Complex Hyperbilirubinemia in the Neonate

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- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

- Understand the consequences of mild, moderate and severe hyperbilirubinemia.
- Understand the basic physiology and risk factors for the development of hyperbilirubinemia in the term and preterm infant.
- Understand the appropriate evaluation and management of complex hyperbilirubinemia.
ARS #1:

What is the lower level of Total serum bilirubin in the premature infant that can cause bilirubin-induced neurologic dysfunction?

a. 5 mg/dl
b. 10 mg/dl
c. 15 mg/dl
d. 20 mg/dl
ARS #2:

Causes of increased bili production include all except:

- a. Isoantibodies to ABO, Rh, minor blood groups
- b. G-6-P deficiency
- c. Crigler-Najjar syndrome I and II
- d. Spherocytosis
- e. cephalohematoma
A 24 yo woman with no prenatal care delivers a term infant with apgars of 9 and 9 who appears healthy in the delivery room. Cord blood should be sent for direct antibody (Coombs test), blood type and Rh determination.

True or False
Case presentation: Consultation to Pediatric Hematology Service:

- 6 day old white male born at 36 1/7 weeks with Rh isoimmunization and significant hemolytic anemia.
- Mother: G2 P2 Blood type: A-; antibody titer: 1:16 @ 28 weeks, + rhogam
- 34 weeks gestation: amniocentesis w/ Delta OD 450 considered “low risk”
- 36 weeks: PROM, NSVD, Apgars 9/9, cord blood: Coombs +, blood type A+
- 18 hrs of life: jaundiced: serum bili-18.5
  - IVF, triple phototherapy, 15 cc/kg PRBCs for Hct 30/retic 20%, IV IgG x 2
- 48 hrs: bili 10mg/dl-single phototherapy, d/c IVF
- 72 hrs: bili 11.9-triple phototherapy
- 96 hrs: bili-19
- ??? causes of rebound hyperbilirubinemia, management, consequences
A history Lesson: jaundice in the neonate

Centuries ago: Icterus neonatorum—neonatal jaundice

1724: true jaundice first described in detail (Juncker)

1875: bilirubin noted in basal ganglia on autopsies in infants w/ severe jaundice (Orth)

1903: “kernicterus” new name for CNS autopsy findings (Schmorl)

1958: first recognized that jaundice will fade away if baby is put in sunlight (UK nurse w/ no name)

1950’s-1970’s: very aggressive management for Rh Hemolytic dz

1980’s: very aggressive management, almost no kernicterus

1990’s: early discharges, less interventions, increased kernicterus
Consequences of Kernicterus

- **Definition:** permanent neurologic disability due to bilirubin deposition in critical structures in the CNS

- **Acute bilirubin toxicity:**
  - Phase 1: Days 1-2: poor suck, lethargy, high-pitched scream, seizures
  - Phase 2: Days 3-5: hypertonia, opisthotonus, retrocollis, fever
  - Phase 3: Days 7+: hypertonia

- **Bilirubin induced neurologic dysfunction (BIND):**
  - Phase 1: 1st year of life: hypotonia, increased DTRs, tonic neck reflexes, delayed motor development
  - Phase 2: choreoathetoid CP, ballismus, tremor, upward gaze, dental dysplasia, sensorineuronal hearing loss, and cognitive impairment
Hyperbilirubinemia: Incidence and Physiology

- **Incidence:**
  - Term/near term infant - Extremely common: elevated Total serum bilirubin (TSB): 60%
  - Pre-term: more common, more severe, lasts longer

- **Normal physiology:**
  - RBC’s → hemolyzed, release hgb
  - w/in Reticuloendo system: heme oxygenase degrades heme → biliverdin
  - Biliverdin → unconjugated bilirubin + albumin → liver
  - UGT1A1 conjugates bilirubin
  - Conjug bili is excreted: → bile duct → gall bladder → intestine → stool
Physiologic Jaundice

- **Definition:** elevated total serum bili (TSB)-1st week of life
- **Peak:** day 3-5, normalizes to adult levels within a few weeks
- **Any TSB > 17 at 96 hrs is NOT physiologic jaundice**

- **Causes:**
  - increased production of bili
  - Higher HCT w/ shorter life span of RBCs (70d)
  - Immature hepatic glucuronosyl transferase needed for conjugation and excretion

Breastfeeding jaundice: mild dehydration, lower caloric intake, delayed passage of meconium
Jaundice in the Pre-Term Infant

- More common, more severe, lasts longer
  - Immature RBCs, liver, GI systems
  - Delayed enteral feeds due to NEC, other illnesses
  - Kernicterus is rare but can occur at lower TSB levels: 10-14 mg/dl
Pathologic Hyperbilirubinemia

- **Mechanisms:**
  - Increased bilirubin production
  - Impaired bilirubin conjugation
  - Impaired bilirubin excretion
  - Other issues
Increased bilirubin production:

- **Isoantibodies:**
  - ABO incompatibility-usually type O mother/A or B baby:
    - 15% of pregnancies/5% symptomatic
  - Rh incompatibility-mother: Rh-/baby Rh+, usually prior pregnancy/exposure to antigen, much more rare due to rhogam at 28 weeks
  - Other minor blood group antigen discrepancies: kell, duffy

Enzyme deficiencies: G6PD deficiency, Pyruvate kinase deficiency

- G6PD: 10% of AA males in US,
  - Can lead to mild to severe hyperbilirubinemia
  - Significant risk factor for kernicterus
Impaired Bilirubin Conjugation

- **Gilbert Syndrome:** autosomal recessive:
  
  UGT1A1 activity is mildly decreased in hepatocytes leading to benign unconjugated hyperbilirubinemia.

