NEONATAL JAUNDICE

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CAUSES OF PHYSIOLOGIC HYPERBILIRUBINEMIA - 1

Definition:

Full term infant 6-8 mg/l00 ml by 3 days

Premature infant 10-15 fig/100 ml by 5 days

- **An increased bilirubin load : more than 8.5 mg/kg/day**

- **Increased RBCs volume/kg**
- **Decreased fetal RBCs survival - 90 days**
- **Increased early-labeled bilirubin**
- **Increased resorption of bilirubin from intestines**

CAUSES OF PHYSIOLOGIC HYPERBILIRUBINEMIA - 2

- **Defective uptake of bilirubin from plasma**
  - Decreased y protein
  - Binding of y and z proteins by other anions
  - Decreased caloric intake
- **Defective bilirubin conjugation and excretion**
  - low levels of UDPGT
  - Inhibition of conjugation by maternal steroids

Nonphysiologic Hyperbilirubinemia

- ✓ Jaundice < 36 hours of age
- ✓ Serum bilirubin > 12 mg / 100 m1.
- ✓ Jaundice > 8 days
- ✓ Direct-reacting bilirubin > 1.5 mg / 100 m1.
- ✓ Bilirubin increasing by > 5 mg /100 m1/ day

Causes For Neonatal Hyperbilirubinemia
Overproduction - 1

- Fetal-maternal blood group incompatibility- Rh,ABO,others
- Hereditary spherocytosis , elliptocytosis, somatocytosis
- Nonspherocytic hemolytic anemias
- G6PD deficiency and drug Pyruvate kinase deficiency
- Other red-cell enzyme deficiencies
- a-thalassemia
- B-thalassemia
- Vitamin K induced hemolysis

Causes For Neonatal Hyperbilirubinemia
Overproduction - 2

Extravascular blood :

petechiae, hematomas

pulmonary, cerebral, or occult hemorrhage

Polycythemia:

Maternal-fetal or feto -fetal transfusion

Delayed clamping of the umbilical cord

Causes For Neonatal Hyperbilirubinemia
Overproduction - 3

Increased enterohepatic circulation:

- **Pyloric stenosis**
- **Intestinal atresia or stenosis including annular pancreas**
- **Hirschsprung disease**
- **Meconium ileus or meconium plug syndrome**
- **Fasting or hypoperistalsis from other causes**
- **Drug-Induced paralytic ileus {hexamethonium}**
- **Swallowed blood**

Causes For Neonatal Hyperbilirubinemia
Undersecretion - 1

Metabolic and endocrine conditions:

- Familial nonhemolytic jaundice types 1 and 2 (Crigler- Najjar syndrome)
- Galactosemia
- Hypothyroidism, Tyrosinosis, Hypermethioninemla
- Drugs and hormones: Novobiocin, Pregnanediol
- Certain breast milks
- Lucey-Driscoll syndrome
- Infants of diabetic mothers
- Prematurity
- Hypopituitarism and anencephaly

Causes For Neonatal Hyperbilirubinemia
Undersecretion - 2

Obstructive disorders:

- Biliary atresia
- Dubin.Johnson and Rotor's syndrome
- Choledochal cyst
- Cystic fibrosis (inspissated bile).
- Tumor or band (extrinsic obstruction)
- *a*, antitrypsin deficiency

Causes For Neonatal Hyperbilirubinemia

Mixed

- Sepsis
- Intrauterine Infections:
  Toxoplasmosis, Rubella, Syphilis,
  Herpes simplex, Hepatitis,
  Cytomegalovirus inclusion dis.
- Respiratory distress syndrome

TRANSPORT OF BILIRUBIN IN PLASMA

- ✓ Unconjugated bilirubin binds to albumin

  in a 2:1 molar ratio.
- ✓ Organic anions take % of binding sites.
- ✓ 25 mg/100 m1 UCB saturates all sites of 3

  gm/10q m1. albumin.
- ✓ Albumin binding is affected by: hypoxia, ph,

Transfer of Bilirubin Into The Brain

- ✓ Unbound UCB (free) diffuses easily into the brain.
- ✓ The concentration of free UCB determines the amount entering the brain.
- ✓

Kernicterus

***Definition* :**

Yellow discoloration of specific areas of brain usually the basal ganglia and hippocampus caused by bilirubin.

***Staging* :**

Stage I : Hypotonicity , lethargy, poor suck
Stage II : Spasticity , opisthotonus , seizures, fever
Stage III : Spasticity decreased
Stage IV : Spasticity , athetosis , deafness, mental retardation.

