Neonatal Jaundice: Etiologies and how and when to evaluate

10:30 – 11:15 a.m.

Bernadette Vitola, MD
I have no relevant financial relationships to disclose.
Objectives

• Describe neonatal jaundice
• Identify clinical findings
• Review the etiologies of unconjugated and conjugated hyperbilirubinemia
• Understand important tests needed to confirm diagnosis to determine treatment
Types of Jaundice

• Neonatal jaundice can be caused by either unconjugated or conjugated hyperbilirubinemia

• Most causes of unconjugated hyperbilirubinemia are relatively benign but can frequently require phototherapy

• Conjugated hyperbilirubinemia is NEVER normal and should always be investigated
Physical Findings

• There are no physical findings that can differentiate between unconjugated and conjugated hyperbilirubinemia

• Jaundice starts in the face/eyes and progresses caudally, but visual assessment of degree of jaundice is often inaccurate.

• Jaundice may be difficult to identify in darker-skinned infants. Scleral icterus is helpful.

• Signs/symptoms of dehydration and/or sepsis
When To Evaluate

• Jaundice in 1st 24 hours, T bili >5 mg/dl
• Jaundice that seems excessive for infant’s age
• Jaundice beyond 2 weeks in formula-fed infant and 3 weeks in breast-fed infant
Unconjugated Hyperbilirubinemia
Risk Factors for Severe Unconjugated Hyperbilirubinemia

- Prematurity
- Breastfeeding
- Poor feeding
- Hemolysis
  - ABO incompatibility, cephalohematoma, spherocytosis, G6PD
- Sepsis
- Asphyxia
- Gilbert syndrome
- Sibling required phototherapy
Treatment

• Use nomograms to determine when to treat with phototherapy or exchange transfusion

• If total bilirubin >25 mg/dl at any age, medical emergency requiring admission for phototx +/- exchange transfusion

• Consider IVIG if isoimmune hemolysis
Bilirubin Nomogram

Guidelines for phototherapy in infants ≥36 weeks gestation and 2000 g, or ≥35 weeks gestation and 2500 g

Subcommittee on hyperbilirubinemia, Pediatrics 2004
Guidelines for exchange transfusion in ≥35 weeks gestation

The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.

Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 μmol/L) above these lines.

Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.

Measure serum albumin and calculate B/A ratio (See legend)

Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin

If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Subcommittee on hyperbilirubinemia, *Pediatrics* 2004
A 4 week old full-term healthy breastfeeding male presents with persistent jaundice since shortly after birth.

He is eating and growing well and the parents report no issues. His stool is yellow per parents report.

A fractionated bilirubin shows a total bilirubin of 8.2 mg/dL, unconjugated bilirubin 3.5 mg/dL, conjugated bilirubin 4.1 mg/dL.

What next?
Conjugated Hyperbilirubinemia
Conjugated Hyperbilirubinemia

- Cholestasis is defined as reduced bile flow and abnormal accumulation of conjugated, or direct, bilirubin, indicating impaired hepatobiliary function.
- Conjugated hyperbilirubinemia is defined as >20% of total bilirubin.
- Occurs in 1:2500 live births.
- NEVER a normal finding and needs evaluation.
- Is NOT caused by breast milk jaundice.
- Early referral to Pediatric Gastroenterology recommended since certain diseases require timely intervention.
Incidence of Cholestatic Disorders

Suchy FJ. *Pediatr Rev* 2004
Etiologies

• **Infectious**
  – Sepsis, UTI, CMV, E. Coli sepsis assoc w/galactosemia

• **Anatomic**
  – Biliary atresia, choledochal cyst, inspissated bile/sludge

• **Metabolic**
  – Galactosemia, tyrosinemia, fatty acid oxidation disorder, congenital disorder of glycosylation, mitochondrial disorders

• **Endocrine**
  – Hypothyroidism, panhypopituitarism
• Genetic
  – Alagille syndrome, cystic fibrosis, alpha-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis, congenital hepatic fibrosis

• Toxins
  – Medications, TPN

• Vascular
  – Heart failure
  – Shock
  – Budd Chiari (occlusion of hepatic veins)
Clinical Presentation

• Aside from jaundice, clinical presentation of the cholestatic infant can vary widely depending on the etiology.
• Infants with cholestasis due to infection or a metabolic disease, such as galactosemia or tyrosinemia, are often ill-appearing.
• Infants with biliary atresia are often healthy-appearing with no apparent symptoms until later in the disease course. However, can be associated with situs inversus, malrotation, polysplenia, asplenia.
Clinical Presentation

- Congenital TORCH infection often associated with LBW, microcephaly, purpura, chorioretinitis, intracranial calcifications

Clinical Presentation

- Cholestasis as a result of a genetic mutation may have associated physical findings, such as a heart murmur, vertebral anomalies, typical facial features and eye findings in Alagille syndrome.

http://greatnonprofits.org/organizations/gallery/alagille-syndrome-alliance
Acholic Stool

• The triad of jaundice, acholic stools and dark urine should alert the clinician to the possibility of cholestasis, especially biliary atresia.
A 4 week old full-term healthy breastfeeding male presents with persistent jaundice since shortly after birth.

