Neonatal Hyperbilirubinemia: Risk Assessment and Management

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Objectives

- Importance and Impact on infant health
- Physiologic and Pathologic causes of hyperbilirubinemia in newborns
- Guide to a systematic risk assessment
- Management
- Follow up
- Common parent/provider questions
Hyperbilirubinemia

- Elevated levels of bilirubin in the blood, >95$^{th}$ percentile based to the hour specific nomogram.
- Severe hyperbilirubinemia is defined as > 25mg/dL
- One of the primary causes of hospital readmission of neonates
- Usually peaks between 3-5 days of life
Bilirubin Encephalopathy

- highly neurotoxic substance
- can bind to brain tissue and cause neurologic dysfunction

- **ACUTE** (hypotonia, **lethargy**, poor suck ➔ irritability, high pitched cry, intermittent hypertonia ➔ seizures, fever, apnea, coma)

  VS

- **CHRONIC** (movement disorders, auditory neuropathy, oculomotor dysfunction, GI concerns)

  ➔ **KERNICTERUS**
Causes?
INCREASED ERYTHROCYTE BREAKDOWN

- Physiologic Jaundice
- Trauma
- Blood Incompatibility
- Infection
- Enzyme Deficiency
- Globin Synthesis Defect
- Membrane conditions

DECREASED BILIRUBIN CLEARANCE

- Physiologic Jaundice
- Breastmilk Jaundice
- Anatomic Obstruction
- Liver enzyme defect
- Drug Induced
- Liver Disease
- Metabolic
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Physiologic Jaundice

INCREASED BREAKDOWN

→ increased breakdown of red blood cells – 2-3x more than adults
→ birth trauma

DECREASE CLEARANCE

→ Gestational age-dependent physiologic deficiency of glucuronyl transferase enzyme -
  • 0.1% of adult activity at 30 weeks.
  • 1% of activity at 40 weeks.
Red blood cell haemolysis

Unconjugated bilirubin + albumin

Liver

Unconjugated bilirubin

UGT 1A1

Conjugated bilirubin

Hepatocyte

Stool

Excretion

Small intestine

Enterohepatic circulation

Unconjugated bilirubin

β-glucuronidase

Conjugated bilirubin
How to simplify etiology and importance of early follow up for parents?
Causes of Exaggerated Physiologic Jaundice
**BREASTFEEDING/BREASTMILK Jaundice**

- **Breastfeeding jaundice**
  - 1st week of life
  - exaggerates physiological jaundice
  - mild dehydration, delayed passage of meconium

- **Breast milk jaundice**
  - 6-14 days of life, can continue for over 1 month
  - ↑ β glucuronidase and fatty acids that inhibit enzymes involved in conjugation and intestinal absorption, ↑ enterohepatic circulation
TRAJMA/BRUISING

- More RBCs that go through hemolysis --> more bilirubin production
- Examples:
  - nuchal cord
  - cephalohematoma
  - bone/vascular injury
- Assisted delivery – vacuum or forceps

*often bilirubin peaks will be later for these infants ~5-7 days
PATHOLOGIC CAUSES:
Blood Type Incompatibility
Antibody Screen

- Maternal and fetal blood can mix during the pregnancy and delivery process. Maternal antibodies in the form of IgG can cross the placenta (both Rh and ABO antibodies).
- Indirect Coombs Test (aka antibody screen) tests the mother’s blood for potential antibodies that could affect the newborn.
- Direct Coombs Test identifies the presence of "foreign" antibodies that have adhered to the infant's rbcs, which is a potential cause of hemolysis - using a reagent.
- A positive test does not mean the infant will have hyperbilirubinemia but places the baby at higher risk.

