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Review Article

Neonatal Jaundice–up to date Review

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ABSTRACT

Jaundice is the visible manifestation of chemical bilirubinemia. In adults sclera appears jaundiced when serum bilirubin exceeds 2 mg/ dl. In neonates, evaluation of sclera is difficult because of physiological photophobia. Icterus, however, becomes apparent on the skin when serum bilirubin reaches more than 5 mg/ dl. Almost all neonates (60% Term and 80% Preterm) will have bilirubin greater than 5 mg/ dl in the first week of life and about 6% of term babies will have levels exceeding 15 mg/ dl. Approximately 60% of term babies and 85% of preterm babies will develop clinically apparent jaundice.1,2 Most of these babies have so-called 'physiological jaundice', which typically becomes clinically apparent on day 3, peaks on day 5 to 7 and resolves by day 14. Physiological jaundice is usually benign, however if unconjugated serum bilirubin levels get too high, bilirubin can cross the blood brain barrier where it is neurotoxic, particularly to the auditory nerve and basal ganglia. Brain injury and life long disability can result. Because of this, it is important to identify those babies at risk of the rare complication of acute bilirubin encephalopathy and kernicterus.1,2 The clinical challenge is identifying the tiny minority with pathological neonatal jaundice from the large majority with benign physiological jaundice. There are important cues that jaundice may be pathological. Phototherapy mat. Phototherapy is a safe, effective method for lowering serum bilirubin, and reduces the need for exchange transfusion. The level for starting phototherapy is based on observational data only. This article provides a framework for the Diagnosisi,prevention and management of hyperbilirubinemia in newborn infants of 35 or more weeks of gestation.

KEY WORDS : Physiological Jaundice, Bilirubin, Phototherapy, Hyperbilirubinemia.

Physiologic Jaundice

(non-pathologic unconjugated hyperbilirubinemia):

Term Infants

50–60 % of all newborns are jaundiced in the first week of life. •Total serum bilirubin peaks at age 3–5 d (later in Asian infants). Mean peak total serum bilirubin is 6 mg/dL (higher in Asian infants). 2. Preterm Infants: •Incidence of visible jaundice is much higher than in term infants. •Peak is later (5–7d). •Because of ↑ risk of bilibubin encephalopathy (see below), "physiologic" jaundice is more difficult to define and jaundice should be followed closely (1).

Definition of Non-Physiologic Jaundice

Jaundice in the first 24 hours •Bilirubin rising faster than 5 mg/dL in 24 hours •Clinical jaundice >1 week •Direct bilirubin >2 mg/dL •In healthy term infants total serum bilirubin concentration >15 mg/dL •Lower levels in preterm infants, "sick" infants, and hemolytic disease.

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Bilirubin Metabolism

As red blood cells are lysed, they release hemoglobin. Heme molecules (from hemoglobin) are converted to bilirubin. Bilirubin (unconjugated or indirect) is bound to serum albumin and transferred to the liver where it is conjugated to glucuronate by glucuronyl transferase. Conjugated (direct) bilirubin is excreted into bile. A fraction of bilirubin from the stool is reabsorbed into the blood via the portal circulation (enterohepatic circulation) (2-3).

Bilirubin Encephalopathy

The mildest form of bilirubin encephalopathy is sensorineural hearing loss due to damage to the cochlear nuclei. Severe encephalopathy causes kernicterus. Factors predisposing to neurotoxicity of unconjugated hyperbilirubinemia include: •When bilirubin concentration exceeds the binding capacity of serum albumin •Displacement of bilirubin from albumin by acidosis or certain drugs (e.g., sulfonamides, ceftriaxone) •Sepsis •Preterm infants due to↑ risk due lower serum albumin concentrations and ↑ risk for acidosis and sepsis (4-5).