He is eating and growing well and the parents report no issues. His stool is yellow per parents report.

A fractionated bilirubin shows a total bilirubin of 8.2 mg/dL, unconjugated bilirubin 3.5 mg/dL, conjugated bilirubin 4.1 mg/dL.

What next?
Stool Color Card
Initial Evaluation

• Look for signs of sepsis/acute illness
• Assess liver synthetic function
  – PT/INR
  – Albumin
  – Glucose
• Look for other evidence of cholestasis
  – Alkaline phosphatase
  – γ- glutamyl transferase (GGT)
Diagnosis

• Anatomic
  – Abd US to evaluate for choledochal cyst, sludge, inspissated bile

• Endocrine
  – TSH, free T4, cortisol

• Infectious
  – UA, urine culture, septic workup if appears ill or febrile, urine CMV, consider adenovirus, enterovirus, TORCH workup
Diagnosis

• **Metabolic**
  – Review newborn screen
  – Serum amino acids (organic and amino acidemias), urine organic acids (tyrosinemia), acylcarnitine profile and free carnitine (fatty acid oxidation disorders), ammonia (urea cycle defects), lactate/pyruvate (mitochondrial)

• **Genetic**
  – Sweat test
  – Alpha-1 antitrypsin phenotyping
  – Genetic mutations (JAG1, FIC1, BSEP, MDR3)
  – Ophtho exam, thoracic films, echo
Background of Biliary Atresia

- Incidence 1/4,000-1/20,000 live births
- An obliterative cholangiopathy of unknown etiology
- Universally fatal by 1-2 years of life if untreated
- Primary treatment is excision of atretic biliary tree and Kasai portoenterostomy
- Supportive care with optimizing nutrition, vitamin supplementation, portal hypertension management, and other sequelae of chronic liver disease
Types of Biliary Atresia
Kasai Portoenterostomy

Kasai Procedure

- Small intestine attached directly to liver
- Liver
- Stomach
- Small intestine
- Rest of intestine stitched to small intestine to form the "Roux-en-Y connection."
# Effects of Age at Kasai

Table 2. Clearance of jaundice after Kasai operation: prognostic factors. Clearance of jaundice is defined as bilirubin level <20 μmol/L.

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Jaundice clearance rate (%)</th>
<th>N jaundice clearance/ N Kasai operations</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical pattern of the extrahepatic biliary remnant</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type 1</td>
<td>82.6</td>
<td>19/23</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>63.2</td>
<td>48/76</td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>45.4</td>
<td>79/174</td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>32.4</td>
<td>231/712</td>
<td></td>
</tr>
<tr>
<td>BA splenic malformation syndrome</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Absent</td>
<td>40.1</td>
<td>330/823</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>28.6</td>
<td>24/84</td>
<td></td>
</tr>
<tr>
<td>Age at Kasai operation</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1st month of life (age &lt;31 days)</td>
<td>51.5</td>
<td>51/99</td>
<td></td>
</tr>
<tr>
<td>2nd month of life (age 31 to 60 days)</td>
<td>43.1</td>
<td>185/429</td>
<td></td>
</tr>
<tr>
<td>3rd month of life (age 61 to 90 days)</td>
<td>31.6</td>
<td>114/360</td>
<td></td>
</tr>
<tr>
<td>4th month of life and after (age &gt;90 days)</td>
<td>27.7</td>
<td>36/130</td>
<td></td>
</tr>
</tbody>
</table>

