Hyperbilirubinemia in the Neonate: Risk Assessment, Screening and Management

Second Edition
Objectives

- Summarize the mechanisms of bilirubin production and clearance
- Describe a systematic process to assess and monitor neonatal hyperbilirubinemia
- Identify infants at risk for severe hyperbilirubinemia
- Identify prevention strategies for at-risk infants
- Describe the recommended treatment modalities for severe hyperbilirubinemia
- Summarize the current consensus guidelines for early intervention, treatment, and follow-up of neonates at risk for severe hyperbilirubinemia
- Identify resources for staff and family education related to neonatal jaundice and hyperbilirubinemia
Hyperbilirubinemia
**Bilirubin Production**

Erythrocyte

- Hemoglobin
  - Tissue Heme
  - Hemoglobin (20%)
  - Erythrocyte Hemoglobin
    - Heme Oxygenase
      - Iron - (iron pool for recycling)
      - CO - Carbon Monoxide ---- pulmonary excretion
    - Heme (80%)
  - Globin - amino acid pool for recycle

- Biliverdin
  - Bilirubin Reductase
  - Unconjugated Bilirubin + Serum albumin

- Reticulo-endothelial System

- Liver
**Types of Bilirubin**

- **Conjugated - direct**
  - Water-soluble
  - Easily excreted in urine and stool
  - Less toxic form
  - Requires $O_2$ and glucose

- **Unconjugated - indirect**
  - Fat or non-water soluble
  - Potentially more toxic
  - Bound vs. unbound to albumin

Clinical management decisions are based on total serum bilirubin levels (by heel-stick sampling).
Bilirubin Clearance

Liver → Bilirubin glucuronide (conjugated bilirubin) → β-glucuronidase → Unconjugated Bilirubin → Enterohepatic Circulation

Unconjugated Bilirubin → Bilirubin in Stools → Gastro-intestinal tract
Development of Severe Hyperbilirubinemia

- **Increase in bilirubin production**
  - Such as Rh, ABO incompatibility, G6PD deficiency, septicemia, extravascular blood, polycythemia

- **Decrease in bilirubin excretion**
  - Bowel obstructions, hereditary defects, hypothyroidism

- **Combination of both**
  - Seen in prematurity, infection, G6PD deficiency
Increases in Bilirubin Production: Hemolysis

- Genetic factors
  - G6PD deficiency
  - Erythrocyte enzymatic defects

- Antibody mediated
  - Rh/ABO incompatibility

- Acquired hemolytic disorders
  - Infection
  - Drugs

- Additional cause
  - Polycythemia
  - Maternal diabetes
  - Extravasation of blood
Decrease in Bilirubin Excretion

- Increased enterohepatic circulation
  - Bowel obstructions
- Maternal liver disease
- Hereditary defect
  - Crigler-Najjar, Lucey-Driscoll
- Hypothyroidism
- Hypopituitarism
Combination of ↑ Production & ↓ Excretion

- Prematurity
- Infection
  - Bacterial sepsis, viral, protozoal
- G6PD deficiency
Major Risk Factors for Severe Hyperbilirubinemia

- Pre-discharge TSB/TcB in the high-risk zone
- Jaundice observed in the first 24 hours
- Blood group incompatibility, other known hemolytic disease
- Gestational age 35-36 weeks
- Previous sibling received phototherapy
- Exclusive breastfeeding
- Bruising/cephalohematoma
- Asian race
Risk Factors for Severe Hyperbilirubinemia (con’t)

- **Minor risk factors**
  - Pre-discharge TSB/TcB in the high-intermediate risk zone
  - Gestational age 37-38 weeks
  - Jaundice observed before discharge
  - Male gender
  - Maternal age ≥25 years

- **Decreased risk**
  - TSB/TcB in the low-risk zone
  - Gestational age ≥41 weeks
  - Exclusive bottle feeding
  - Black race
  - Discharged from hospital after 72 hours

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Causes of Lactation Failure

- Lack of clinician-initiated education
- Lack of on site certified consultants
- Lack of documentation of infant latching
- Inadequate measure of milk transfer
- Inappropriate follow-up and record of urine and stool pattern changes
Hour-Specific Bilirubin Nomogram
Early Onset of Severe Hyperbilirubinemia

- Early Onset
  - TSB/TcB values are >75th percentile prior to 72 hours of age
  - Acute/rapid rise in TSB/TcB
  - ↑ risk for potential adverse events
  - Frequent causes: ABO, Rh incompatibility
Late Onset Hyperbilirubinemia

- Late Onset
  - TSB/TcB values >95th percentile beyond 72 hours of age
  - Frequent causes: Breast-fed infants with G6PD deficiency, familial, or ethnic risk factors
  - Need follow-up monitoring at the time of discharge
# Potential Neurotoxicity of Bilirubin