N. B. Some bilirubin encephalopathy is asymptomatic in the neonatal period

Causes of Kernicterus

- ✓ *UCB levels > 20 – 25 mg / 100 m1.*
- ✓ *UCB levels of < 20 mg / 100 m1 in low birth weight infants with RDS, hypoxia or acidosis.*
- ✓ *Kernicterus is more likely to occur with increase in UCB, increased organic anions, decreased albumin, decreased ph,*

Bilirubin Concentrations and Kernicterus

Serum bilirubin concentrations at which kernicterus of sequelae of hyperbilirubinemic encephalopathy were noted in premature newborns ; observational studies.

Study (Year)	Concentration , mg/dl
Crosse et al 14 (1955)	>18
Meyer 15 (1956)	>18
Crosse et al 16 (1958)	>22
Crosse and Obst 17 (1961)	>22
Koch et al 18 (1959)	>20
Hugh-jones et al 19 (1960)	>30

Danger Signs in Jaundiced Infants

- Family history of significant hemolytic disease
- Vomiting
- Lethargy
- Poor feeding
- Fever
- Onset of jaundice after the third day
- High-pitched cry
- Dark urine
- Family history of litigation (!)

Premature Newborns at Risk for Kernicterus

- Birth weight < 1500 g
- Hypothermia
- Asphyxia
- Acidosis
- Hypoalbuminemia
- Sepsis
- Meningitis
- Drugs that affect albumin binding
- Serum bilirubin > 10 mg /dl

Clinical Tests For Hyperbilirubinemia

- ✓ Serum bilirubin , direct and indirect
- ✓ Blood typing of mother and infant
- ✓ Coombs test on infant
- ✓ Identification of antibody
- ✓ CBC , reticulocytes count
- ✓ Serum albumin
- ✓ Test of bilirubin binding
- ✓ Liver function tests
- ✓ T4

Evaluation of Infants in the Hospital or Infants for Whom Follow-up Is Easy

Maneuver	*Indications*
Blood type and group, mother	All mothers
Follow infant for significant jaundice	All infants
Measure bilirubin level	All infants with significant jaundice
Blood type, Group,Coombs test	TB >240-260 umol/L (14-15 mg/dl) and group O or Rh-negative mother
Follow bilirubin level until peak	Infants with evidence of hemolysis

Evaluation and Follow-up of Jaundiced Infants in Whom Repeated Follow –up Tests Are Difficult or Unreliable

Maneuver	*Indications*
Blood type & group, *mother*	All mothers
Blood type and group, *infant* (cord blood)	Infants of Rh-negative or group O mothers (or all infants if selective testing is not feasible)
Direct Coombs' test, *infant* (cord blood)	Incompatibility with mother (or all infants if selective testing is. Not feasible)
Close clinical follow – up for jaundice	Infants with evidence of isoimmunization
Serum bilirubin level	1. Jaundice in the first 24 hours OR 2. Moderate jaundice AND either a. Positive Coombs test OR b. Parents anxious OR c. Baby has other signs of illness 3. Marked jaundice

Additional Laboratory Evaluation of the Jaundiced Term Infant

Maneuver	*Indications*
Complete blood Cell count or hemoglobin level	Suspicion of hemolytic disease or anemia (e.g. early jaundice or TB*>240umol / L (14 mg / dL) in first 48 h)
Reticulocytes count , blood smear	Questionable value : consider if infant is anemic or there is a strong clinical suspicion of hemolytic disease other than isoimmunization
Glucose-6-phosphate dehydrogenase screen	Consider in Asian or Mediterranean infants (especially males) with TB> 260 umol/L (15 mg/dl) particularly if late onset jaundice
Direct bilirubin level and / or urine dipstick for bilirubin	Persistent jaundice (>2wk) or baby ill

Causes of Cholestasis in the Neonate

Anatomic abnormalities: A. Extrahepatic

1. Biliary atresia
2. Biliary hypoplasia
3. Bile duct steniosis
4. Choledochal-pancreatico-ductal junction anomaly
5. Spontaneous perforation of bile duct
6. Choledochal cyst
7. Mass (neoplasia, stone)
8. Bile / mucous plug

