Hyperbilirubinemia in the Newborn by Alex Rabinovich

Definition
Jaundice is the yellowish discoloration of the skin, sclera, and/or mucous membranes caused by tissue deposition of bilirubin.

Epidemiology
• 60% of term newborns and 80% of preterm newborns have jaundice. Nearly all newborns will develop physiologic jaundice within the first 2 weeks of life.

Pathogenesis
Bilirubin metabolism
• 80-90% of bilirubin comes from hemoglobin breakdown from RBC. The remaining 10-20% comes from heme-containing proteins.
  - Heme → CO + Biliverdin
    o enzyme: Heme oxygenase
    o location: Spleen, Liver
  - Biliverdin → Unconjugated Bilirubin
    o enzyme: Biliverdin reductase
    o location: Plasma
• Unconjugated Bilirubin → Conjugated Bilirubin
  o enzyme: UGT (conjugates bilirubin with glucuronic acid)
  o location: Liver
  o purpose: conjugated bilirubin stored in biliary system, and excreted into intestines and via urine.
• Conjugated Bilirubin → Urobilinogen + Stercobilin
  o enzyme: Bacterial enzymes
  o location: Intestines
  o purpose: excretion via stool (BROWN color) or urine (only deconjugated bilirubin = Dark urine color)
• Conjugated Bilirubin → Unconjugated Bilirubin
  o enzyme: Beta Glucuronidase
  o location: Intestines
  o purpose: Reabsorption via Enterohepatic Circulation

Physiologic Jaundice
• An increase in unconjugated bilirubin that is caused by either: Increase Bilirubin Production, Decreased Bilirubin Clearance, or Increased Enterohepatic Circulation.
  a) increased turnover of neonatal RBC (shorter RBC lifespan)
  b) decrease in UGT activity
  c) increased beta-glucuronidase activity and decreased intestinal bacteria concentration

Pathologic Jaundice
• Jaundice in the first 24 hours of extrauterine life.
• STB > hour specific 95%ile from figure 1.
• Conjugated Bilirubin > 25.6 – 34.2 umol/L
• Rate of STB rise > 3.4 umol/L per hour
• Jaundice of 2 wks of age in TERM newborn

Normal Ranges for Bilirubin:
Unconjugated
- Birth – 2 days < 130 umol/L
- 3 – 5 days < 200 umol/L
- > 1 month < 17 umol/L
Conjugated
- Neonates < 10 umol/L
- Others < 2 umol/L
Albumin-Conjugated (Delta)
- > 14 days < 3 umol/L

1 mg/dL is approximately 17.2 umol/L

Conjugated Bilirubin is Water Soluble and is NOT reabsorbed by intestinal epithelial cells.

Unconjugated Bilirubin is Fat Soluble and is easily absorbed by intestinal epithelium and phospholipids membranes (BBB, Skin, Sclera etc.).

Unconjugated is toxic to cells.
Approach to Hyperbilirubinemia

Conjugated

a) Hepatic
1. Infectious (Sepsis, Hep B, TORCH - Toxoplasmosis, Other (syphilis), Rubella, Cytomegalovirus, HSV)
2. Metabolic (galactosemia, tyrosinemia)
3. Drugs
4. TPN (total peripheral nutrition ?)
5. Idiopathic

b) Post-Hepatic
1. Biliary atresia
2. Choledochal cyst
3. Bile duct obstruction

Unconjugated

a) Physiologic
(Occurs in nearly all newborns and resolves within the first several weeks of life)

b) Pathologic
1. Hemolytic
   a. Immune
      i. ABO incompatible
      ii. Rh incompatible
      iii. Kell, Duffy Cells, etc …
   b. Non-Immune
      i. Splenomegaly
      ii. Sepsis
      iii. AV malformation
      iv. Spherocytosis
      v. Elliptocytosis
      vi. G6PD deficiency
      vii. Pyruvate Kinase deficiency
      viii. Alpha thalassemia
2. Non-Hemolytic
   a. Hematoma
   b. Polycythemia
   c. Sepsis
   d. Breast Milk
   e. Hypothyroidism
   f. Infant of Diabetic Mother
   g. Gilbert’s (UGT enzyme disorder, decrease clearance)
   h. Crigler-Najjar (UGT enzyme disorder, decrease clearance)

Increase Production
- ABO, RH incompatibility
- Spherocytosis, Elliptocytosis
- G6PD
- Increased Hemoglobin production
- Polycythemia
- Hemorrhages
- IDM
- Sepsis

Decreased Clearance
- UGT enzyme problems
- Hypothyroidism
- Galactosemia

Increased Enterohepatic Circulation
- Breastfeeding failure jaundice
  o Decreased caloric intake →
  o Increased enterohepatic circulation
  o Cessation of breastfeeding reduces STB significantly. ??? - controversial
  o May also be due to dehydration?
- Breast milk jaundice
  o A component in milk that increases enterohepatic circulation. ?
- Impaired intestinal motility (obstruction)