## Effects of Age at Kasai

### Table A

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Survival with native liver (SE: standard error)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-year SNL</td>
<td>10-year SNL</td>
</tr>
<tr>
<td>Anatomical pattern of the extrahepatic biliary remnant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>24</td>
<td>87.3% (SE: 6.9%) [18]</td>
</tr>
<tr>
<td>Type 2</td>
<td>75</td>
<td>60.9% (SE: 6.3%) [26]</td>
</tr>
<tr>
<td>Type 3</td>
<td>173</td>
<td>47.1% (SE: 4.0%) [67]</td>
</tr>
<tr>
<td>Type 4</td>
<td>719</td>
<td>34.9% (SE: 1.9%) [199]</td>
</tr>
<tr>
<td>BA splenic malformation syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>829</td>
<td>42.8% (SE: 1.8%) [287]</td>
</tr>
<tr>
<td>Age at Kasai operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 days</td>
<td>99</td>
<td>53.5% (SE: 5.2%) [37]</td>
</tr>
<tr>
<td>31 to 60 days</td>
<td>435</td>
<td>43.5% (SE: 2.5%) [152]</td>
</tr>
<tr>
<td>61 to 90 days</td>
<td>361</td>
<td>35.5% (SE: 2.6%) [99]</td>
</tr>
<tr>
<td>&gt;90 days</td>
<td>132</td>
<td>31.0% (SE: 4.3%) [30]</td>
</tr>
</tbody>
</table>
# Effect of Race on Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Kasai ≤ 60 DOL</th>
<th>Kasai &gt; 60 DOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at Kasai (d)</td>
<td>46.9 (95% CI 43.5-50.4)</td>
<td>82.6 (95% CI 76.6-88.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>170 (55.6)</td>
<td>158 (39.5)</td>
</tr>
<tr>
<td>Female</td>
<td>136 (44.4)</td>
<td>242 (60.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>179 (57.8)</td>
<td>182 (45.6)</td>
</tr>
<tr>
<td>African American</td>
<td>16 (5.2)</td>
<td>82 (20.5)*</td>
</tr>
<tr>
<td>Hispanic</td>
<td>33 (10.8)</td>
<td>53 (13.1)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>56 (18.3)</td>
<td>38 (9.6)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (5.8)</td>
<td>31 (7.6)</td>
</tr>
<tr>
<td>Missing information</td>
<td>6 (2.1)</td>
<td>14 (3.6)</td>
</tr>
<tr>
<td>Payor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>143 (46.7)</td>
<td>165 (48.8)</td>
</tr>
<tr>
<td>Private Insurance</td>
<td>147 (48.2)</td>
<td>159 (46.8)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (5.1)</td>
<td>15 (4.4)</td>
</tr>
</tbody>
</table>

*P<0.03

Vitola, et al. NASPGHAN, 2015
Measuring Fractionated Bilirubin

**FIGURE 2**
Patients with BA have elevated DB and CB levels immediately after birth. A. Mean DB levels at 0 to 24 hOL (n = 6), 24 to 48 hOL (n = 24), 48 to 72 hOL (n = 11), and 72 to 96 hOL (n = 12). Each subject’s earliest measurement per interval was used. B. CB levels. The dashed lines indicate the upper limits of normal: 0.5 mg/dL (A) and 0.3 mg/dL (B).

**FIGURE 3**
Patients with BA have elevated DB, but not TB, levels at 24 to 48 hOL. Shown are the mean DB (A) and TB (B) levels for controls (n = 300; collection time: 39 ± 5.8 hOL) versus patients with BA (n = 24; collection time: 34 ± 6.2 hOL). The dashed lines indicate the upper limits of normal (A, 0.5 mg/dL), or the approximate phototherapy level at 34 hOL (B, 11.2 mg/dL). * P < .0001.

**FIGURE 4**
The majority of patients with BA have a DB/TB ratio of ≤0.2. Shown are the mean DB/TB ratios for controls (n = 242) versus patients with BA (n = 24). Only subjects with a TB level of >5 mg/dL were used for analysis. The dashed line indicates the recommended normal limit (0.2). * P < .0001.


<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases of BA</td>
<td>144</td>
<td>29</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Received Kasai operation</td>
<td>135 (93.8%)</td>
<td>28 (96.6%)</td>
<td>39 (97.5%)</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>≤60 days</td>
<td>68 (47.2%)†§</td>
<td>17 (58.6%)‡</td>
<td>24 (60.0%)§</td>
<td>26 (74.3%)</td>
</tr>
<tr>
<td>61–90 days</td>
<td>45 (31.3%)</td>
<td>8 (27.6%)</td>
<td>15 (37.5%)</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td>≥91 days</td>
<td>22 (15.3%)</td>
<td>3 (10.3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Without Kasai operation</td>
<td>9 (6.2%)</td>
<td>1 (3.4%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Stool Color Card and Survival

Fig. 1. The 5-year overall survival rates in cohort B (dotted line), which represents the era of stool color card screening program, and in cohort A (solid line), which represents the era before the stool color card screening program, were 89.3% and 55.7%, respectively ($P = 0.002$).

Fig. 2. The 5-year overall survival rates in subjects who were jaundice-free (dotted line) versus those who were not jaundice-free (solid line) at 3 months after Kasai operation was 89.8% and 44.8%, respectively ($P < 0.001$).

Take Home Points

• Conjugated or direct bilirubin should be obtained in ANY infant more than 3 wks of age with jaundice. Don’t forget to check the sclera and the stool!

• Conjugated hyperbilirubinemia is NEVER normal even if less than 20% of the total.

• PT/INR and glucose should be sent on any infant with conjugated hyperbilirubinemia to assess liver function.

• Early referral to a Pediatric Gastroenterologist is imperative to ensure timely assessment and to establish a diagnosis, but…

• YOUR early assessment is crucial for the best outcomes for these babies.
Questions?


Contact Information

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