HYPERBILIRUBINEMIA
Neonatal Protocol Implementation

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Hyperbilirubinemia

Objectives

- Review the consequences of hyperbilirubinemia
- Review pathophysiology of hyperbilirubinemia
- Review most common etiologies
- Review new and not so new diagnostic tools
- Review current therapies and recommendations
- Discuss the health care professional’s role in preventing kernicterus
Hyperbilirubinemia - Why do we care?

- Kernicterus is BAD!
- Public Cares
- JCAHO Cares
- Lawyers Care
Hyperbilirubinemia
Kernicterus

- KERNICTERUS/Bilirubin encephalopathy
  - Pathologic findings
    - yellow staining of basal ganglia and other brain stem nuclei
    - neuronal necrosis is dominant histopathologic feature
Kernicterus (Bilirubin Encephalopathy) - 1984 to 2000

- 100 cases documented in 15 years
- 98% breastfed (2 formula fed were G6PD deficient)
- Discharge age 12-75 hrs
- 33% < 37 weeks

(Johnson et al. J Pediatrics 2002;140:396-403)
Hyperbilirubinemia
Kernicterus
Hyperbilirubinemia
Kernicterus

MRI
Clinical Presentation of Acute Bilirubin Encephalopathy

- Initial Phase
  - slight stupor (lethargy, sleepiness)
  - slight hypotonia
  - poor sucking, slightly high pitched cry

- Intermediate Phase
  - Moderate stupor, irritability
  - Variable tone (usually hypertonic, some with retrocollis-opisthotonos)
  - Minimal feeding, high-pitched cry

- Advanced Phase
  - Deep stupor to coma
  - Tone usually hypertonic with opisthotonos
  - No feeding, shrill cry
Hyperbilirubinemia
Kernicterus
Hyperbilirubinemia
Chronic bilirubin encephalopathy

- Chronic Bilirubin Encephalopathy
  - Extrapyramidal, abnormalities (athetosis)
  - Gaze abnormalities
  - Hearing disturbances
    - Brain Stem Audiometric Evoked Response
  - Intellectual deficits, but minority in mentally retarded range
- This is the one cause of CP we can prevent!!!!!
Jaundice in newborns
common but dangerous

WASHINGTON (AP) — Susan Sheridan recalls frantically rac-
ing her days-old son to doctor
after doctor because his skin was
so yellow — only to be assured
that jaundice is a rite of infancy.
But as pediatricians looked on,
the baby’s neck suddenly arched
backward and he began a
strangely high-pitched, catlike
howl.

“We all watched Cal suffer
brain damage before our eyes,”
said Sheridan.

Jaundice strikes 60 percent of
newborns as their livers slowly
begin functioning in the first
days of life. The vast majority re-
cover easily. But a few suffer ex-
treme jaundice that, if untreated,
dramatically damages their brains.
Like Cal Sheridan, now 8, they’re
left with a severe type of cere-
bral palsy — his intellect un-
touched but trapped behind un-
working muscles — or injuries
such as hearing loss.

His disability was prevent-
able, once thought virtually van-
quished. Nobody knows how
many babies still are harmed.
But, spurred on by Sheridan and
other parents, federal health of-
icials and a pediatricians’ group
are preparing new campaigns to
protect babies from jaundice-
caused brain damage and track
See Jaundice: Page 2

Susan Sheridan’s son, Cal,
suffers from cerebral palsy
caused by jaundice.
Hyperbilirubinemia
Public Concerns

- **PICK** (Parents of Infants and Children with Kernicterus)
  - Advocacy, educational and support group
  - Instrumental in drawing attention to reemergence of kernicterus and its prevention
Hyperbilirubinemia
JCAHO Concerns

- JCAHO Sentinel Event ALERT
  - April 2001
  - Identified:
    - Risk factors
    - Root causes
      - Failure to evaluate in first 24 hours
      - Failure to interpret level in age of hours not days
      - Failure to have nursery protocol
      - Evaluating level visually
  - Risk reduction strategies
Hyperbilirubinemia

- Education is the first defense for preventing kernicterus!!