<table>
<thead>
<tr>
<th>Postnatal Age</th>
<th>Bilirubin levels*</th>
<th>Why this level can be dangerous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any age</td>
<td>Any jaundiced baby with any neurological signs suspicious for bilirubin induced neurodysfunction (BIND)</td>
<td>Any baby with signs suspicious for BIND must be assumed to have severe hyperbilirubinemia until proven otherwise</td>
</tr>
<tr>
<td>Over 72 hours age</td>
<td>TSB &gt;99.9&lt;sup&gt;th&lt;/sup&gt; percentile (correlates to TSB ≥ 25 mg/dl)</td>
<td>These TSB levels may exceed the binding ability of serum albumin and the neurotoxicity risk increases exponentially</td>
</tr>
<tr>
<td></td>
<td>TSB &gt;95&lt;sup&gt;th&lt;/sup&gt; and &lt;99.9&lt;sup&gt;th&lt;/sup&gt; percentile (correlates to TSB of 17 and 25 mg/dl)</td>
<td>Low levels of albumin (&lt;3.4 g/dl) can be seen in term newborns and, more commonly near-term or bruised infants</td>
</tr>
<tr>
<td>Less than 72 hours age</td>
<td>TSB &gt;95&lt;sup&gt;th&lt;/sup&gt; percentile and postnatal age</td>
<td>During the first 72 hours, the binding ability of albumin is compromised and lower TSB levels may be potentially neurotoxic</td>
</tr>
<tr>
<td></td>
<td>TSB &gt;75&lt;sup&gt;th&lt;/sup&gt; percentile and a rate of rise &gt; 0.20 mg/dl/hour</td>
<td>An increase in bilirubin load at &gt; 1 mg per 5 hours or ~ 5 mg/day is likely to result in a TSB &gt;95&lt;sup&gt;th&lt;/sup&gt; percentile and may reach neurotoxic levels</td>
</tr>
</tbody>
</table>
Risk of Bilirubin Entry

These conditions ↑ neurotoxicity by:
- ↓ Bilirubin-albumin binding
- ↓ Brain blood flow
- Disrupting the blood-brain barrier

- Asphyxia
- Prematurity
- Hypoalbuminemia
- Bilirubin-displacing drugs
- Hyperosmolality
- Hypercarbia
- Acidosis
- Hypoxic injury
# Clinical Progression of Bilirubin Encephalopathy

<table>
<thead>
<tr>
<th>Clinical Evaluation</th>
<th>Non-specific, Subtle</th>
<th>Progressive Toxicity</th>
<th>Advanced Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mental Status</strong></td>
<td>Sleepy + poor feed</td>
<td>Lethargy + irritability</td>
<td>Semi-come or seizures</td>
</tr>
<tr>
<td><strong>Muscle Tone</strong></td>
<td>Slight Decrease</td>
<td>Hyper- or hypotonia depending on arousal state or Mild Nuchal / Truncal arching</td>
<td>Markedly increased (oposthotonus) or, decreased tone or, bicycling movements</td>
</tr>
<tr>
<td><strong>Cry</strong></td>
<td>High-pitched</td>
<td>Shrill</td>
<td>Inconsolable</td>
</tr>
</tbody>
</table>
Reasons for Re-emergence of Kernicterus

- Early discharge
- Lack of concern about jaundice
- Over-reliance on visual assessment
- Birubin test considered as a healthcare cost
- Limited experience with severe jaundice
- Clinicians were not consistently using the AAP practice guidelines
Case Presentation, Cal

- BW: 2863g
- Gestation: 37 wks
- D.O.B.: 3/23 @ 2352
- Discharge: 36 hrs of age
- Breastfeeding
- Blood type-mom: O Rh+
- Blood type-infant: A Rh+
Case Presentation, Cal

Age 4 days: very sleepy, poor feeding, “yellow to toes,” seen by MD

7% wt loss, No TSB done
2 calls to MD overnight

Age 5 days: seen in office and admitted for signs of lethargy, poor feeding

TSB=34.6 mg/dl
Double phototherapy X 3 days
No exchange transfusion
JCAHO Sentinel Alert on Kernicterus

1st issued May of 2001 to hospitals in the United States

- Prompted by an increase in number of reported cases
- Cited risk factors, root causes, risk reduction strategies, and follow-up recommendations

Re-issued July 2004 to hospitals in the United States

- Recommended updated AAP guidelines be followed
Key Recommendations to Reduce Severe Hyperbilirubinemia

- Promote & support breastfeeding
- Establish institutional protocols to identify & evaluate all infants
- Obtain TSB/TcB levels on jaundiced infants in the 1st 24 hrs
- Visual estimations can lead to errors
- Use age in hours to interpret TSB/TcB levels
- Infants <38 weeks & breastfeeding are at higher risk
- Perform systematic risk assessment at time of discharge
- Give written and verbal information to parents about jaundice
- Utilize phototherapy and exchange transfusion when indicated
- Provide appropriate follow-up based on risk assessment