Causes Of Unconjugated (Indirect) Hyperbilirubinemia

1. Increased lysis of RBCs (i.e., increased hemoglobin release) •Isoimmunization (blood group incompatibility: Rh, ABO and minor blood groups) •RBC enzyme defects (e.g., G6PD deficiency, pyruvate kinase deficiency) •RBC structural abnormalities (hereditary spherocytosis, elliptocytosis) •Infection (sepsis, urinary tract infections) •Sequestered blood (e.g., cephalohematoma, bruising, intracranial hemorrhage)•Polycythemia •Shortened life span of fetal RBCs (80 vs. 120 d)
2. Decreased hepatic uptake and conjugation of bilirubin •Immature glucuronyl transferase activity in all newborns: term infants have 1% of adult activity, preterm infants have 0.1%. •Gilbert Syndrome •Crigler Najjar Syndrome (Non-hemolytic Unconjugated Hyperbilirubinemia): inherited conjugation defect (very rare) •Pyloric stenosis (mechanism is unknown) •Hypothyroidism •Infants of Diabetic Mothers (polycythemia is also common) •Breastmilk Jaundice (pregnanediol inhibits glucuronyl transferase activity)
3. Increased enterohepatic reabsorption •Breast feeding jaundice (due to dehydration from inadequate milk supply) •Bowel obstruction •No enteric feedings (6-9)

Evaluation Of Jaundice (Unconjugated)

1. Initial evaluation: •Total and direct bilirubin •Blood type and Rh (infant & mother) •Hematocrit •Direct Antiglobulin (Coombs) Test on infant
2. Later evaluation (as indicated): •RBC smear, reticulocyte count (if evidence or suspicion of hemolytic disease) •Blood culture, urinalysis, urine culture •Thyroid function tests, G6PD assay, Hgb electrophoresis
3. Preterm Infants: Because of ↑ risk of bilibubin encephalopathy, therapy should be started at lower bilirubin concentrations. In general, bilirubin shoud not be allowed to exceed the infant's weight in kg x 10 (e.g., for 1.0 kg infant, keep bilirubin <10 mg/dL).

Conjugated (Direct) Hyperbilirubinemia (Cholestasis)

Clinically, jaundice is green compared to jaundice due to unconjugated hyperbilirubinemia (yellow). 1. Hepatocellular diseases: A. Hepatitis: •Neonatal idiopathic hepatitis •Viral (Hepatitis B, C, TORCH infections) •Bacterial (E. coli, urinary tract infections) B. Total parenteral nutrition C. Hepatic ischemia (post-ischemic damage) D. Erythroblastosis fetalis (late, "Inspissated Bile Syndrome") E. Metabolic disorders (partial list): •Alpha-1 antitrypsin deficiency •Galactosemia, tyrosinemia, fructosemia •Glycogen storage disorders •Cerebrohepatorenal disease (Zellweger) •Cystic fibrosis •Hypopituitarism 2. Biliary tree abnormalities: A. Extrahepatic biliary atresia: In first 2 weeks,, unconjugated bilirubin predominates; elevated conjugated bilirubin is late. B. Paucity of bile ducts (Alagille's vs. non-syndromic) C. Choledochal cyst D. Bile plug syndrome(10-14)

Evaluation And Managenment Of Cholestasis

1. Initial evaluation: •Total and direct bilirubin •AST, ALT, GGT, urine reducing substances •Hepatic ultrasound 2. Later evaluation (as indicated): •Hepatitis B and C serology •α1-antitrypsin deficiency studies •Very long chain fatty acids •Brain sonogram •HIDA scan •Cholangiogram 3. Management: •Conjugated bilirubin is not toxic. •Management is treatment of cause. •Phototherapy will cause "bronzing" with conjugated hyperbilirubinemia.

Immature newborn brain is susceptible to toxicity from unconjugated bilirubin resulting in "Kernicterus" or "bilirubin brain damage". Jaundice is the visible manifestation of chemical bilirubinemia. In adults sclera appears jaundiced when serum bilirubin exceeds 2 mg/ dl. In neonates, evaluation of sclera is difficult because of physiological photophobia. Icterus, however, becomes apparent on the skin when serum bilirubin reaches more than 5 mg/ dl. Almost all neonates (60% Term and 80% Preterm) will have bilirubin greater than 5 mg/ dl in the first week of life and about 6% of term babies will have levels exceeding 15 mg/ dl (10-13).

1. Source of production

Bilirubin is derived from the breakdown of heme proteins which are present in hemoglobin, myoglobin and certain heme containing enzymes. Three fourths of the bilirubin comes from hemoglobin catabolism. One gram of hemoglobin results in the production of 34 mg of bilirubin. A normal term newborn produces about 6-10 mg/kg/ day of bilirubin (14).