Causes of Cholestasis in the Neonate

Anatomic abnormalities: B. Intrahepatic

1. Idiopathic neonatal hepatitis

2. Intrahepatic cholestasis, persistent

   a. Nonsyndromic paucuty of intrahepatic ducts (apparent absence of bile ductules)

   b. Arteriohepatic dysplasia (Alagille syndrome)

   c. Byler disease (severe intrahepatic cholestasis with progressive hepatocellular disease)

   d. Trihydroxycoprostanic acidemia (defective

Causes of Cholestasis in the Neonate

Anatomic abnormalities: B. Intrahepatic

3. Intrahepatic cholestasis,recurrent syndromic?)

a. Familial benign recurrent cholestasis

b. Hereditary cholestasis with lymphedema (Aagenaes)

4. Congenital hepatic fibrosis

5. Caroli disease (cystic dilation of intrahepatic ducts)

Causes of Cholestasis in the Neonate

II. Metabolic disorders

A. Disorders of amino acid metabolism

1. Tyrosinemia
2. Hypermethioninemia

B. Disorders of lipid metabolism

1. Wolman disease
2. Niemann-Pick disease
3. Gaucher disease

C. Disorders of carbohydrate metabolism

1. Galactosemia
2. Fructosemia
3. Glycogenosis IV

Causes of Cholestasis in the Neonate

II. Metabolic disorders

D. Uncharacterized metabolic disease defect

1. a –Antitrypsin dificiency
2. Cystic fibrosis
3. Idiopathic hypopituitarism
4. Hypothyroidism
5. Neonatal iron storage disease
6. Indian childhood cirrhosis
7. Multiple acyl-CoA dehydrogenation dificiency
   (glutaric acid typeII

Causes of Cholestasis in the Neonate

III. Hepatitis

A. Infectious

1. Cytomegalovirus
2. Hepatitis B virus (? Non-A, non-B virus)
3. Rubella virus
4. Hypothyroidism
5. Varicella virus
6. Coxsakie virus
7. ECHO virus
8. Toxoplasmosis
9. Syphilis
10. Tuberculosis
11. Listeriosis

B. Toxic

1. Cholestasis associated with parenteral nutrition
2. Sepsis with possible endotoxemia (urinary tract infection, gastroenteritis)

Causes of Cholestasis in the Neonate

IV. Genetic / chromosomal

A. Trisomy E
B. Down syndrome
C. Donahue syndrome (Liprechaunism)

V. Miscellaneous

A. Histiocytosis X
B. Shock
C. Intestinal obstruction infection, gastroenteritis

Initial Workup for Suspected Cholestasis

- Fractionated serum bilirubin and serum bile acid determinations
- Index of hepatic synthetic function (prothrombin time)
- Stool color
- Cultures (blood, urine , spinal fluid)
- HB,AG, TORCH, and VDRL titers
- a–Antitrypsin phenotype
- Metabolic screen (urine/ serum amino acids, urine reducing substances)
- Thyroxine and thyroid – stimulating hormone
- Sweat chloride test
- Ultrasound
- Duodenal intubation for bilirubin content
- Hepatobiliary scintigraphy
- Liver biopsy

Consequences of Persistent Cholestasis - 1

Effect	*Management*
Malnutrition	Replace with dietary formula or supplement containing medium – chain triglyceride
Malabsorption of dietary long-chain triglyceride	Adequate protein (vegetable protein)
	Adequate calories (complex starch)
Fat-soluble vitamin deficiency	
A (night blindness,thick skin)	Replace with 10,000 to 15,000 IU/day as Aquasol A
E (neuromuscular degeneration)	Replace with 50 to 400 IU /day as oral a -tocopherol (may require parenteral administration)
D (metabolic bone disease)	Replace with 5000 to 8000 IU/day vitamin D or 3 to 5 ug/kg/day 25-hydroxycholeciferol
K (hypoprothrombinemia)	Replace with 2.5 to 5.0 mg every other day as water-soluble derivative of menadione
Micronutrient deficiency	Calcium / phosphate / zinc supplementation
Deficiency of water – soluble vitamins	Supplement twice recommended daily allowance

Suggested Medical Management of Consequences of Persistent Cholestasis - 2

EFFECT	*MANAGEMENT*
Retention of biliary constituents	
Bile acids and cholesterol (itch / xanthomas)	**Choleretics (phenobarbital 5-10 mg /kg/day)** **Bile acid binders (cholestyramine 8-16gm/day**
Trace elements, such as copper (? Hepatotoxicity)	**?Avoid copper-enriched food** **?Chelating agents**
Progressive liver disease Portal hypertension (variceal bleed, ascites, hypersplenism)	**Inter management (control bleeding, salt restriction(**
End – stage liver disease	**Transplantation**