles with phospholipid
- "solubilizes" fat and cholesterol in water
- 95% reabsorbed in terminal ileum - recirculated

Functions of bile
- Micellize dietary fat in gut lumen
  - Chylomicrons
  - Lymphatic system
- Excrete cholesterol from liver
- Excrete bilirubin

In cholestasis, injury impairs the bile salt secretory apparatus
- Disruption of actin filaments around canaliculus
- Loss of villous processes
- Interruption of transport pumps: MRP3 (multi drug resistant-associated protein 3)

Histologic patterns of injury
- Normal portal tract
- Ballooning degeneration of hepatocytes
- Bile duct inflammation (Bactrim)
- Portal fibrosis, loss of bile ducts (8 mos later)
- Necrosis (acetaminophen)
- Fat accumulation
Injury impairs bile salt secretion into the canaliculus, reduces bile flow and bilirubin excretion: conjugated bilirubin rises

- Infectious
  - Viral
  - Bacterial
- Toxic
  - Drug
  - TPN
- Metabolic
  - Galactosemia
  - Fructosemia
  - Tyrosinemia
  - α1-antitrypsin
- Blockage
  - Cystic fibrosis

Remember: the elevated conjugated bilirubin is merely a symptom of the underlying pathobiology - impaired bile flow - "cholestasis"

NB: bile salts are detergents - their accumulation in the hepatocyte leads to ongoing injury and fibrosis

Consequences of impaired bile flow - cholestasis

- Fat malabsorption
  - Steatorrhea - fatty, bulky stools
  - Fat soluble vitamin deficiency
    - D - rickets
    - K - hypoprothrombinemia - bleeding
- Hypercholesterolemia
  - Xanthomata
- Hyperbilirubinemia
- Injury to liver - cirrhosis

Causes of cholestatic jaundice in infancy

- Surgical
- Metabolic
- Infectious
- Genetic
- Toxic

Surgical causes

- Sclerosing cholangiopathy
  - Choledochal cyst
  - Biliary atresia
  - Caroli's disease
  - Progressive - fibrosis, cirrhosis
  - Early intervention - < 10 weeks can prevent cirrhosis
- Bile plug syndrome
- Cholelithiasis
  - TPN
  - ECHMO

Obstructive cholangiopathies

- Progressive - fibrosis, cirrhosis
- Early intervention - < 10 weeks can prevent cirrhosis
Obstructive cholangiopathies
- Kasai procedure
- Porto-enterostomy
- Resection
- Incision porta
- Dripping bile
- Roux-en-Y anastamosos

Idiopathic cause
- Neonatal / giant cell hepatitis
- 40% of cholestatic hepatitis
- Males > female 2:1
- Ballooning degeneration
- Multinucleated giant cells
- May resolve
- May progress to cirrhosis, liver failure
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**Metabolic causes**
- **α1-antitrypsin deficiency**
  - PiZZ phenotype
  - 1:2000 live births
  - Autosomal recessive
  - Low serum levels of α1-antitrypsin
  - Altered protein - impaired secretion RER to Golgi
  - Accumulation of α1-antitrypsin in hepatocyte
  - Hepatocellular injury, cholestasis, cirrhosis
  - PAS positive diastase resistant staining on histology
  - Severity variable

**Galactosemia**
- Hydrolysis of lactose to glucose and galactose
- Transferase deficiency
- AR, 1:50,000
- Vomiting, diarrhea, hypoglycemia
- Cholestatic hepatitis early
- Rapid cirrhosis, ascites, liver failure
- Reducing sugar in urine
- Neg gluc oxidase dipstick
- Lactose-free formula

**Tyrosinemia**
- AR
- Deficiency of fumarylacetoacetate hydrolase
- Last enzyme in the tyrosine degradation pathway
- Intermed metab, maleylacetoacetate, fumarylacetoacetate responsible for the hepatic and renal symptoms
- Cholestatic hepatitis, progressive failure
- Inc plasma tyrosine
- Succinylacetone in blood or urine
- Hepatocellular carcinoma by 3 yrs
- Rx: phylalnine/tyrosine-free formula

**Abagille’s Syndrome**
- Triangular facies
- Bossing, pointed chin
- Cholestasis
- Pruritis, xanthomata, cholesterol
- Cardiac anomalies
- PPS, TOF, coarctation
- Bone
- Hemi, butterfly vertabrae
- Short skin
- Retinal pigment
- Paucity of intrahepatic bile ducts
- Chromosome 20 deletion (20p)

**Cystic fibrosis**
- Viscid mucus in bile ducts
- Cholestatic syndrome in infancy
- Biliary cirrhosis in teens
- Can be associated with meconium ileus

**Septicemia**
- Gram negative
- LPS
- TORCHES infections
  - Toxoplasmosis
  - Rubella
  - CMV
  - Herpes
  - Syphilis

**Newborn CMV hepatitis intranuclear inclusion bodies in bile duct epithelium**
Toxic causes
- Total parenteral nutrition
  - Amino acid solution and lipid
  - Dose related
  - Low birth weight, sick, septic, asphyxiated
  - Can lead to cirrhosis and liver failure
  - Do not exceed
    - Protein - 1.5 gm/kg/day
    - Fat - 1 gm/kg/day

Clinical approach to jaundiced infant
- Unconjugated
  - Benign - Physiologic/hemolytic/breast milk
- Conjugated
  - Serious - must be expeditious
  - Ultrasound - fasted - feed during exam
  - Gallbladder contraction
  - HIDA scan - loading dose of phenobarbitol
  - ? Excretion into gut
  - MRCP - MR cholangio-pancreatogram
  - α1-antitrypsin level
  - TORCHES titers
  - Metabolic screen - urine, serum
  - Sweat test
  - Operative cholangiogram, liver biopsy

TPN injury: bile plugging, rosette formation

HIDA scan: non-excretion