2. Metabolism

Bilirubin is bound to albumin for transport in the blood. This bound bilirubin does not enter the central nervous system and is nontoxic. ii. Upon reaching the liver, only bilirubin enters the liver cell and gets bound to ligandin which helps to transport it to the site of conjugation. iii. Conjugation occurs with glucuronic acid to produce mono- and diglucuronides which are water soluble. iv. The conjugated bilirubin is transported with the bile to the gut. In the sterile newborn gut, there is an enzyme called beta- glucuronidase which converts bilirubin glucuronide into unconjugated bilirubin which is reabsorbed into the circulation. This is called enterohepatic circulation and is particularly important in babies who are infrequently fed from birth. With frequent feeding early colonization of gut occurs. These bacteria reduce bilirubin glucuronide into stercobilin which is excreted in stool, thus inhibiting the enterohepatic circulation (14-16).

Assessment Of Jaundice Clinical Criteria

It is very widely used and utilizes the principle that clinical jaundice first becomes obvious in the face followed by a downward progression as it increases in intensity. Assessment of jaundice should be done in natural light. The finger is pressed on the baby's skin, preferably over a bony part, till it blanches. The underlying skin is noted for yellow color. Extent of jaundice thus detected gives a rough estimate of serum bilirubin. Clinical estimation of bilirubin by experienced person, though reliable, has to be confirmed by laboratory methods (14-17).

Physiological Jaundice

Immaturity in bilirubin metabolism at multiple steps results in the occurrence of hyperbilirubinemia in the first few days of life. These are: • Increased bilirubin load on the hepatic cell • Defective uptake from plasma into liver cell • Defective conjugation • Decreased excretion • Increased entero-hepatic circulation Characteristics of physiological jaundice • First appears between 24-72 hours of age • Maximum intensity seen on 4-5th day in term and 7th day in preterm neonates • Does not exceed 15 mg/ dl • Clinically undetectable after 14 days. • No treatment is required but baby should be observed closely for signs of worsening jaundice.

Pathological jaundice Presence of any of the following signs denotes that the jaundice is pathological. Treatment is required in the form of phototherapy or exchange blood transfusion. One should investigate to find the cause of pathological jaundice. • Clinical jaundice detected before 24 hours of age • Rise in serum bilirubin by more than 5 mg/ dl/ day • Serum bilirubin more than 15 mg/ dl • Clinical jaundice persisting beyond 14 days of life • Clay/white colored stool and/or dark urine staining the clothes yellow • Direct bilirubin >2 mg/ dl at any time Causes of jaundice Hyperbilirubinemia in the first week of life is usually of the indirect variety. Causes are usually classified based on the time of onset of jaundice. While referring a baby with jaundice make sure that either the mother is referred or mother's blood sample is sent (14-19).

1. APPEARING WITHIN24 HRS OF AGE: Hemolytic disease of newborn: Rh, ABO and minor group incompatibility Infections: intrauterine viral, bacterial; malaria G-6PD deficiency
2. APPEARING WITHIN24-72 HRS OF AGE: Physiological Sepsis neonatorum Polycythemia Concealed hemorrhages: cephalhematoma, subarachnoid bleed, IVH. Increased enterohepatic circulation
3. APPEARING AFTER 72 HRS : Neonatal hepatitis Extra hepatic biliary atresia Breast milk jaundice Metabolic disorders

Remember that • The age of appearance may overlap and the above mentioned grouping is only a general classification. • Infection must be ruled out in jaundice appearing any time after third day of life. • Even after extensive investigations, cause remains uncertain in over one third of cases. • Neonatal jaundice may be multifactorial in origin.

Risk Factors Of Jaundice

A simple pneumonic for risk factors is JAUNDICE J - Jaundice within first 24 hrs of life A - A sibling who was jaundiced as neonate U - Unrecognized hemolysis N – Non-optimal sucking/nursing D - Deficiency of G6PD I - infection C – Cephalhematoma / bruising E - East Asian/North Indian (20-22).

Common Causes In India

Physiological : Blood group incompatibility • Intrauterine and postnatal infections • G-6PD deficiency • Bruising and cephalhematoma • Breast milk jaundice

1. Breast Milk Jaundice :

This condition may persist as a prolonged physiological jaundice or it may appear for-the first time after the first week. It is common in solely breast fed babies and the intensity is maximum between 10-14 days of life. The bilirubin levels are never high enough to require exchange though phototherapy may occasionally be necessary. If bilirubin is less than 15 mg/ dl at 3 weeks one need not worry. But if bilirubin is > 15 mg/dl at 3 weeks, cessation of breast milk for 48 hours will decrease bilirubin levels dramatically and breast milk can be resumed without any risk of recurrence of jaundice. However, more frequent breast feeds without cessation results in improvement in many (20).