*Evidence shows that an infant with ABO incompatibility but with a coombs negative test does NOT place the infant at higher risk due to the ABO incompatibility alone.*
Unconjugated Hyperbilirubinemia

*ABO incompatibility*

- the most common cause of hemolytic disease in newborn
- 0.3 - 2.2%
- most commonly O/A
- Hydrops very rare
- milder than Rh, severity can not be predicted

Fetal RBCs express less ABO antigen compared to adult RBCs. Also in contrast to Rh Antigens, ABO Antigens are expressed by a variety of tissues (in both fetus and adult) reducing the chance of these antibodies binding to RBCs.
Coombs positive due to true sensitization vs Maternal administration of Rh immunoglobulin?
Important to look at mother’s antibody testing for active Anti D titers

Infant is still considered on the more conservative risk curve though likely due to maternal RhIg administration
* Once mother is sensitized, even if Rh immunoglobulin is given during subsequent pregnancies, there is a higher risk of antibody mediated hemolysls
Unconjugated hyperbilirubinemia

**G6PD deficiency**

G6PD is needed to clear free radicals that cause oxidative damage. G6PD deficiency causes increased risk of hemolytic anemia in states of oxidative stress (infection, certain chemical exposure, and certain foods, e.g., fava beans).

- most common cause of **non-immune** hemolytic anemia
- gene located on X chromosome, > 400 mutations described
- 12.2% of AA males, 4.1% AA females, 4.3% Asian males
- newborn screening
- 21% (26/125) of cases with kernicterus
- G6PD level recommended for any infant receiving phototherapy with an appropriate genetic/geographic background, and for any neonate who does not respond well to phototherapy
Risk FACTORS
Risk Factors for Development of Severe Hyperbilirubinemia

Major Risk Factors

- Predischarge TSB or TcB level in the high-risk zone
- Jaundice observed in the first 24 hours
- Blood group incompatibility with + Coombs test, other known hemolytic disease (i.e. G6PD).
- **Gestational age 35 – 36 weeks**
- Cephalohematoma or **significant bruising**
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
- **East Asian race**
- Previous sibling received **phototherapy**
Family history of need for phototherapy

- East Asian Race – polymorphisms in UGT gene causing lower levels of functioning gene expression. Can be in other familial subgroups also
- Family history of Gilbert Syndrome – can predispose infants to exaggerated physiologic jaundice. Affects 9% of the general population
Other causes:

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Retrospective Study:

Prevalence of significant jaundice requiring re-admission to hospital for phototherapy. Compared to neonates ≥ 40 weeks

<table>
<thead>
<tr>
<th>Likelihood of need for readmission for PTX.</th>
<th>35-36 weeks</th>
<th>36-37 weeks</th>
<th>37-38 weeks</th>
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<tbody>
<tr>
<td></td>
<td>13.2 X</td>
<td>7.7 X</td>
<td>7.2 X</td>
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Risk Factors for Development of Severe Hyperbilirubinemia in Infants

- Minor Risk Factors
  - Predischarge TSB or TcB level in the high intermediate-risk zone
  - **Gestational age 37-37w6d weeks**
  - Jaundice observed before discharge
  - Previous sibling with jaundice
  - **Macrosomic, infant of a diabetic mother**
  - Maternal age ≥ 25 yr
  - Male gender
Infant of diabetic mothers

- Mother with elevated blood glucose
- Infant with elevated blood glucose
- Hyperinsulinemia
- Higher metabolic rate
- Polycythemia
Risk Factors for Development of Severe Hyperbilirubinemia in Infants

- **Decreased Risk**
  - TSB or TcB level in the low-risk-zone
  - Gestational age ≥ 41 weeks
  - Exclusive formula feeding
  - Discharge from hospital after 72 hours
  - Black race **
Management
Routine Protocol:

- Mother and baby blood type and coombs test
- Risk factors assessment
- Serum bilirubin at 24-48 hours of life
- Appropriate early follow up
- * remember visual assessment is not a good predictor at 1-3 days
Visual estimation....

<table>
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<tr>
<th>Zone</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>µmol/L</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>&gt;250</td>
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<tr>
<td>~mg/dL</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
<td>&gt;15</td>
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Department of Neonatal Medicine Protocol Book; Royal Prince Alfred Hospital

Interpret all bilirubin levels according to the infant’s age in hours.

