Neonatal Hyperbilirubinemia

Background

1. Definition
    - Elevated bilirubin in a newborn caused by either an increased production or a decreased clearance of bilirubin
2. General information
    - Hyperbilirubinemia becomes dangerous at very high levels, when bilirubin can cross the blood brain barrier, causing kernicterus
    - Hyperbilirubinemia is common
    - Kernicterus is rare

Pathophysiology

1. Pathology of disease
    - Bilirubin
        - RBCs breakdown → heme → unconjugated bilirubin → bilirubin conjugated in liver → excreted via bile to intestine → excreted with stool
        - Liver does not begin conjugating bilirubin until several days after birth
        - If baby not stooling well, can be re-absorbed (enterohepatic cycling)
        - Neonatal RBCs less stable, shorter half-life
    - Peak serum bilirubin level (generally)
        - Term: 3-4 days old
        - Pre-term: 4-6 days old
    - Conjugated (direct) bilirubin
        - Fraction of circulating bilirubin conjugated with glucuronic acid by the liver
    - Elevated unconjugated (indirect) bilirubin
        - Most common
        - Usually non-pathologic in etiology
    - Elevated conjugated (direct) bilirubin
        - Rare
        - Usually associated with pathologic etiology
2. Incidence, prevalence
    - Unconjugated hyperbilirubinemia
        - Term (>38 wks GA): 65% visibly jaundiced
        - Near-term (35-38 wks GA): 80% visibly jaundiced
        - <2% become severely hyperbilirubinemic (TsB >20)
        - Kernicterus
            - Rare, likely under-reported, so exact incidence unknown
            - ~ 10 cases per year reported to US national registry
    - Conjugated hyperbilirubinemia: 1 in 2500 live births
3. Risk factors
    - For unconjugated hyperbilirubinemia
        - Major
            - Visible jaundice in first 24 hr

                - Blood group incompatibility (with direct antibody or Coombs test positive) or other known hemolytic dz
                - Gestational age <38 wk
                - Previous sibling receiving phototherapy
                - Cephalhematoma or significant bruising
                - Exclusive breast feeding
                - East Asian race
            - Minor
                - Jaundice before discharge
                - Previous sibling with jaundice
                - Macrosomic infant of diabetic mother
                - Maternal age >25 yo
                - Male gender
            - Negative (protective) risk factors
                - Gestational age ≥41 wk
                - Exclusive bottle feeding
                - Black race
                - Discharge from hospital >72 hr
    - For kernicterus
        - Premature
        - Low birth weight
        - Sepsis
        - Hemolysis
        - Perinatal asphyxia
4. Morbidity / mortality
    - Unconjugated hyperbilirubinemia → lethargy / poor feeding / may lead to dehydration → decreased bilirubin clearance → increased total serum bili [vicious cycle]
    - Kernicterus
        - Results from unconjugated bilirubin crossing blood brain barrier and depositing in / damaging basal ganglia

Diagnostics

1. History
    - Presence of risk factors
        - Pregnancy history
        - Birth history
            - Birth weight, gestational age, traumatic, bruising, perinatal asphyxia / compromise
        - Feeding history
            - Breast vs. bottle, frequency, volume, percent weight loss (>10% weight loss concerning), urine and stooling pattern
        - Family history
            - Previous sibling with jaundice or requiring phototherapy