Risk Factors
- Maternal Diabetes
- Asian and Native Race
- Prematurity (GA < 37 wks)
- Altitude
- Polycythemia
- Male Sex
- Breast feeding
- Weight Loss
- Sibling with PHx of Jaundice
- BW < 2.5 kg
- Sepsis
- Delayed pass of meconium
- Low serum albumin < 25 g/L
- Blood group incompatible
- Drugs
- Metabolic/Resp Acidosis

On examination
- Extent of Jaundice
- Bruising
- Weight Loss/Dehydration
- Color of Stool and Urine

Laboratory Tests / Investigations
- CBC (Hb, Retic)
- Bilirubin (total and unconjugated)
- Coombs test
- Electrolytes
- Albumin levels
- Culture Screen
- Hematology smear
- G6PD screen
- LFT
- TSH
- End tidal Carbon Monoxide
- CXR

Clinical Features
- Yellowing skin from head to toe
- Sclera icterus @ values of 103-137 umol/L
- Palms and Soles jaundiced @ values of 205-222 umol/L
- Pallor
- Hematoma
- Hepatosplenomegaly
**Kernicterus**

- Deposition of unconjugated bilirubin in brain cells causing necrosis (Basal Ganglia, Thalamus, Cerebellar Nuclei, Cranial Nerve Nuclei – oculomotor, auditory) = Bilirubin Encephalopathy
- Occurs when not enough Albumin to bind bilirubin, hence free unconjugated bilirubin can pass the BBB.

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Lethargy</td>
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<td>Poor sucking</td>
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**Prognosis**

- Good if treated early
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**Management**

1. If STB is above 95%ile on nomogram within the first 24 hours of extrauterine life, consult specialist (likely hemolytic, sepsis)
2. Follow the table below for hour specific STB guidelines from nomogram in figure 1.

<table>
<thead>
<tr>
<th>STB at Discharge</th>
<th>Action</th>
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<tbody>
<tr>
<td>&lt; 40%ile</td>
<td>D/C with visual check in 48 hrs</td>
</tr>
<tr>
<td>40 – 95%ile</td>
<td>Clinical Evaluation</td>
</tr>
<tr>
<td></td>
<td>D/C with mandatory bilirubin check in 24-48 hrs</td>
</tr>
<tr>
<td>&gt; 95%ile</td>
<td>1. Clinical Evaluation</td>
</tr>
<tr>
<td></td>
<td>2. Delay D/C</td>
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<td></td>
<td>3. Phototherapy or Exchange Transfusion</td>
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4. Initiate **Phototherapy** if needed with the below protocol
   - Phototherapy promotes the conversion of unconjugated bilirubin to conjugated bilirubin via photoisomerization.
     - The converted products are easily excreted and are less toxic to tissues.
   - Should NOT be used in hyperbilirubinemia due to increased conjugated bilirubin (Bronze Baby effect)
   - S/E: Hypernatremia via dehydration, Eye Damage, Skin Discoloration, Loose Stools,

   Phototherapy depended on BW and Hourly STB (detailed guidelines found in L2N Handbook of Guidelines)

<table>
<thead>
<tr>
<th>Age (hr)</th>
<th>Photo in infants with no RF</th>
<th>Photo in infants with RF</th>
<th>Exchange if Photo Fails</th>
<th>Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>Pathologic Cause → further investigations with specialist required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-48</td>
<td>170-260</td>
<td>140-225</td>
<td>340</td>
<td>430</td>
</tr>
<tr>
<td>49-72</td>
<td>260-310</td>
<td>225-270</td>
<td>430</td>
<td>510</td>
</tr>
<tr>
<td>&gt;72</td>
<td>&gt;310</td>
<td>&gt;270</td>
<td>430</td>
<td>510</td>
</tr>
<tr>
<td>&gt; 2wks</td>
<td>Should be further investigated</td>
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- Initiate **Plasma Exchange** therapy with the same guidelines as outlined in the L2N Handbook
  - Rapidly eliminates bilirubin from the circulation
  - Bilirubin and Electrolytes are measured regularly
  - Complications: Graft vs. Host Disease, Thrombocytopenia, Portal Vein Thrombosis, Electrolyte Imbalance
  - Reserved for patients with HEMOLYTIC hyperbilirubinemia

5. IV IG may reduce the need for Exchange Transfusion by inhibiting hemolysis.

**References**

2. UpToDate
   a. “Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn”.
   b. “Clinical features and management of unconjugated hyperbilirubinemia in term infants”.
   c. “Bilirubin metabolism”.
5. “In House Guidelines”. Level 2 Nursery, McMaster University Medical Centre.