- When documenting bilirubin levels ALWAYS note phototherapy level for infant based on risk

  e.g. 13.6/0.2 @ 83 HOL Low intermediate risk
  Ptx level: 18.8 low risk curve
  Vs
  13.6/0.2 @ 83 HOL Low intermediate risk
  Ptx Level: 16.5 on middle curve for age
Hour Specific Bilirubin Nomogram

(from Bhutani, et. al. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy-term and near-term newborns, Pediatrics 1999.)
Factors that affect Phototherapy Level

+ Coombs Test
Age: <38 weeks
+ Symptomatic Sepsis
Asphyxia requiring NICU admission
+ G6PD Deficiency risk
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 infants <2500g or <35wks:
* use the low birth weight table OR
* use the highest risk curve up to 96 hours of life
Provide appropriate follow-up based on the time of discharge and the risk assessment.
Low risk

- Term babies with normal weight loss and no other risk factors do not require repeat bilirubin value if performed at 24-48 hours of age

- * consider Coombs positive?
- * family history
- * significant bruising
Low intermediate risk

Will require close follow up (in 24-48 hours) if:

- Less than 38 weeks
- Excess weight loss >7%
- Breastfeeding exclusively
- Significant bruising or Cephalohematoma
- Sibling history of requiring phototherapy
- Hemolytic disease risk
High intermediate risk

Requires follow up in 24-48 hours:

- All babies regardless of gestational age

If baby is coombs positive or has major risk factors, may be advisable to obtain repeat bilirubin value to assess rate of rise while inpatient if value is <2 away from phototherapy level.
High risk

Require repeat bilirubin in 6-24 hours with close assessment of risk factors and age
Considering Rate of Rise?

- While inpatient (assuming <72 hours old) a rate of rise of >0.2mg/dL/hr has significant potential to raise a HIR bili over phototherapy within 24 hours

- * After 72 hours – a lower rate of rise can also be significant as the curve begins to plateau. An average rate of rise can be calculated for age ranges using the bhutani curve to assess risk
Hour Specific Bilirubin Nomogram

When to start Phototherapy?
Guidelines for phototherapy in hospitalized infants of 35 or more weeks’ gestation

- Phototherapy includes double bank lights and a biliblanket
- It is an option to provide conventional phototherapy in hospital at TSB levels 1-2 mg/dL below
- **general rule:** 1 or less with term baby no risk factors
  - 2 or less with <38 wks or + risk factors
- **If value is above phototherapy level** *always look at the exchange transfusion level*
What to consider in an outpatient setting when thinking about readmission?

- Within 1mg/dL below phototherapy level
- Rate of rise: >5mg/dL/per day
- At risk of lost to follow up
- Poor feeding despite adequate supply
- Signs of Acute Bilirubin Encephalopathy
When to check next bilirubin once phototherapy is started?

- If term infant with no other risk factors and below phototherapy level – appropriate to check in 24 hours
- If coombs positive – appropriate to check in 6-12 hours
- If above phototherapy level – appropriate to check in 6-12 hours
If the bilirubin level continues to increase while under phototherapy, consider:

- Check intensity
- How much time is the baby actually received therapy
- Consider hemolysis
- Feeding assessment
- Blood type with Coombs test
- H/H
- Reticulocyte count
- Peripheral smear
- G6PD deficiency?
Considering IV IG, exchange transfusion....
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When to stop phototherapy?

- Bilirubin level has shown some decrease

- Bilirubin level is a safe distance from phototherapy level
Phototherapy case:

- 3320g 39w0d female born via SVD to a 22y.o G2P1->2 mother. Mother O+/ Baby A-/coombs positive. No other risk factors known at this time.
- T bili at 6 hours of life= 6.6. --> started phototherapy
- @ 12 HOL =9.8 H/H 16.4/48.8, retic 5.8%.
- @ 15 HOL =10
- @ 48 HOL =12.8
- @ 66 HOL =13.0, LUL: 15.1mg/dL MRC
- * phototherapy discontinued
- 6 hour Rebound T bili 13.4
- Infant discharged with follow up in 24 hours....
Case 2 continued ... 