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Assessment Techniques

- **Visual**
  - Most widely used method
  - Cephalocaudal progression

- **BUT**
  - Not reliable
  - Not accurate
Assessment Techniques

- **Total Serum Bilirubin Levels (TSB)**
  - Primary test and monitoring method
  - Unrestricted ability to obtain the test
  - Universal bilirubin testing
  - Evaluate by infant’s age in hours
Assessment Techniques

- Transcutaneous Bilirubin Measurement (TcB)
  - Non-invasive
  - More accurate than visual assessment
  - Facilitates home and clinic follow-up
Assessment Techniques

TSB monitoring remains the primary diagnostic test to accurately identify bilirubin levels, and TSB levels must be determined prior to beginning any treatment.
Assessment Techniques

End-Tidal Carbon Monoxide Measurement (ETCOc)

- Rapid
- Non-invasive
- Rules out hemolysis as a contributor to jaundice
- The only clinical test that provides information about the rates of heme catabolism and bilirubin production

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Clinical Vigilance Can Prevent the Worst

Consider these factors when assessing for discharge:

1. Visual assessment of jaundice
2. Evaluation of clinical risk factors
3. Universal TSB/TcB evaluation
4. Hour-specific bilirubin designation of risk
5. Evaluation of hemolysis if TSB >75th percentile
Management Techniques
Supporting Lactation

- Prenatal breastfeeding education
- Supportive hospital routines
- Evaluation of breastfeeding technique
- Identification of lactation risk factors
- Intervention for breastfeeding problems
- Early follow-up assessment of lactation and infant weight
Management Techniques

Phototherapy
Management Techniques

Phototherapy (con’t)

Phototherapy units should allow for maximum adsorption of bilirubin in a range from 420-480 nm.
Management Techniques
Phototherapy (con’t)

- Adverse Effects
  - Dehydration
  - Lack of visual-sensory input in animals
  - Watery diarrhea
  - Skin rashes
  - Hyperthermia
  - \(\downarrow\) maternal-infant interaction

- Syndromes
  - Bronze Baby Syndrome (in case of direct hyperbilirubinemia)
  - Vulnerable Child Syndrome

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Management Techniques
Exchange Transfusions

- **Absolute indications:**
  - Signs of Acute Bilirubin Encephalopathy (intermediate or advanced)
  - Hazardous TSB levels >30 mg/dl (in infants with no risk factors) or >23 mg/dl (with higher risk factors)
  - Failure of intensive phototherapy for infants with severe hyperbilirubinemia (substantial decline in bilirubin after 3-4 hours, such as >2 mg/dl in 4 hours)
  - Onset of any clinical neurologic signs in infants with excessive hyperbilirubinemia
Emerging Research: Bilirubin as Natural Antioxidant

- Potent antioxidant when bound to albumin
- Protective component for the body
- May provide primary protection from ischemia-related injuries and retinopathy of prematurity
- Antioxidant effect not fully understood
## Therapies Under Investigation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolic Process</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tin protoporphyrin</td>
<td>Heme degradation</td>
<td>Heme-oxygenase inhibitor</td>
</tr>
<tr>
<td>Zinc or Tin mesoporphyrin</td>
<td>Alternate heme catabolism</td>
<td>Heme excreted in bile (currently in US studies)</td>
</tr>
<tr>
<td>Agar, Charcoal</td>
<td>↓ Enterohepatic</td>
<td>Sequester bilirubin circulation in bowel (used outside the US)</td>
</tr>
<tr>
<td>Homeopathic Agent</td>
<td>Metabolic Process</td>
<td>Mechanism</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Bilirubin Oxidase</td>
<td>↓Enterohepatic circulation</td>
<td>Degrade bilirubin in gut</td>
</tr>
<tr>
<td>Herbal products</td>
<td>Usually cathartics</td>
<td>Increase stool excretion</td>
</tr>
</tbody>
</table>
Follow-up Care Map

Risk Assessment

Evaluation:
Bili workup

Bili Follow-up 24hrs

Bili Follow-up 48hrs

95th %ile

75th %ile

40th %ile

Visual follow-up

Serum Bilirubin (mg/dl)

High Risk Zone

Low Risk Zone

Postnatal Age (hours)

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Association of Women's Health Obstetric and Neonatal Nurses
Use a System Approach

- **Prenatal education** through post discharge evaluation

- **Inpatient**
  - Evaluate jaundice with vital signs
  - Corroborate with TcB/TSB
  - Peer-review of cases with TSB >25 mg/dl

- **Post discharge follow-up**
  - Risk-based and/or TSB/TcB

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Your Role as the Nurse Includes

- Supporting and teaching breastfeeding
- Identifying and monitoring jaundice
- Coordinating discharge planning for at-risk infants
- Assuring proper treatment
- Educating parents
- Partnering with other healthcare professionals through a multidisciplinary team
Further Information Available From

- AWHONN
- CDC
- JCAHO
- AAP
- PICK
- Cochrane Library
- AHRQ
Make a Difference by Using Evidence in Your Nursing Practice