        - Ethnicity
            - Asian, Native American increased risk; black race decreased risk; G6PD more common in Mediterranean, Middle East, Arabian peninsula, Southeast Asia and Africa
2. Physical exam
    - Vital signs
    - General appearance, hydration status, activity level
    - Skin (perform in well-lit [ideally sunlit] room, but recognize degree of potential inaccuracy of exam): bruising, hematomas, skin color (can be deceptive) focusing on inferior-most leading edge of jaundice
        - General rule for leading edge of jaundice:
            - Nipple line: total serum bili = ~ 5 mg/dL
            - Waist: total serum bili = ~ 10 mg/dL
            - Knees: total serum bili = ~ 15 mg/dL
            - Ankles: total serum bili = ~ 20+ mg/dL
    - Head: cephalhematoma, other signs of trauma
    - Abdomen: hepatomegaly, splenomegaly
    - Anus: patency
    - Neuro: signs of kernicterus
        - High pitched cry
        - Opisthotonus
        - Irritability
        - Poor sucking
        - Lethargy
        - Gaze paralysis
3. Laboratory evaluation
    - Need to investigate etiology if receiving phototherapy or if bilirubin rising rapidly
    - Neonatal
        - Total serum bilirubin (TsB) vs. transcutaneous bilirubin (TcB) measurement
            - TsB preferable and more accurate
            - TcB reasonable for screening, often within +/- 2 mg/dL, but occasionally much more inaccurate; if exam and TcB are discrepant, always check TsB
            - TcB of no value after phototherapy initiated - should only follow TsB!
        - Direct bilirubin if >7 days age; if still visibly jaundiced at > 3 weeks age, re-check direct bilirubin
        - If need to investigate etiology of unconjugated hyperbilirubinemia: (due to requiring phototherapy or rapid rise of TsB)
            - CBC with manual differential and peripheral smear review
            - Reticulocyte count (elevated in hemolysis)
            - Cord blood type and direct antibody (Coombs) test
            - Consider RBC G6PD assay: if unexplained hemolysis, and especially if ethnicity suggestive of risk for G6PD deficiency

        - Perform this test only after retic count normalizes (2-3 weeks later) - elevated retic count can cause falsely normal assay
    - Consider urine for reducing substances
    - Consider sepsis work up (if indicated by clinical history, physical exam, or CBC)
    - Consider cath U/A and urine culture (even in asymptomatic neonate) if >24 hrs age and hyperbilirubinemia persisting / not responding to phototherapy, without other explanation)
    - Consider albumin - if low, decreased binding of bili, so may want to give albumin IV
  - If conjugated hyperbilirubinemia noted
    - LFTs + GGT
    - PT (to assess liver synthetic function)
    - Serum CO2 (to assess for acidosis suggestive of inborn error of metabolism)
    - Ammonia (to assess liver function)
    - Urine reducing substances (to evaluate for galactosemia)
    - TSH and free T4
    - Cultures of blood and urine
    - Alpha-1-antitrypsin genotype
    - Sweat chloride vs. genotype for cystic fibrosis
- Maternal
  - ABO type
  - Rh(D) type
  - Screen for isoimmune antibodies

4. Diagnostic imaging
   - Rarely consider (if worried about extravascular blood collection)
     - Head U/S
     - Abdominal U/S
   - If conjugated hyperbilirubinemia noted
     - Abdominal U/S: recommended first study
     - ERCP vs. MRCP: if needed, discuss with pediatric gastroenterology
   - Other (if conjugated hyperbilirubinemia noted)
     - Liver biopsy
     - Duodenal aspirate via nasoduodenal tube (if bilirubin level in aspirate < serum, highly suggestive of biliary atresia)
5. Diagnostic criteria
   - Unconjugated hyperbilirubinemia
     - TsB at level requiring phototherapy or exchange transfusion intervention
   - Conjugated hyperbilirubinemia
     - Total bilirubin <5 mg/dL, direct bilirubin >1 mg/dL
     - Total bilirubin >5 mg/dL, direct bilirubin >20% of total bilirubin

