Case Studies in Neonatal Jaundice

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Learning Objectives

- Summarize the mechanisms of bilirubin production and clearance in the neonate.
- Apply a process to assess and monitor neonatal hyperbilirubinemia.
- Identify strategies to assess risk in neonates.
- Describe the recommended levels for intervention and treatment modalities for severe hyperbilirubinemia.
- Summarize the updated consensus guidelines for early prevention, intervention, and treatment.

Who are NOT included in the 2022 AAP Guidelines?

- Infants < 35 weeks gestation
- Infants from resource constrained countries

Definition

- Total serum bilirubin greater than the 95th % on the nomogram.
- Usually unconjugated
- Hyperbilirubinemia can then be considered severe when:
  - Neonate has jaundice within the first 24 hours of life.
  - Rate of increase in total bilirubin is too high.
  - Level of conjugated bilirubin is too high.
  - Neonate has signs or symptoms suggestive of a serious illness

Epidemiology

- 60% of term newborns
- 80% of preterm newborns
- 2% will have severe hyperbilirubinemia thus not common.
- Acute bilirubin encephalopathy is 1:10,000 births.
- Chronic bilirubin encephalopathy at 1:100,000 births.
- Learning Objectives

Case Study

You are a PA in an outpatient clinic. The next patient is a 7do boy with the chief complaint of ”yellow skin.” His mother says he was born vaginally at 36 weeks gestation. The labor and delivery were uncomplicated and he had no postnasal complications. Newborn screen is normal. Mom states he sleeps often and breastfeeds about 4x /day.

Exam: Jaundiced infant with non-palpable liver and spleen

Laboratory: T bili 17.5mg/dl

Which of the following is the most likely cause of this patient's symptoms?

a) Decreased secretion of conjugated bilirubin by hepatocytes
b) G6PD deficiency
c) Increased enterohepatic circulation of bilirubin
d) Increased levels Ig A in the mother's breast-milk
e) Increased number of bowel movements

Case Study

You are an experienced pediatric PA seeing a 2-week-old boy brought into the office for a well child visit. He's the first-born child of an uncomplicated pregnancy.

PMHx: Mild unconjugated hyperbilirubinemia at 48 hours after delivery which did not require treatment. There are no signs of jaundice, and his bilirubin levels are normal today in the office.

Which of the following is the most likely cause of this infants earlier child's jaundice?

Answers

a) Aspirin toxicity
b) Cirrhosis of the liver
c) Immature hepatic bilirubin clearance
d) Iron deficiency
e) Pernicious anemia

Enterohepatic Circulation of Bilirubin

- Breakdown of Hgb from RBC
- Hepatocytes catalyze unconjugated bilirubin into conjugated bilirubin.
- Bilirubin secreted into bile
- Travels to digestive tract

Case Study

- You are new graduate PA student seeing a 1-day-old boy in the ward because of a call by a nurse about jaundice x 4 hours. Nursing notes jaundice began on face and has spread to his trunk. G1P1. Her pregnancy, labor and delivery were all uneventful.
- Exam: Scleral icterus and jaundice affecting face and trunk.
- Lab: T bili: 14mg/dl, D bili is 0.4mg/dl

Which of the following is the next most appropriate initial investigation?

a) Bilirubin (transcutaneous)
b) Coombs test
c) Daily total and direct bilirubin measurement the next day
d) Measure G6PDH levels
e) Measure glucuronic acid levels

Screening for Isoimmune Hemolysis

- 2004
- RECOMMENDATION 2.0: Clinicians should perform ongoing systematic assessments during the neonatal period for the risk of an infant developing severe hyperbilirubinemia. Blood Typing
- RECOMMENDATION 2.1: All pregnant women should be tested for ABO and Rh (D) blood types and have a serum screen for unusual isoimmune antibodies RECOMMENDATION 2.1.1: If a mother has not had prenatal blood grouping or is Rh-negative, a direct antibody test (or Coombs' test), blood type, and an Rh (D) type on the infant's (cord) blood are strongly recommended
- RECOMMENDATION 2.1.2: If the maternal blood is group O, Rh-positive, it is an option to test the cord blood for the infant's blood type and direct antibody test, but

it is not required provided that there is appropriate surveillance, risk assessment before discharge, and follow-up.

