Breast Milk Jaundice: A diagnosis without evidence

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LEARNING OBJECTIVES
1. Background: Origins of BMJ
2. Clinical Condition: BMJ
3. Bilirubin: Metabolism
4. Current evidence
5. Management options
18 day old female preterm (34 weeks AGA) on exclusive breast feeds. Good weight gain, good urine output, seedy yellow stools Taiwanese ancestry with history of 3 episodes of phototherapy use for rising bilirubin levels (peak TSB 13-17 mg/dL). Office: bilirubin is 15.6 mg/dL.
<table>
<thead>
<tr>
<th>Current Practice and Evidence</th>
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<tbody>
<tr>
<td>Repeat TSB in 24 hrs</td>
<td>For infant &gt;37 wks; no risk factors</td>
</tr>
<tr>
<td>Place infant in sunlight</td>
<td>No evidence and not recommended</td>
</tr>
<tr>
<td>Supplement with formula</td>
<td>No evidence and not appropriate</td>
</tr>
<tr>
<td>Start home phototherapy</td>
<td>For infant &gt;37 wks, no risk factors</td>
</tr>
<tr>
<td>Use urgent phototherapy</td>
<td>For late preterm + / - risk factors</td>
</tr>
<tr>
<td>Crash-cart approach</td>
<td>Any signs of lethargy or poor feeding</td>
</tr>
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</table>
INTRODUCTION

Breast milk jaundice was introduced as a clinical diagnosis in 1963 by Newman and Gross\(^1\) based on a report of 5 exclusively breastfed newborns who were compared to those who were also supplemented with cow’s milk.

*Yearbook. Advances in Peds. 2014. Vinod K. Bhutani and Ronald J. Wong. ED. Michael Cabana*
INTRODUCTION

In the subsequent landmark study that linked the diagnosis to decreased UDP-glucuronosyltransferase (UGT) activity, Arias et al\textsuperscript{2} described a syndrome of severe and a prolonged unconjugated hyperbilirubinemia associated with breastfeeding in 7 full-term, unrelated newborn infants. Curiously, the study cohort included “3 Jewish, 2 Italian, 1 Negro, and 1 Chinese mothers” (2).

A case report in the New England Journal of Medicine\textsuperscript{3} coined the phrase “breast milk jaundice”.

Neonatal Hyperbilirubinemia: Need for Efficient Bilirubin Load Clearance

Production

Hepato-biliary Excretion

Enterohepatic Re-Circulation

BILI LOAD
Origins of Breast Milk Jaundice

HYPERBILIRUBINEMIA IN BREAST-FED INFANTS
Arthur J. Newman and Samuel Gross
*Pediatrics* 1963;32;995
Newman and Gross Study

1. Sample size: n=11

2. Hyperbilirubinemia for a period of from 2 to 6 weeks following birth.

3. Account for but a small percentage of the newborn infants in the Cleveland area.

4. Insufficient measurements of all desirable data to support an exact etiology.
# Newman and Gross Observations

<table>
<thead>
<tr>
<th>Infants rehospitalized</th>
<th>All Breast fed</th>
<th>Breast fed, supplemented by cow’s milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Age at Study</td>
<td>5 days</td>
<td>13 to 37 days</td>
</tr>
<tr>
<td>Average TSB decline</td>
<td>0.32 mg/day</td>
<td>2.5 mg/day</td>
</tr>
<tr>
<td>Range, TSB decline</td>
<td>0.03-0.7 mg/day</td>
<td>1.3-4.0 mg/day</td>
</tr>
<tr>
<td>Anicteric by</td>
<td>15-21 days</td>
<td>30-40 days</td>
</tr>
</tbody>
</table>
Retrospective Confounding Issues

- Exchange transfusion was the only treatment option
- Influence of ongoing studies by Arias et al
- Not a randomized control study: inherent bias
- Dramatic effect to reduce bilirubin captured clinician's imagination
- Formulas being heavily marketed (in 1960s)

“Introduction of cow’s milk formulas should be carried out…… an extensive investigation for prolonged hyperbilirubinemia in otherwise well infants who have been wholly breast fed from birth”. 
Prolonged Neonatal Unconjugated Hyperbilirubinemia Associated with Breast Feeding and a Steroid, *Pregnane-3 (Alpha), 20 (Beta)-Diol*, in Maternal Milk That Inhibits Glucuronide Formation *In Vitro*.

“Prolonged neonatal jaundice has been associated with breast feeding (1-4)…clinical syndrome had not been described nor elucidated.

- 7 full-term, unrelated, newborn infants.

2. Graven, S. N. Personal communication.
3. Silverberg, M. Personal communication.
The Landmark Arias Study

- They studied the effect of milk from mothers (3 Jewish, 2 Italian, 1 Negro, 1 Chinese mothers) of the 7 jaundiced (TSB: 15.4 to 26.1 mg/dL) infants (BW: 2.74-3.94 kg, postnatal age 10-19 days), from control mothers.