- Nurses, parents, and physicians all need to be aware of the risk of hyperbilirubinemia
Peak

- **full term** - average peak at 6-8 mg/dL on day 3
- **preterm** - average peak at 10-12 mg/dL on day 5
- infants of Asian and Native American descent have higher peak bilirubin values
Hyperbilirubinemia

- Physiologic Jaundice
  - Factors contributing to physiologic jaundice
    - greater number and shorter lifespan of RBCs
    - decreased ability to conjugate bilirubin
    - decreased ability to excrete bilirubin/increased enterohepatic circulation
    - method of feeding
Hyperbilirubinemia

Factors that r/o diagnosis of physiologic jaundice

- sick baby
- jaundice in first 24 hrs
- increase of more than 5 mg/dL per day
- direct bili > 1.5
- Indirect level > 12
Hyperbilirubinemia Pathophysiology

- Three mechanisms of pathophysiology
  - Increased bilirubin load
  - Impaired clearance
  - Increase in enterohepatic circulation
Causes of Hyperbilirubinemia in Kernicterus Registry

- Idiopathic 37%
- Hemolysis 14%
- G6PD deficiency 25%
- Other 23%
Hyperbilirubinemia
Increased Bilirubin Load

- Hemolytic Disease
  - Immune
    - Rh, ABO, other antibodies
  - Hereditary Red Cell Disorders
    - Sickle Cell, spherocytosis
  - Congenital Enzyme deficiencies
    - G-6-PD
    - Galactosemia

- Extravascular blood
  - cephalahematomas, ICH, bruising, swallowed blood

- Polycythemia
  - Twin to twin transfusion, maternal-fetal hemorrhage, SGA, delayed cord clamping

- PRBC transfusions
- Infection
Hyperbilirubinemia
Impaired Clearance

- Prematurity
- Metabolic/endocrine disorders
  - Crigler-Najjar
  - Gilbert’s
  - Tyrosinemia
  - hypothyroidism
  - hypopituitarism
- Medications
  - benzyl alcohol, some cephalosporins
- Alterations in hepatic function
  - hypoxia, hypothermia, sepsis
Hyperbilirubinemia
Increased EHC

- Increased Enterohppheric Circulation
  - Breast milk jaundice
  - Congenital anomalies
    - Pyloric stenosis
    - Intestinal obstruction
  - Delayed passage of meconium
    - meconium ileus, plug
Hyperbilirubinemia

- Breastfeeding vs Breast milk Jaundice
  - Breast feeding jaundice
    - early onset
    - usually relates to inadequate caloric intake in first few days of life resulting in increased EHC
  - Breastmilk jaundice
    - late onset - usually appears after first week
    - may persist for weeks or months
    - breast milk may hormonally affect conjugation and excretion of bilirubin
Hyperbilirubinemia
Diagnosis

- Diagnosis
  - VISUAL INSPECTION – NOT RELIABLE
  - TRANSCUTANEOUS
  - ETCO
  - LABORATORY TESTS
Hyperbilirubinemia Diagnosis

- **Visual Assessment** by experienced attending pediatricians to differentiate
  - No Jaundice
  - Moderate Jaundice
  - Marked Jaundice

- Shown to be poorly correlated to serum bilirubin values
  - (Davidson LT, Am J Dis Child 61:958-980, 1941)
Hyperbilirubinemia Diagnosis

- Non-invasive Measurement
  - Transcutaneous
    - BiliCheck™ (Respironics)
    - Minolta HM-103
  - ETCO monitoring
Hyperbilirubinemia
Lab Evaluation

LABORATORY EVALUATION

- T/D Bili
- Blood Type
- Coombs
- CBC and Retic Ct
- Newborn screens
- Smear
- Liver Enzymes
- Viral/Bacterial Cultures
- Serum Albumin
- G6PD screening
- Other tests for inborn errors
Hyperbilirubinemia

Treatment

- Treatment
  - Phototherapy
  - IVIG
  - Exchange Transfusion
  - Appropriate post discharge follow-up
**Hyperbilirubinemia Treatment - OLD**

**Guidelines for Phototherapy**

### TABLE 20.8
**GUIDELINES FOR THE USE OF PHOTOTHERAPY IN PRETERM INFANTS <1 WEEK OF AGE**

<table>
<thead>
<tr>
<th>Weight (g)</th>
<th>Phototherapy</th>
<th>Consider exchange transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>500–1000</td>
<td>5–7</td>
<td>12–15</td>
</tr>
<tr>
<td>1000–1500</td>
<td>7–10</td>
<td>15–18</td>
</tr>
<tr>
<td>1500–2500</td>
<td>10–15</td>
<td>18–20</td>
</tr>
<tr>
<td>&gt;2500</td>
<td>&gt;15</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

*Bilirubin values in milligrams per deciliter.