Differential Diagnosis

1. Unconjugated hyperbilirubinemia
    - Key differential diagnoses (by age)
        - <24 hours age (must worry about pathologic etiology!)
            - Hemolysis (isoimmune, RBC membrane defect, RBC enzymatic defect)
            - Infection
            - Extravascular blood collection (cephalhematoma, intraventricular hemorrhage, etc.)
            - Polycythemia
            - Infant of diabetic mother
        - 1-3 days age
            - Usually physiologic jaundice
            - Breastfeeding jaundice (breastfeeding failure, >10% weight loss, dehydration)
            - Infection
            - Polycythemia
            - Extravascular blood collection (cephalhematoma, intraventricular hemorrhage, etc.)
            - Infant of diabetic mother
        - 3-7 days age
            - Usually physiologic jaundice
            - Breastfeeding jaundice
            - Infection
            - Prolonged effect from cause noted in early age ranges above
        - Persistence beyond 1 week of age
            - Usually breast milk jaundice (due to inhibitors of conjugation / glucuronidation in breast milk)
            - Prolonged effect from cause noted in early age ranges above
    - Extensive differential diagnoses (by cause)
        - Hemolysis
            - Isoimmune
                - ABO, Rh(D), or minor antibody incompatibility
            - RBC membrane defect
                - Hereditary spherocytosis, hereditary elliptocytosis
            - RBC enzymatic defect
                - G6PD deficiency, pyruvate kinase deficiency, congenital erythropoietic porphyria
        - Infection
            - Bacteremia
            - UTI
            - Meningitis
            - Viremia
            - Other

        - Defect in bilirubin conjugation
            - Gilbert's syndrome
            - Crigler-Najjar syndrome
            - OATP-2 polymorphism
        - Metabolic disease
            - Congenital hypothyroidism
            - Galactosemia
        - Intestinal obstruction
2. Conjugated hyperbilirubinemia
    - Key differential diagnoses
        - Extrahepatic obstruction
            - Extrahepatic biliary atresia
            - Choledochal cyst
            - Inspissated bile / mucus plug
            - Cholelithiasis / biliary sludge
        - Infection
            - Viral: TORCH, HIV, adenovirus
            - Bacterial: sepsis, UTI, syphilis
        - Metabolic / genetic disease
            - Alagille syndrome
            - Nonsyndromic paucity of interlobular bile ducts
            - Alpha-1-antitrypsin deficiency
            - Cystic fibrosis
            - Congenital hypothyroidism
        - Toxic
            - Drugs
            - Parenteral nutrition
        - Miscellaneous
            - Shock / hypoperfusion
            - Intestinal obstruction
    - Extensive differential diagnoses
        - Extrahepatic obstruction
            - Tumors / masses
            - Neonatal sclerosing cholangitis
            - Spontaneous perforation of bile ducts
        - Infection
            - Protozoal: Toxoplasma
        - Metabolic / genetic disease
            - Progressive familial intrahepatic cholestasis, types 1-3 (Byler dz)
            - Congenital hepatic fibrosis (Caroli's dz)
            - Inborn errors of metabolism
            - Neonatal hemochromatosis
            - Hypopituitarism / septo-optic dysplasia
        - Miscellaneous
            - Idiopathic neonatal hepatitis

Acute Treatment

1. Unconjugated hyperbilirubinemia
    - ABCs
    - Hydration
        - If patient dehydrated, consider supplemental PO feedings (with expressed breast milk or formula) vs. IV fluid hydration to increase bilirubin clearance
    - Feeding
        - Early and frequent feeding recommended; cessation of breastfeeding not recommended
    - Phototherapy
        - See Treatment thresholds
        - Only appropriate for unconjugated hyperbilirubinemia; causes "bronze baby syndrome" (discolored skin that will not normalize for months) if used for conjugated hyperbilirubinemia
        - Uses specific wavelength of blue light to photoisomerize unconjugated bilirubin into a more hydrophilic form, that can be cleared via the kidneys / urination
        - Maximize skin exposure of neonate (even remove diaper, if feasible and if can keep newborn thermostable)
        - Maximize intensity of phototherapy, ideally via 2 banks of lights from above and a "bili blanket" below
        - Re-check TsB within 4-8 hrs. after starting phototherapy to ensure adequate response (decreasing level)
        - If TsB near threshold for phototherapy, baby appears well, and caregivers are trustworthy, can consider home phototherapy with a "bili blanket" or "bili suitcase", and daily outpatient re-checks with measurement of TsB
        - Exposure to sunlight not effective/safe and not recommended
    - IVIG
        - Consider if immune-related hemolytic cause and if bilirubin continuing to rise despite intensive phototherapy
    - Double-volume exchange transfusion
        - Rarely necessary
        - Only as a last resort if TsB exceptionally high and/or above double-volume exchange transfusion threshold and not decreasing rapidly
    - Treatment thresholds
2. Conjugated hyperbilirubinemia
    - Treat underlying cause