- Pregnant and postpartum (Guernsey, Jersey and Holstein) cows glucuronyl transferase activity in vitro.

Breast feeding started at age 2 to 4 days. Rehospitalized for jaundice at age 9 to 14 days.
Fig. 1. Course of hyperbilirubinemia in infant A.M., whose mother continued breast feeding.
Fig. 2. Course of hyperbilirubinemia in infant L.M., whose mother temporarily stopped breast feeding.
Composite
The inhibitor: lab findings

Milk obtained from the mothers of the seven infants consistently inhibited glucuronyl transferase activity in vitro when compared with 99 specimens of milk obtained from 71 women whose infants did not demonstrate this syndrome. A steroid that competitively inhibits glucuronyl transferase activity in vitro has been isolated from inhibitory but not from non-inhibitory human milk. The steroid has been identified as pregnane-3(alpha), 20(beta)-diol.............

“the significance of this unusual isomer ....require further study”.
Breast-Milk Hyperbilirubinemia — Report of a Case

Captain Harvey P. Katz, M.C., USA†, and Captain Theodore A. Robinson, M.C., USA‡


IT has become evident that several substances may interfere with the capacity of the newborn infant to conjugate bilirubin, thereby resulting in varying degrees and duration of hyperbilirubinemia in the neonatal period. Prolonged and unexplained acholuric jaundice has been observed in several breast-fed infants, but only recently has a biochemical basis for this clinical observation been described. An inhibitor substance occurring postnataally in the breast milk of some women that was clinically associated with prolonged neonatal icterus has been identified. This report presents an additional case of persistent indirect hyperbilirubinemia with a demonstrable inhibitor substance in the maternal breast milk, representing the longest duration of the jaundice reported in this syndrome.
Figure 1. Response of the Serum Bilirubin Concentration to Dietary Change.
Prolonged Unconjugated Hyperbilirubinemia
Clinical study of prolonged jaundice in breast- and bottle-fed babies: C. R. WINFIELD and R. MACFAUL. Cambridge Military Hospital, Aldershot, UK.

Prolonged neonatal jaundice may be a sign of serious but rare disease (Arias et al).

We have been unable to find an incidence of breast milk jaundice quoted by these authors or in studies since.

A recent impression that prolonged neonatal jaundice was occurring more frequently led us to study the incidence of prolonged jaundice in breast- and bottle-fed infants.
N=893.

Breast feed at discharge: 55%

Jaundice lasting for 3 weeks or more: n=12 (2.4% of all breast-fed babies), none in bottle-fed infant (0%).

3 of the jaundiced babies gained weight poorly in the first 3 weeks of life, but after that age failure to thrive was not associated with the prolonged jaundice.
Natural Course Studied

Jaundice was first noted in the 12 babies (37 to 41 weeks GA) in whom it became prolonged between the 2nd and 5th day of life. It reached its peak (daily estimations) between the 3rd and 14th day (mean 6-7 days). Clinical jaundice persisted for variable periods beyond the last estimation of serum bilirubin measured (7 to 12 mg/dL). In Case 12 the jaundice disappeared 2 days after the mother stopped breast feeding her baby at 38 days of age…

But in the remainder jaundice faded while the babies were still being breast fed.
Inhibitor was thought to be \(3(\alpha),20(\beta)\)-pregnandiol.

European researchers discovered the inhibiting substance: non-esterified fatty acid (NEFA). The strong association between BMJ, elevated values of NEFA, and unstimulated lipase in UG1TA1-inhibitory milk was confirmed.

2 theories were offered (? defects in metabolism):

1) Milk triglyceride digestion altered;

2) Inhibition may facilitate the enterohepatic recirculation of bilirubin (reabsorption of bilirubin from intestinal lumen).

Breast-feeding per se does not result in an increased incidence of neonatal hyperbilirubinemia; it is rather those infants who receive insufficient amounts of breast milk who develop the condition.
Bilirubin Metabolism
Genomics of Bilirubin Metabolism

Increased Bilirubin Production

- HO-1 polymorphisms: Heme-oxygenase

Decreased Bilirubin Clearance

- UGT gene polymorphisms
- G6PD polymorphisms
- Crigler-Najjar Syndromes (complete or partial absence of UGT gene activity).