Infant arrives at follow up clinic.
T/D Bili: 19.1/0.4 @ @ 100 HOL  PTx level: 17.7

-readmitted for phototherapy. Received another 36 hours of phototherapy, discontinued at 138 HOL.
Things to consider when treating with phototherapy

- It is NOT mandatory to check H&H and retic% on every baby – when is it beneficial?
- Bilirubin value should decrease during phototherapy treatment before discontinuing lights
- Consider age of baby and risk factors to assess safe range to stop phototherapy to decrease risk of readmission
- If initial bilirubin is above phototherapy level always check exchange transfusion level. If coombs positive and within 1-2 of exchange level consider IVIG
- How important are rebound bilirubin levels?
When to follow up after phototherapy treatment:

- **Within 24-48 hours of discharge** – rebound bilirubin needed BUT NOT NECESSARY PRIOR TO DISCHARGE.

- If infant has significant risk factors consider a rebound bili prior to discharge
Provide parents with written and verbal information about newborn jaundice.

Call PCP or bring infant to the ER if over the weekend with poor feeding, increased sleepiness or no urine output in >8 hours.
Transcutaneous bilirubin checks

PROS:
- Accurate across different skin color variations, gestational age
- Accurate within 1-2mg/dL if value below 11mg/dL (insufficient data on values over 11 to be significant)
- Less invasive – good screen tool

CONS:
- Consider cost based on population and need for confirmatory serum bilirubin levels
- Does not measure conjugated bilirubin levels
Why is conjugated bilirubin important?

- Elevated conjugated bilirubin levels help differentiate the etiology of hyperbilirubinemia, detected other serious diseases such as
  - Biliary atresia, Alagille Syndrome, Alpha 1 antitrypsin deficiency +

- Should not begin phototherapy without a normal baseline conjugated bilirubin as this may exacerbate other conditions and possibly cause more liver/biliary damage
Commonly asked questions?
Will sunlight help?

- Evidence shows: Yes sunlight is just as effective
- 2015 – study in Nigeria showed sunlight using a filter canopy that removed harmful UV rays was just as effective as conventional phototherapy
- However is NOT TO BE ADVISED as the risk of sunburn, overheating, dehydration, hypothermia all outweigh the benefits. There are also safer and more reliable alternative interventions

Will supplementing formula help?

- Evidence shows: Yes. Breastmilk vs formula does have different growths in gut flora which then change how effectively bilirubin is broken down. Larger volumes of supplement also benefit in infant who have low intake jaundice.

However the benefits of breastmilk on gut health including decreasing overall inflammation outweighs the risk of higher bilirubin levels and should be weighed against risk and benefits of interruption.

- What about fluids: The mechanism of action proposed includes direct dilution for IV fluids and enhancement of peristalsis to reduce enterohepatic circulation by oral fluids. No significant evidence to show oral or IV fluid supplementation will significantly decrease bilirubin levels.


Are we being too conservative?
Incidence rate

- Globally stable in western countries ~ 8 in 100,000 diagnosed with severe hyperbilirubinemia (>25mg/dL)
- Kernicterus rates of ~ 2004 0.44-1.5 in 100,000 newborns
  previously: 1994 1.5 in 100,000 newborns
  1988 5.1 in 100,000 newborns
- Incidence rates remain low due to the early monitoring, identifying at risk infants and timely interventions
- Key concept is there is not defined bilirubin level at which kernicterus begins – the range remains the same for those with acute signs that resolve and those with chronic sequelae
- Obstacles in obtaining reliable data:
  - absence of a population based data reporting system
  - variable timeliness to intervention and follow up
  - admitting at variable stages of acute encephalitis signs
THE END

QUESTIONS ??