### TABLE 20.7
**MANAGEMENT OF UNCONJUGATED HYPERBILIRUBINEMIA IN THE TERM NEWBORN**

<table>
<thead>
<tr>
<th>Age (hr)</th>
<th>Consider phototherapy</th>
<th>Phototherapy</th>
<th>Exchange transfusion if intensive phototherapy fails</th>
<th>Exchange transfusion and intensive phototherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>25–48</td>
<td>≥12 (170)*</td>
<td>≥15 (260)</td>
<td>≥20 (340)</td>
<td>≥25 (430)</td>
</tr>
<tr>
<td>49–72</td>
<td>≥15 (260)</td>
<td>≥18 (310)</td>
<td>≥25 (430)</td>
<td>≥30 (510)</td>
</tr>
<tr>
<td>&gt;72</td>
<td>≥17 (2900)</td>
<td>≥20 (340)</td>
<td>≥25 (430)</td>
<td>≥30 (510)</td>
</tr>
</tbody>
</table>

*Values in parentheses are mcmol/L.

Data from American Academy of Pediatrics, Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia. 10.
Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation

- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316
Hyperbilirubinemia

Exchange Transfusion

- Exchange Transfusion

  - Purpose is to prevent kernicterus
  - Complications

    - cardiac arrest, air embolism, thrombocytopenia, portal vein thrombosis, NEC, electrolyte imbalances, GVHD, infection
Hyperbilirubinemia
Pharmacological/Other Treatment

• Pharmacological
  • IVIG

• Other
  • Adequate IV therapy for dehydration
  • Frequent feeds
  • Glycerin
Hyperbilirubinemia

- Should you supplement breastfed newborns with water?
  - NO!
- Serum bilirubin levels are higher in infants supplemented with water or dextrose than unsupplemented infants
Don’t Water the Babies!!!
Do Feed Babies

- The more times a baby breast feeds in the first 24 hours the less likely their serum bilirubin will be >15mg/dL on Day 6
  
  Yamauchi, *Pediatrics* 1990;86:171
Hyperbilirubinemia
Risk Assessment

- Risk factors for development of severe hyperbilirubinemia
  - predischarge bilirubin above 75th percentile (Bhutani’s chart)
  - jaundice observed in first 24 hours
  - blood group incompatibility, positive DAT
  - G6PD deficiency
  - gestational age < 38 weeks
  - previous sibling with jaundice
  - cephalhematoma or significant bruising
  - exclusive breast feeding
  - East Asian race
### Risk Assessment

**Figure 1.** Hour-specific bilirubin nomogram with the predictive ability of the predischarge bilirubin value for subsequent severe hyperbilirubinemia, >95th percentile tract.

**Table**: Risk of severe hyperbilirubinemia in different risk zones.

<table>
<thead>
<tr>
<th>Risk-zone</th>
<th>Percentiles</th>
<th>Probability of severe hyperbilirubinemia</th>
<th>Likelihood Ratio of severe hyperbilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-</td>
<td>&gt;95th</td>
<td>2/5</td>
<td>14.08</td>
</tr>
<tr>
<td>Upper-Int.</td>
<td>76-95th</td>
<td>1/8</td>
<td>3.20</td>
</tr>
<tr>
<td>Lower-Int.</td>
<td>40-75th</td>
<td>1/46</td>
<td>0.48</td>
</tr>
<tr>
<td>Low-</td>
<td>&lt;40th</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1/23</td>
<td>1</td>
</tr>
</tbody>
</table>

Bhutani, V. J of Perinatology, 2001: 21:S78
Hyperbilirubinemia
AAP Guidelines

- Promote and support successful breastfeeding
- Establish nursery protocol for assessment of jaundice
  - Include nursing judgement for TSB/TcB without physician order
- Measure TSB if jaundice in first 24 hrs
- Interpret TSB levels according to the infant’s age in hours NOT DAYS
- Visual estimation of jaundice can lead to errors
- Perform systematic risk assessment on all infants prior to discharge
Hyperbilirubinemia
AAP Guidelines

- Infants < 38 weeks gestation, particularly if breastfed, are high risk
- Provide parents both written and oral information
- If there is any doubt, a TSB or TcB level should be done
- Provide follow-up for all infants, especially those discharged before 72 hrs of age
- An infant whose bilirubin is > 25 should be treated immediately
Follow-up

- “If a newborn is discharged at < 36 hours of age, the bilirubin level can only be going in one direction”
- “We recommend follow-up of the infant discharged before 72 hours within 2 days”

Jeffrey Maisels, NeoPrep, Sept 2005
Hyperbilirubinemia Assessment
Hospital ID: __________________________________

NPQIC Page 1 of 1

Instructions: Please complete this form in full and, when finished, click the 'Save Record' button and select 'Complete' from the drop-down list at the bottom of the form.