Other familial genetic syndromes
Liver

Plasma

BR

UGT1A1

BMGs + BDG

Canalicular Membrane

Process of Glucuronidation

Water soluble bilirubin species

Plasma Membrane
Genetics of bilirubin conjugation

- UGT gene is a superfamily of genes
- UGT1 gene is located on chromosome 2q 37 and UGT2 genes are on chromosome 4q13 and 4q28
- Enzyme glucoronidate endobiotic substances: bilirubin, steroids, bile acids.
- Bilirubin metabolism: UG1TA1 gene is well characterized.
- Abnormalities lead to neonatal hyperbilirubinemia.
Genetics of bilirubin conjugation

- UGT1A1 mutations are a known cause of unconjugated hyperbilirubinemia in patients with type I and type II Crigler-Najjar syndrome and in Gilbert syndrome.

- In the neonate, those with Crigler-Najjar syndrome show severe-to-moderate life long unconjugated hyperbilirubinemia.

- In contrast, mutations in the coding region, but not the regulatory region of UGT1A1 in Gilbert syndrome, are a risk factor for neonatal hyperbilirubinemia and BMJ.
Additional (TA) sequence in promoter of gene encoding bilirubin conjugating enzyme UDP-glucuronosyltransferase 1A1

Diminishes promoter activity, reducing enzyme expression

- $(TA)_6/(TA)_6$ Normal homozygote
- $(TA)_6/(TA)_7$ Heterozygote
- $(TA)_7/(TA)_7$ Variant homozygote (Gilbert syndrome)
Gilbert Syndrome (GS)

- GS is arguably a common syndrome known in humans.
- Most frequently (TA)$_7$TAA,
  - affects up to 36% of African-Americans,
  - only 3% of Asians affected.
- In Asians, a second common heterozygous mutation in the coding exon 1 of the UGT-1A1 gene (G71R) which is a variant cause of Gilbert syndrome.
Clinical Impact of GS

- The clinical signs are of a latent condition.
- Gilbert's disease occurs in ~6% of US population.
- It is a contributory factor of prolonged neonatal jaundice in breast-fed infants and may precipitate jaundice when co-inherited with other disorders of heme metabolism.
- May lead to pharmacological variation in drug glucuronidation and unexpected toxicity from therapeutic agents.
Clinical Conditions
Successful breast feeding

- **Output Assessment**
  - Wet (soaked) diapers (3-4/24hrs)
  - Stools (3-4/24hrs)
  - Each progressive stool changes color

- **Intake Assessment**
  - Frequent feeds (>8/24hrs)
  - Satiated after feeds
  - Swallowing heard/felt
  - Breast fill before & soften after feed.

 Mothers should call if any of the above sign is absent
Effect of Breastfeeding Frequency in First 24 Hours and TSB > 15mg/dL on Day 6 in Japanese Newborn

Modified from Yamauchi, Pediatrics 1990; 86:171
Biologic and Clinical Risk Factors

- Prematurity
- Hypothyroidism
- Galactosemia
- G6PD deficiency
- Urosepsis, other bacterial infections, TORCH group
- Inborn errors of metabolism
- Hypopituitarism

**Clinical:** Male, Asian, African-American, European +/- hemolysis.
### What is Prolonged Hyperbilirubinemia?

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Age: 7-14 days</th>
<th>mg/dL</th>
<th>molar units</th>
</tr>
</thead>
<tbody>
<tr>
<td>10th</td>
<td>1.6 mg/dL</td>
<td>27.4 µmol/L</td>
<td></td>
</tr>
<tr>
<td>40th</td>
<td>5.0 mg/dL</td>
<td>85.5 µmol/L</td>
<td></td>
</tr>
<tr>
<td>75th</td>
<td>9.7 mg/dL</td>
<td>165.9 µmol/L</td>
<td></td>
</tr>
<tr>
<td>90th</td>
<td>12.9 mg/dL</td>
<td>220.6 µmol/L</td>
<td></td>
</tr>
<tr>
<td>95th</td>
<td>14.4 mg/dL</td>
<td>246.2 µmol/L</td>
<td></td>
</tr>
<tr>
<td>99th</td>
<td>17.2 mg/dL</td>
<td>294.1 µmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Distribution of TSB levels at age 7 to 14 days (168 to 336 hrs) (n=439).
BMJ and Kernicterus
Kernicterus in Breast fed Infants

- "Breast feeding" labelled as a major risk factor: without defining breast milk intake in epidemiological studies.

- Most anecdotal cases: starvation, dehydration or preterm.

- 90% of cases reported in Kernicterus Registry were breast fed (starvation, dehydration, primi-gravidas with no lactation counseling).