Approach to a jaundiced baby The following four questions need to be answered What is the birth weight? What is the gestation? What is the postnatal age in hours? Is the jaundice physiological or pathological? If the jaundice is physiological and baby is well only observation is necessary. Workup for pathological jaundice 1. R e vie w mat e rn al an d p e ri n at al his t o ry Family history of jaundice, liver disease Previous sibling with jaundice for blood group incompatibility Maternal illness during pregnancy Previous history of malaria Traumatic delivery, delayed cord clamping, oxytocin use Birth asphyxia, delayed feeding, delay in meconium passage Breast feeding.(20-22)

2. Physical examination

Prematurity Small for gestation: polycythemia, hepato-splenomegaly, cataract, rash. Extravascular bleed: cephalhematoma Pallor: hemolysis, blood loss Petechiae: sepsis, TORCH infections Hepatosplenomegaly: Rh-isoimmunization, sepsis, TORCH infections

3. Laboratory Tests

Serum bilirubin total and direct* Blood group and Rh for mother and baby* Direct Coomb's test on infant Hematocrit* Peripheral smear for RBC morphology, evidence of hemolysis and, reticulocyte count Sepsis screen Liver and thyroid function tests in cases with prolonged jaundice TORCH titres.(23-25)

Prolonged Jaundice

Babies with prolonged jaundice (visible jaundice persisting for greater than 2 weeks in term babies and greater than 3 weeks in preterm babies) should be reviewed for history suggestive of obstructive jaundice e.g. acholic pale stools. In all babies with prolonged jaundice, blood should be taken for total and conjugated bilirubin level. • Predominantly unconjugated prolonged jaundice (conjugated SBR less than 30 micromol/l): is usually benign breast milk jaundice but consider performing thyroid function tests to exclude thyroid agenesis/dysplasia or hypopituitarism, and a urine culture to exclude a UTI. • Predominantly conjugated prolonged jaundice (conjugated SBR greater than 30 micromol/l): is always pathological and the baby should be investigated for intra-hepatic (e.g hepatitis) and obstructive (e.g biliary atresia) causes of prolonged jaundice. (see Conjugated Jaundice Guideline) There should be no delay in investigation because age at diagnosis of biliary atresia is an important prognostic factor for successful surgical repair. So such babies should be referred urgently to a tertiary Paediatric centre that has the facilities to investigate these babies and particularly to exclude biliary atresia.

Management

Management of jaundice is directed towards reducing the level of bilirubin and preventing CNS toxicity. 1. Prevention of hyperbilirubinemia i. Early and frequent feeding ii. Adequate hydration 2. Reduction of bilirubin: This is achieved by phototherapy or/and exchange transfusion (23-29).

Phototherapy

Phototherapy is the first line treatment for neonatal jaundice and is effective in most babies in reducing TSB level. Its efficacy depends on wavelength and luminance of the light source and the skin surface area illuminated by the light.

This involves exposure of the naked baby to blue, cool white or green light of wave length 450-460 nm. The light waves convert the bilirubin to water soluble nontoxic forms which are then easily excreted. Every attempt should be made to find out the cause of jaundice. The advantages of phototherapy are that it is noninvasive, effective, inexpensive and easy to use. Clinical assessment of bilirubin level should not be relied upon in an infant under phototherapy. Frequent feeding every 2 hrly and change of posture should be promoted in an infant receiving phototherapy. Eye shades should be fixed.External genitalia may be covered as long as the infant is receiving phototherapy. Additional oral intake of plain water or glucose water is neither recommended nor necessary (23-25).

Risk Factors

Babies with any of the risk factors below should start phototherapy according to the line one below that indicated by their gestational age. These risk factors include: • Haemolysis, • G6PD deficiency, • Asphyxia, • Proven sepsis, • Any baby who is unwell: e.g. lethargy, temperature instability, respiratory distress, acidosis. albumin less than 30gram/L (if measured) In babies with severe (close to exchange levels) or rapidly rising SBR, the efficacy of phototherapy can be optimised by removing all clothes and nappy and having more than one light above the baby and having the baby lie on a fibre optic or LED. Phototherapy mat. Phototherapy is a safe, effective method for lowering serum bilirubin, and reduces the need for exchange transfusion. The level for starting phototherapy is based on observational data only (29).