2022

- KAS 1: If the maternal antibody screen is positive or unknown because the mother did not have prenatal antibody screening, the infant should have a direct antiglobulin test (DAT) and the infant's blood type should be determined as soon as possible using either cord or peripheral blood. (Aggregate Evidence Quality Grade B, Recommendation)

Prevention of Hyperbilirubinemia Associated with Hemolytic Disease

- Determine ABO blood group and Rh(D) type
- Mother receives an antibody screen to determine need for Rh immunoglobin.
  - RhoGAM at 28 weeks of gestation and then again within 72 hours postpartum
- Maternal antibody screen is positive or unknown then infant should have a direct antiglobulin test (DAT, Coombs).
- Coombs test will be positive either due to Rh or ABO incompatibility.
- Rh incompatibility:

Coombs Test Negative

- Hemoglobin Low (<13.5 g/dL)
  - Ex: cephalohematoma
- Hemoglobin Elevated (>22g/dL)
  - Infant of diabetic mothers, occur during a transfusion, like twin-twin, maternal-fetal transfusion or delayed cord clamping
- Coombs Test Negative
- Hemoglobin Normal (13.5-22 g/dL)
  - Check CBC, LDH, reticulocyte, smear, haptoglobin, electrophoresis
  - Evaluate reticulocyte count, LDH and hemoglobin.
  - Spherocytes or elliptocytes should be seen on smear

Hemoglobin Electrophoresis: HbF 80% and HbA 20%

- Sickle cell disease: HbA substituted with HbS
- B thalassemia: HbA missing

Case Study:

A 5 do infant to a G1P1 mother comes to the office for her initial visit. Exclusively breastfeed every 2 hrs, even at night. Has adequate urine output and stooling. Uncomplicated term birth. Mother was group B strep negative. Both are A+ blood type.
Exam: Alert child with jaundice to face and trunk.
Lab: Total Bilirubin: 14mg/dl Direct Bilirubin: 1mg/dl

Which of the following is the most appropriate next step?

a) Admission to hospital for phototherapy
b) Admission to hospital for sepsis rule-out
c) Advise mother to stop breastfeeding and use only formula till jaundice resolves
d) Follow up in 1-2 days and encourage more feeds
e) Send labs: T bili, D bili, CBC, peripheral smear, Coombs, G6PD deficiency test-quantitative

Benign Neonatal Hyperbilirubinemia

- "Physiologic jaundice"
- Immaturity of hepatic conjugation system
- RBC (HbF) turnover after birth
- Median peak TSB of 8-9 mg/dL on DOL 3-5
- ALL infants should be screened for hyperbilirubinemia (with TcB or TSB) while in the nursery!

Case Study

You are a rural PA seeing a 4 week old Japanese girl for her 1 month well child check. Parents note that she developed jaundice 3 days ago and had a negative hemolysis workup at that time.

Feeding Hx: exclusively DBF q3 for 10 min on each breast with adequate stooling and urien output.

FHx: is significant for UGT1A1 mutation present in her mother

Exam: Adequate growth on growth chart. Alert infant with jaundice of the face 'and upper trunk

Lab:

- Serum bilirubin: 10mg/dl
- Indirect serum bilirubin 9.3mg/dl
- Direct serum bilirubin 0.7 mg/dl
- **Which of the following is the most appropriate next step?**

a) Advise mother to breastfeed more often
b) Continue breastfeeding and close observation
c) Substitute breastmilk with formula
d) Genotyping for UGT1A1
e) Check CBC, LFT, and coags

Benign Neonatal Hyperbilirubinemia

- Breast FEEDING jaundice
  - Inadequate oral intake → less excretion of conjugated bilirubin → reconverted to unconjugated bilirubin by glucuronidase increased enterohepatic circulation
  - Treatment
- Breast MILK jaundice
  - Inhibition of glucuronyl transferase; conjugated → conjugated
  - Continue feeding, consider trial of formula

Case Study

You are an ED PA who is seeing a 3-week-old male is brought to the ED by his parents for jaundice and hypotonia.

BHx: 39 weeks via an uncomplicated vaginal delivery. Noted to have jaundice at birth which has persisted. Exclusively breastfed and produces 6 to 7 wet diapers per day.