- Late prematurity, G6PD deficiency and un-identified hemolysis are dominant risk factors.
G6PD: population genetics

- X-linked
- Numerous mutations
- Manifest hemolysis with stress: oxidants, drugs and infections
- Functional severe mutations cause hemolysis in absence of stress
- G6PD deficiency may relate to tissue other than the RBC
- Different mutations are characteristics of populations: Asian, African, Southern Europe

The nightmare event

- A healthy baby at 36 weeks GA
- Doing well on breast feeds.
- There is some jaundice
- Parents wake up to find a very jaundiced baby who is sleepy and does not look well.
- They rush to the ED
### Presence of G6PD Deficiency In U.S. Military Personnel: by Gender and Self-reported Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity (Sub-totals)</th>
<th>Female (8,428, 13.3%)</th>
<th>Male (54,874, 86.7%)</th>
<th>Total (63,302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (42,126)</td>
<td>0.0%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Afr.-American (11,276)</td>
<td>4.1%</td>
<td>12.2%</td>
<td>10.2%</td>
</tr>
<tr>
<td>AsIan (2,123)</td>
<td>0.9%</td>
<td>4.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td>American-Indian (804)</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hispanic (5,304)</td>
<td>1.2%</td>
<td>2.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Other (1,809)</td>
<td>1.8%</td>
<td>3.0%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

66/71 infants (93%) evaluated for jaundice >14 days had PUJ. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was the most commonly identified association of PUJ (24%).

- Median PUJ was 5 weeks (range: 5-8 wks).
- PUJ in siblings: OR 2.9; 1.1-7.6
- **G6PD deficiency: OR 4.0;1.1-14.1**
- By 8 weeks, PUJ disappeared in all infants.
Gilbert’s Syndrome [(TA)\textsubscript{7} Variant] and Hyperbilirubinemia in G-6-PD Normal Neonates

![Bar chart showing the incidence of hyperbilirubinemia (\%) for different UGT genotypes and G-6-PD status.]

- Normal homozygous
- Heterozygous
- Variant homozygous

- G-6-PD normal

0 %
20 %
40 %
60 %

Incidence of hyperbilirubinemia (%)
Gilbert’s syndrome [(TA)7 variant] and hyperbilirubinemia in G-6-PD deficient neonates

Kaplan et al, Proc Natl Acad Sci USA, 1997;94:12128-32
G-6-PD Deficient Neonates: Are Sitting Ducks: With Prolonged Hyperbilirubinemia

- Predilection for diminished bilirubin conjugation
- High allele frequency of variant UGT1A1 promoter
  - in African-Americans/ Nigerians
- Most will have moderate hemolysis & hyperbilirubinemia
• 3 week old female preterm (32 weeks AGA), Taiwanese ancestry with history of 3 episodes of phototherapy use for rising bilirubin levels (TSB levels 13-17 mg/dL).

• Family history of G6PD deficiency in maternal uncle and cousin (son of maternal aunt).

• G6PD screen (quantitative): 11.1 IU/g Hb

• ETCOc = 1.5 ppm
“Volcano Eruption” Concept

• The stage is set (PUJ)...
• If exposed to oxidative trigger of hemolysis
  – Adds to bilirubin production
• Late prematurity
  – Adds to diminished conjugation
• These events can trigger extreme hyperbilirubinemia
Current Evidence
Do breast fed infants have higher levels of jaundice or hyperbilirubinemia?

Percentile curves for exclusively breast-fed infants are 1 mg/dL higher than those for exclusively formula-fed infants.
Current Evidence

- Breast Milk Jaundice: No direct evidence
- Some may have sub-optimal milk intake.
- Late preterm infants are at risk for starvation.
- Gilbert syndrome (in ~6% of population)
- Late prematurity (~7%).
- Thusfar, no causative agent in breast milk.
Current Evidence

✓ Early Initiation: <1 hour age.

✓ Exclusive breastfeeding

✓ Identify sub-optimal intake for each day until day 5
  ✓ No sounds or feel of milk being swallowed
  ✓ Weight loss >3%
  ✓ No change in pre-post breast feed weight (after day 3)
  ✓ Dehydration: urine output <4 diaper change
  ✓ No change in stool color: transitional to mustard yellow
Research: casein in an infant’s diet

1. Consumption of casein hydrolysate formula lowers neonatal jaundice levels.


3. **STUDY**: The L-aspartic acid in hydrolyzed casein accounts most beta-glucuronidase inhibition.

   
Changes You May Wish to Make in Practice

1. Teach parents and staff of the multifactorial nature of prolonged unconjugated hyperbilirubinemia sometimes associated with exclusive breast feeding.

2. Refrain from using the former clinical “diagnosis” of breast milk jaundice.
Breast milk intake leads to an unmasking of an underlying genetic disorder (UGT/G6PD).

Use of beta-glucuronidase inhibitors, found in casein hydrolysate, has been useful.

Identification of optimal UGT activities remains a clinical conundrum to the management of PUJ.

“Breast milk jaundice” is not a clinical disorder.
Sampling of AAP National Policies

- Committee On Hospital Care (1 Sep 2003). Family-Centered Care And The Pediatrician’s Role. Pediatrics 112: 691-696.