1. Does your hospital have a transcutaneous bilimeter?
   Yes No

2. Does your hospital have a policy, protocol or order-set which addresses neonatal hyperbilirubinemia assessment?
   Yes No

3. Which of these components does it include? (check as many as applicable)
   - Bilirubin level measured at 12 hours of age
   - Bilirubin level measured at 24 hours of age
   - Bilirubin level measured at 48 hours of age
   - Bilirubin level measured prior to discharge if discharge prior to 48 hours of age
   - Nomogram used to determine if bilirubin level is in the high risk zone based on age IN HOURS
   - All mothers receive instructions about jaundice before discharge
   - Nurses have the ability to initiate a bilirubin test
   - Babies discharged before 48 hours of age are seen by a provider within 48 hours of discharge

www.projectredcap.org
Treatment

- What guidelines are in place to ensure providers are assessing the level of severity of the serum bilirubin level?
- Is the level plotted by multiple people in hour of life on both the phototherapy and exchange transfusion charts?


Hyperbilirubinemia
Hyperbilirubinemia

- **Definitions/Facts**
  - Bilirubin = the end product of the catabolism of heme
  - Bilirubin is lipophilic - difficult to excrete, however crosses biological membranes (blood brain barrier, liver cell membrane) easily
  - Indirect - unconjugated free bilirubin + unconjugated bound bilirubin (non water soluble). It is fat soluble and potentially toxic.
  - Direct- conjugated bilirubin (water soluble)
  - Total bilirubin = direct + indirect (conjugated + unconjugated)
Hyperbilirubinemia

Biosynthesis of Bilirubin

Hemoglobin → Biliverdin → Bilirubin → Bilirubin Diglucuronide (Excreted)

- Heme oxygenase
- Biliverdin reductase
- Glucuronyl transferase

Heme

± Fe + CO

$O_2$
Hyperbilirubinemia
Rh hemolytic disease

In 1940, Landsteiner and Weiner discovered the Rh antigen using rhesus monkeys.

In 1968 began using Rhogam.

Before Rhogam, 1% of all pregnant women developed Rh alloimmunization.

Since treatment, 11 out of 10,000 births are affected and of those affected, ~9% will require intrauterine transfusions.
Hyperbilirubinemia
Rh Disease Pathophysiology

- Fetal RBC’s that have the surface Rh (D) antigen cross the placenta into the circulation of the mother who does not have the Rh (D) antigen on her RBC’s.
- Mother produces antibodies that cross the placenta
- Antibodies attach to the surface of the Rh antigen on the fetal RBC.
- The antibody coated RBC’s undergo lysis by lysosomal enzymes released by macrophages.
- Prolonged hemolysis results in severe anemia and excess production of bilirubin.
Hyperbilirubinemia
Erythroblastosis Fetalis

- Jaundice
- Anemia
- Hydrops
  - edema
  - pleural/pericardial effusions
  - ascites
  - cardiomegaly
  - liver dysfunction
  - DIC

FIGURE 12-6. Hydrops fetalis due to severe Rh incompatibility
G6PD Deficiency

- Glucose-6-phosphate dehydrogenase is a cytoplasmic enzyme
- Converts G6P to pentose phosphate and produces NADPH
- X linked disease, females may exhibit symptoms
- Most commonly seen in infants of Mediterranean, African and Asian descent
Direct Hyperbilirubinemia

- Galactosemia
- TORCH
- Hepatitis
- Sepsis
- Biliary Obstruction
- TPN related cholestasis
- Alpha one antitrypsin deficiency
- Other metabolic disorders
PHOTOTHERAPY
NURSING IMPLICATIONS

- Measure irradiance
- Naked, positioning
- Eye and gonad shields
- Monitor temp, intake/output
- Skin care
- Monitor side effects
- Parent education
Hyperbilirubinemia Phototherapy-Side Effects

- Frequent watery stools
- Hyperthermia
- Increased insensible H2O loss
- Rash
- Irritability
- Bronze baby syndrome
- Impaired infant parental bonding