FHx: Family history is unremarkable

PE: Jaundiced infant with scleral icterus, reduced muscle tone throughout the body. Also, noted to have impaired upward gaze in the right eye

Lab: hemoglobin 17.0 mg/dl hematocrit 50%, MCV 28.7 pg/cell, total bilirubin 23mg/dl, direct bilirubin 0.3mg/dl

- **Which of the following interventions will provide definitive treatment for the patient's condition?**

a) Intubation and start on IV fluids
b) Initiation of plasmapheresis
c) Liver transplantation
d) Initiation of phototherapy
e) IVIG dose x 1

Pathologic Unconjugated Hyperbilirubinemia

- Hemolytic Intrinsic
  - G6PD deficiency
  - Thalassemia
  - Heredity spherocytosis
- Hemolytic Extrinsic
  - Drugs
  - Isoimmune
  - Sepsis

Gilberts Syndrome

- decrease in the enzyme uridine glucuronyl transferase,

- Crigler-Najjar syndrome
  - complete absence of uridine glucuronyl transferase.

Conjugated Hyperbilirubinemia

- Extrahepatic
- Biliary Atresia
- Choledochal cyst
- Tumor/Mass
- Cystic Fibrosis
- Intrahepatic
- Drugs: sulfonamides, ceftriaxone
- Infections: hepatitis, TORCH
- Genetic: Alagille syndroe

Case Study

You are a PA with 2 years experience seeing a 4 do infant in the ward because of vomiting diarrhea and poor feeding.

Physical Exam: Lethargic infant noted in the chart to be sleeping more than normal for his age. Noted for scleral icterus, jaundice the upper trunk, hepatomegaly and leukocoria.

Lab: RBS: 50, + urine test positive for reducing substances , indicating the presence of sugars with aldehyde groups

Which of the following processes is most likely abnormal?

a) Conversion of galactose 1-phosphate to UDP-glacatose
b) Conversion of UDP-glacatose to UDP-glucose
c) Conversion of lactose to galactose
d) Excretion of galactose by the kidney

e) Execration of glucose by the kidney

Risk Factors: 2004 vs 2022

- Risk factors for the development of severe hyperbilirubinemia not necessarily neurotoxicity
- Some overlap
  - Hemolytic disease
  - Prematurity

J - jaundice within the first 24 hours of birth
A - sibling who required phototherapy as a baby
U - unrecognized hemolysis
N - non-optimal sucking/feeding
D - deficiency of G6PD
I - infection
C - cephalo-hematoma or bruising
E - ethnicity (Asian heritage)

2004 => 2022

2004: AAP Guidelines

- Hemolysis
- Asphyxia
- Significant lethargy
- Temperature instability
- Acidosis
- Sepsis
- Hypoalbuminemia (< 3.0 mg/dL)

2022: AAP Guidelines

- Hemolysis
- Significant clinical instability in the previous 24 hours
- Sepsis
- Hypoalbuminemia (< 3.0 mg/dL)

Consequences of Hyperbilirubinemia

- Bilirubin overwhelms albumin binding capacity.
- Bilirubin is a neurotoxin
- Bilirubin-induced neurologic dysfunction (BIND)
  - Acute bilirubin encephalopathy
  - chronic bilirubin encephalopathy (Kernicterus)
- Acute bilirubin encephalopathy
- 3 phases
  - 1st: mild hypotonia, increased sleepiness, or poor suck.
  - 2nd :high-pitched cry and become difficult to console, febrile, and hypertonic
  - 3rd :apnea, inability to feed, persistent retrocollis and opisthotonos, seizures, coma, and even death
  - Reversible
  - Kernicterus
- Chronic outcome of BIND

- Will develop this within the first year of life after ABE if not treated
- Consequences: cerebral palsy, hearing loss, gaze abnormalities, dental dysplasia, developmental delay and mental deficiency.

What's New

- Evidence for possible harm
- Concern for overtreatment

Exchange Transfusion Guidelines 2022

- Escalation of Care
- Intensive care needed with elevated or rapidly increasing TSB
- Goal is to avoid exchange transfusion and prevent CBE
- Threshold is TSB within 2 mg/dL of the exchange transfusion threshold
- As always – include any direct-reacting bilirubin and use TSB as the definitive test to guide management
- Optimal location for management – NICU capable of performing ET if necessary

Take Home Points in 2022 Guidelines?

- Raise phototherapy threshold on when to initiate
- Revise risk assessment approach
- Change approach to escalation of care