Further Management (24 hrs)

1. Unconjugated hyperbilirubinemia:
    - Bilirubin monitoring with phototherapy
2. Hospital phototherapy
    - Repeat TsB 4-8 hours after initiation of phototherapy to determine pattern of decrease
    - May spread out TsB monitoring if TsB stable or decreasing

- May stop phototherapy when bilirubin reaches <13-14 mg / dL; consider 6-8 hour rebound TsB (after stopping phototherapy) if neonate younger than predicted peak serum bilirubin [Link to relevant pathophysiology above]

3. Home phototherapy: continue to monitor daily serum bilirubin levels
    - Continue to aggressively feed and hydrate newborn; cessation of breastfeeding not recommended
    - Conjugated hyperbilirubinemia: treat underlying cause

Long-Term Care

1. If severe hyperbilirubinemia:
    - Close developmental follow-up
    - Consider neurological consultation and follow-up if any abnormalities
    - Consider head CT vs. MRI
2. Follow for kernicterus signs and symptoms

Follow-Up

1. Return to office
    - Time frame for return visit:
        - All newborn infants should be evaluated within the first 2-3 days after discharge
    - Recommendations for earlier follow-up
        - Increasing jaundice
        - Poor feeding
        - Decreased urine output
        - Decreased stool output
        - Lethargy
2. Refer to specialist
    - Consider neonatology consultation if signs of kernicterus or if exchange transfusion indicated
    - Consider pediatric gastroenterology or neonatology consultation if direct hyperbilirubinemia noted
3. Admit to hospital
    - If requires intensive phototherapy
    - If dehydrated
    - If requires double-volume exchange transfusion
    - If caregivers unreliable

Prognosis

1. Unconjugated hyperbilirubinemia:
    - Very good if treated appropriately
    - If untreated and severe, encephalopathy/kernicterus can lead to irreversible CNS damage including cerebral palsy
2. Conjugated hyperbilirubinemia:
    - Variable, depends upon etiology

Prevention (of kernicterus)

1. Pre-discharge screening of all newborns (exam, consider transcutaneous bilirubin)
2. Early hospital follow-up for all discharged infants (within 2-3 days of discharge)
3. Pre-discharge education for parents
4. Frequent breast feeding along with appropriate support and education for breastfeeding moms (supplementation with water or dextrose water does not prevent hyperbilirubinemia)
5. Prenatal testing of maternal blood type (ABO and Rh), and provision of anti-D antibody (Rhogam) to mothers who are Rh-negative
6. Screening (ABO, Rh, Coombs) of all babies of type O and Rh negative mothers, and mothers with minor antibodies

References

1. American Academy of Pediatrics. Clinical Practice Guideline. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics. 2004 July; 114 (1) 297-316.
2. Kliegman: Nelson Textbook of Pediatrics [Internet].18th ed.Saunders, An Imprint of Elsevier;c2008. 102.3 Jaundice and Hyperbilirubinemia in the Newborn; [cited 2008 July 10]. Available from: http://www.mdconsult.com.offcampus.lib.washington.edu/das/book/body/992867 36-3/723781660/1608/328.html#4-u1.0-B978-1-4160-2450-7..50104-3-- cesec26_2706
3. Porter M, Dennis B. Hyperbilirubinemia in the Term Newborn. Am Fam Physician [Internet]. 2002 Feb 15;65(4):599-606[cited 2008 Jul 10]. Available from: http://www.aafp.org/afp/20020215/599.html
4. DynaMed Editorial Team. Neonatal Hyperbilirubinemia. Last updated 2008 June25. Available from DynaMed: http://www.ebscohost.com.offcampus.lib.washington.edu/dynamed. Accessed July 10, 2008.
5. Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003313. DOI: 10.1002/14651858.CD003313
6. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, Maisels MJ, Lau J; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics. 2004 Jul;114(1):e130-53

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