  Note: G6PD and UGT1A1 deficiency in the same pt can lead to severe hyperbilirubinemia.

- **Crigler-Najjar syndrome I:** severe deficiency of UGT1A1 activity:
  
  leads to severe bili encephalopathy early in life (days to weeks)

- **Human milk jaundice:**
Impaired Bilirubin Excretion

- Elevated direct/conjugated bili: > 20% of TSB if bili > 5mg/dl
- Biliary atresia:
- Choledochal cyst:
- Dubin-Johnson syndrome: AR, due to defect in multiple drug resistance protein 2, black liver, gall bladder not visualized,
  - Dx: total urine coproporphyrin-normal but reversed ratio of isomer 1 (80%) vs 3
  - Prognosis: excellent
  - Treatment: usually unnecessary

Rotor Syndrome: AR, SLC01B1 and B3 gene mutations, pink liver, visualized GB
  - Dx: high urine coprophorphyrin, < 70% isomer 1
Other Causes of Neonatal Hyperbilirubinemia

- Asian Ethnicity: mean peaks of bili: 10 mg/dl
- Prematurity
- Hypothyroidism
- Galactosemia
- Maternal DM
- Infection: UTI, sepsis
- Breastfeeding
- Drugs: sulfa, streptomycin
Evaluations

- Pre-term: maternal blood type, screen for unusual blood group antigens
- If maternal Rh-: cord blood should be tested: Direct Antibody test (Coombs), blood type/Rh, Hct
- If maternal Type O: obtain infant blood type, DAT
- Assess for jaundice: q 8-12 hours
- If excessive: obtain TSB or transcutaneous bili (TcB)
- Compare to AAP Nomograms: for:
  - Designate of Risk for developing a later bili level > 95%
  - Initiate phototherapy based on gestational age and risk
  - Initiate exchange transfusion based on gestational age and risk
Investigations

- Serial TSBs and compare to AAP Nomograms
- Serial HCTs, retic
- Review: peripheral smear-signs of hemolysis, membrane abnl
- G6PD screen: BEFORE transfusion-may be normal if young RBCs
- Sepsis w/u: blood, urine cx’s
- Consider: thyroid panel, review family hx and medications
- U/s liver if conjugated bili
Management:

- **Phototherapy:**
  - Converts bilirubin into lumirubin-water soluble and can be excreted in urine or bile w/o liver conjugation
  - Maximize exposure, minimize distance from the light: single, double, triple
  - Maintain normal temperature and hydration
  - Strongly consider iv hydration if in zone near exchange transfusion

- Only contraindication for phototherapy is: congenital porphyria or a family hx of porphyria results in severe blistering and photosensitivity
Management

- Treat for underlying cause:
  - Antibody mediated process: consider IgG x 1-2
  - If significant anemia: transfuse w/ O- blood
  - Sepsis/infection: antibiotics
  - Dehydration: iv fluids
  - Infusion of albumin if low albumin

Exchange Transfusions:

- Significant risks: Central line clots, infections, NEC, thrombocytopenia, electrolyte imbalances, Graft vs Host dz, death
  - 12% complication rate
  - Maximize phototherapy to avoid Exchange transfusion
Case Presentation

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Case Presentation

- Exchange transfusion was considered @ TSB=19 96 hr old (36+1 week infant)- borderline indication
  - albumin infusion, triple phototherapy, iv fluids con’t
  - ordered blood for exchange
  - repeat bili-2 hrs: TSB-17.8
  - held exchange due to risks
  - repeat bili-2 hrs: TSB-17
  - repeat bili-6 hrs: TSB-16, HCT-30%, retic low
Causes of rebound hyperbilirubinemia in infant

- on-going hemolysis in Rh sensitized infant: maternal high titer ab at 34 weeks: 1:128
- Hct decreased even after initial PRBC transfusion: 46% → 30%
- prematurity-36+1 weeks
- breast feeding
Conclusions

- Kernicterus and bilirubin-induced neurologic dysfunction (BIND) can lead to devastating or more subtle life-long deficits and disability

- Adhering to national (AAP) and international guidelines can minimize the risk of kernicterus to extremely low levels

- Early onset, severe, persistent or rebound hyperbilirubinemia should lead to evaluation for undiagnosed or underlying causes
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True or False
References

References


- Barrington KJ, Sankaran K; Canadian Paediatric Society Fetus and Newborn Committees. Guidelines for Detection, management and prevention of hyperbilirubinemia in term and later preterm newborn infants. Paediatr Child Health 2007;12 (Suppl B):1B-12B