Neonatal Liver Disease

Beyond Newborn Jaundice

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Liver Anatomy - Fetus and Newborn

Liver Function and Physiology

Histological Structure of the Liver

Functions of the Liver

Bilirubin Metabolism

- Breakdown product of RBC, Muscle
- Metabolized and processed in the Liver for excretion.

Bilirubin Production

- erythrocyte hemoglobin
- muscle myoglobin
- cytochromes catalases
Blood Tests of Liver Function

- **Tests of Liver Cell Injury** -
  - **AST**: From cytosol and mitochondria of liver, but also heart, muscle, kidney, RBC
  - Less specific for liver; other (muscle, heart) sources may be considered if AST >> ALT
  - **ALT**: More specific for Liver. Elevated in a variety of conditions (hepatitis)
  - Highest levels seen in shock liver, acute viral infection, drug/toxin injury
  - **LDH**: Nonspecific test. 5 types, one more liver specific. Massively increased in ischemia, sustained elevation in malignancy.

- **Tests of Impaired Bile Flow** -
  - **Alk Phos, GGT, bilirubin**
  - **Bilirubin**: breakdown of heme proteins. Conjugated in liver by UGT for excretion.
  - **Indirect (unconjugated)**: physiologic and BF/BM jaundice, prematurity, Gilbert’s (5% of population), hemolysis,
  - **Direct (conjugated)**: Always pathologic if elevated >2 or > 20% total bilirubin.

- **Tests of Liver Synthetic Function** (failure)
  - **Albumin**: only synthesized in the liver. Half life 20 days. ↓ may reflect protein loss, inflammation, malnutrition, or end stage liver disease.
  - **Coagulation**: liver synthesis of factor VIII, IX, X, XI, Fibrinogen, Prothrombin
  - **Vit K dependent**: II, VII, IX, X, protein C+S.
    - Factor 8 from endothelium, not liver. ↓ VIII = DIC, normal VIII with low V and VII = liver disease.
  - **PT**: Elevated in Vit K deficiency, liver disease, DIC.
  - **Factor V**: not Vit K dependent but liver specific.
Blood Tests of Liver Function

- **Tests of Metabolic Function**
  - **Ammonia (NH3)**: Intestinal production by bacterial urease on protein. Cleared/converted to urea in liver. Normal liver 80% first pass metabolism of ammonia.
  - Liver disease/failure—vascular shunting ↑ NH3. Also elevation w GI bleed and Sepsis.
  - Also ↑ in Urea cycle defects, Fatty acid oxidation d/o.
  - Levels of encephalopathy and NH3 poorly correlated.
  - Transient hyperammonemia of the newborn—premature infants on vent; onset within first 24 hours Ammonia level may be markedly ↑ and dialysis may be necessary. Cause is unknown and, if the newborn survives, there is no further evidence of impaired ammonia metabolism.

- **What is Jaundice/Cholestasis?**

  - **Elevation of Bilirubin—What is Dangerous?**
    - Indirect (Unconjugated) Hyperbilirubinemia
      - High levels of unconjugated unbound bilirubin cross the blood brain barrier
      - Lead to damage (kernicterus) to brainstem nuclei.
      - Lower levels not dangerous (<20mg/dl)
      - Often a combination of immature conjugation, poor PO, hemolysis (ABO)
      - Excretion enhanced by ↑PO intake, maturity, blue light (phototherapy)

  - Also Consider:
    - Ethnicity
    - Prematurity
    - Thyroid
    - Drugs
    - Breastfeeding

  - **Neonatal Hepatitis**
    - Usually also with jaundice/cholestasis
    - Generalized inflammation of the liver
    - Detected by elevated AST/ALT resulting from hepatocellular injury
    - May have hepatomegaly
    - Often viral cause (>20%)
    - Idiopathic Neonatal Hepatitis or “giant cell hepatitis” no known cause and represents up to 50% of cases.
Cholestasis

Direct (Conjugated) bilirubinemia

- Neonatal cholestasis- conjugated(direct) hyperbilirubinemia within the first 90 days
- Dbili > 1.5 to 2.0 mg/dl.
- Dbili > 20% of the total bilirubin.
- Bile trapped in liver causes liver damage
- Any unexplained/unresolving jaundice: Order CBC and a total + direct bilirubin
- Any cholestasis call a Peds GI.

Causes of Neonatal Cholestasis

- Extrahepatic biliary atresia
- Choledochal cyst
- Bile duct stenosis/Spontaneous perforation
- Cholelithiasis
- Inspissated bile/mucus plug
- Extrinsic compression of bile duct (mass)

ESTIMATED FREQUENCY OF VARIOUS CLINICAL FORMS OF NEONATAL CHOLESTASIS

<table>
<thead>
<tr>
<th>CLINICAL FORM</th>
<th>CUMULATIVE PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Idiopathic&quot; neonatal hepatitis</td>
<td>15</td>
</tr>
<tr>
<td>Extrahepatic biliary atresia</td>
<td>25–30</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>7–10</td>
</tr>
<tr>
<td>Intrahepatic cholestasis syndromes</td>
<td>20</td>
</tr>
<tr>
<td>(eg, Alagille, PFIC type 1)</td>
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<tr>
<td>Bacterial sepsis</td>
<td>2</td>
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<tr>
<td>Hepatitis</td>
<td>3–5</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>1</td>
</tr>
<tr>
<td>Rubella, herpes</td>
<td>1</td>
</tr>
<tr>
<td>Endocrine (hypothyroidism, panhypopituitarism)</td>
<td>1</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1</td>
</tr>
<tr>
<td>Inborn errors of bile acid biosynthesis</td>
<td>2–5</td>
</tr>
</tbody>
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PFIC = progressive familial intrahepatic cholestasis.
INTRAHEPATIC ETIOLOGIES