Technique

Six to eight daylight tubes or four blue tubes are mounted on a stand and all electrical outlets are well grounded. Inexpensive commercial phototherapy units are freely available. Tubes are changed after every 1000 hours or 3 months of use. One may use 150 watt halogen bulb (life 1000 hours) for providing effective phototherapy. Blue CFL lamps may also be used which should be changed every 3000h. ii. Check flux with help of fluxmeter. Ideal 6-8 µw/cm2/nm. iii. A Plexiglas shield should be used to cover the tube lights, if the unit is locally made. iv. Baby is placed naked 45 cm away from the tube lights in a crib or incubator. If using closer, monitor temperature of the baby. v. Eyes are covered with eye-patches to prevent damage to the retina by the bright lights; gonads should also be covered. vi. Phototherapy is switched on. vii. Baby is turned every two hours or after each feed. viii. Temperature is monitored every two to four hours. ix. Weight is taken at least once a day. x. More frequent breastfeeding or 10-20% extra fluid is provided. xi. Urine frequency is monitored daily. xii. Serum bilirubin is monitored at least every 12 hours. xiii. Phototherapy is discontinued if two serum bilirubin values are < 10 mg/dl (27-29).

Side Effects Of Phototherapy

Increased insensible water loss: Provide more frequent and for longer duration extra breast feeding. Loose green stools: weigh often and compensate with breast milk. Skin rashes: Harmless, no need to discontinue phototherapy; Bronze baby syndrome: occurs if baby has conjugated hyperbilirubinemia. If so, discontinue phototherapy; Hypo or hyperthermia: monitor temperature frequently (25-28).

Exchange Transfusion

It is still the most effective and reliable method to reduce serum bilirubin. Anticipation and early referral to a higher centre is indicated. Choice of blood for exchange blood transfusion (i) In ABO incompatibility: Use O cells of same Rh type, ideal is to have O cells suspended in AB plasma. (ii) In Rh isoimmunization: In emergency use O-ve blood. Ideal is O -ve cells suspended in AB plasma. One may use baby blood group but Rh –ve blood also. (iii) Other conditions: Baby's blood group.

Prolonged indirect jaundice Following conditions may lead to prolonged indirect jaundice:

• Crigler Najjar Syndrome • Breast milk jaundice • Hypothyroidism • Pyloric stenosis • Ongoing hemolysis, malaria

Conjugated hyperbilirubinemia :

This is rare in the newborn period and is defined as a direct bilirubin level of > 2 mg/dl. It is important to document cause as it is never physiological. A p p r o a c h : The following five questions need to be answered Is the baby symmetric SGA? Is the stool white or clay colored? Is the urine high colored? Are liver and spleen enlarged? Is the baby on total parenteral nutrition? R e m e m b e r Never discharge a baby with conjugated hyperbilirubinemia without attempting to find the cause.

Rule out or establish the diagnosis of extra hepatic biliary atresia within eight weeks of life when it is still surgically correctable. These babies are preferably managed in a Level II neonatal unit. Exclude metabolic conditions especially galactosemia (25-29).

Causes Of Conjugated Hyperbilirubinemia

1. Idiopathic neonatal hepatitis 2. Infections -Hepatitis B, TORCH, Sepsis 3. Malformations -Biliary atresia (extra and intrahepatic), choledochal cyst, bile duct stenosis. 4. Metabolic disorder -Galactosemia Hereditary Fructose intolerance Alpha-l antitrypsin deficiency Tyrosinemia Glycogen storage disease type IV Hypothyroidism 5. Total parenteral nutrition

This review is a compilation of information of neonatal jaundice with respect to its types, etiology, symptoms, diagnosis, treatment and preventive measures. Jaundice is the most common condition that requires medical attention in newborns. Emphasis is given on diagnostic techniques to detect the presence of jaundice in neonate's body. Neonatal Jaundice if diagnosed on time can be cured and the overall increase in death rate of neonates due to this condition can be reduced. Treatment of neonatal jaundice requires blue light, wavelength of 420–448 nm, which oxidizes the bilirubin to biliverdin, a soluble product that does not contribute to kernicterus. Phototherapy machines imported into resource-poor settings often have a short working life, limited by problems maintaining the equipment. Some novel ideas to create effective phototherapy machines with locally available resources are in development [29-

30], but these still need testing and widespread dissemination.

To conclude, neonatal jaundice is an important aspect of neonatal morbidity. There are well-developed systems to identify, investigate and manage the problem in developed health care systems, but much research and development is still needed to address the problem in resource-poor settings.

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