- Idiopathic Neonatal Hepatitis
- Toxic
  - TPN-associated cholestasis
  - Drug-induced cholestasis
- Genetic/Chromosomal
  - Trisomy 18
  - Trisomy 21

INTRAHEPATIC ETIOLOGIES

- Infectious
  - Bacterial sepsis (E. coli, Listeriosis, Staph. aureus)
- TORCHES
- Hepatitis B
- Varicella
- Enteroviruses
- Tuberculosis

COMMON ETIOLOGIES

- Premature infants
  - Sepsis/Acidosis
  - TPN-associated
  - Drug-induced
- Idiopathic neonatal hepatitis
- Extrahepatic biliary atresia
- Alpha-1-antitrypsin deficiency
- Cystic Fibrosis
- Alagille
- Intrahepatic cholestasis syndromes

Important Questions

CLINICAL PRESENTATION

- Jaundice
- Scleral icterus
- Hepatomegaly/Splenomegaly
- Acholic stools
- Dark urine
- Other signs and symptoms depend on specific disease process
Physical Findings

- Vital signs: weight, length, ORC, weight for length
- Global assessment of general health
- Global assessment of nutritional state
- GENIT

- Chest:
  - Auscultation
  - Inspection

- Abdomen:
  - Inspection
  - Auscultation
  - Palpation

- Diaper:
  - Inspect for color, texture, odor

- Neurology:
  - General assessment of tone, reflexes, behavior

Acholic Stools

Importance of Ultrasound

- Quick and noninvasive
- Perform when NPO
- Can rule out BA, gallstones, Choledochal cyst, evaluate liver/spleen size.
- Should be first line when cholestatic

Neonatal Liver Failure

- Relatively rare
- Important to detect early!
- 70% fatal without liver transplant
- Presents with hypoglycemia, coagulopathy
- Often high ammonia
- Encephalopathy difficult to detect in baby
- Usually elevated bilirubin (variable)
- +/- elevated LFT
- +/- hepatosplenomegaly

Etiologies of Fetal Liver Disease

- Neonatal hemochromatosis (most common)
- Infection
- Ischemia/↓ perfusion/Maternal shock/CHD
- HSV
- Placentitis
- Congenital leukemia
- HLH
- Metabolic liver disease
- Hemangioma

Neonatal Hemochromatosis (NH)

- NOT the same as adult hemochromatosis
- Alloimmune disease, similar to ABO
- Maternal Ab to fetal protein suspected
- 80% recurrence in infants of same mom
- In-utero cirrhosis, begins at 24 weeks
- Iron deposits throughout body
- Many stillborn
Recognizing NH
- IUGR, oligohydramnios always present
- Fetal distress
- Liver failure within days of birth
- >80% mortality
- Hypoglycemia, ↑↑ Bilirubin, ↓ albumin
- Significant coagulopathy, ↓ factor V, VII
- Minimal/no elevation in AST/ALT
- Ferritin >800 ng/ml, AFP > 200 ng/ml
- Diagnose with MRI (iron) and buccal Bx

Treating NH
- Controversial antioxidant/chelation blend
- NAC, Selenium, PGE-1, Vitamin E, Desferoxamine (chelator)
- Liver transplant often needed if severe
- If survive, no long term liver effects
- Subsequent pregnancies - IVIG for mother starting at 18 weeks, some success.

Disseminated HSV infection
- Early recognition and treatment are key!
- HSV acquired in utero, peri or postnatal
- Sepsis like picture by day 5-7
- Normal preterm history, U/S, Term birth
- Not IUGR, normal APGAR
- Poor feeding, lethargy, fever, +/- jaundice
- All with ↑↑ ALT, INR
- Many with no lesions or parental HSV Hx

HSV Diagnosis/Treatment
- With any sepsis like picture, treat first
- Initiate IV acyclovir up to 60mg/kg/d
- Decreased mortality
- Send oral/eye/vesicular swab for culture
- Blood for HSV PCR

Shock Liver/Ischemic Liver Failure
- Can be 2° to birth trauma, fetal distress, cardiac lesions, hypoxemia
- Fetal/neonatal liver susceptible to ischemia
- Ductus venosus stays open in hypoxemia
- Blood shunted away from liver
- ↑↑ AST/ALT + INR - improves rapidly
- Delayed, prolonged cholestasis/jaundice
- Hepatomegaly/ascites
- Resolves with supportive care

Metabolic Disease
- Galactosemia - lack of G-1 PUT enzyme
- Cannot metabolize galactose from lactose
- Breast milk or most formulas become toxic
- Lethargy, hypoglycemia, vomiting, liver failure, jaundice, E coli sepsis, cataracts symptoms appear within days of birth
- Early suspicion and switch to soy formula can be life saving.
- Can detect + reducing substances in urine
- Confirm with enzyme analysis/ NBS
Metabolic Disease

- **Hereditary Fructose Intolerance**
- Can present similar to galactosemia but no E coli sepsis or cataracts.
- Only in infant getting formula w sucrose
- Test is for aldolase B gene/activity.