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Review Article

Hyperbilirubinemia in Neonates--A Comprehensive Review

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ABSTRACT

Newborn jaundice occurs when a baby has a high level of bilirubin in the blood. Bilirubin is a yellow substance that the body creates when it replaces old red blood cells. The liver helps break down the substance so it can be removed from the body in the stool. Neonatal hyperbilirubinemia is the most common clinical condition in the newborn requiring evaluation and management and remains a frequent reason for hospital readmission during the first week of postnatal life.[1,2] The high prevalence of neonatal hyperbilirubinemia reflects developmental red blood cell, hepatic, and gastrointestinal immaturities that result in an imbalance favoring bilirubin production over hepatic–enteric bilirubin clearance.[3,4] For most neonates, hyperbilirubinemia is a benign postnatal transitional phenomenon of no overt clinical effect. A subset of infants, however, will develop more significant hyperbilirubinemia. The estimated occurrence of hyperbilirubinemia based on peak total serum bilirubin (TSB) severity has been reported as: more than 17 mg/dL (291 µmol/L), defined as significant, at ~1 in 10; more than 20 mg/dL (342 µmol/L), defined as severe, at ~1:70; more than 25 mg/dL (428 µmol/L), defined as extreme, at ~1:700; and more than 30 mg/dL (513 µmol/L), defined as hazardous, at ~1:10,000 live births. The central nervous system sequelae of kernicterus reflect both a predilection of bilirubin toxicity for neurons (relative to glial cells) and the regional topography of bilirubin-induced neuronal damage characterized by prominent involvement of the globus pallidus and subthalamic nuclei, the eighth cranial nerve and cochlear nuclei, the dorsal midbrain periaqueductal grey, and the dentate nuclei of the cerebellum.[7,10] CBE is classically characterized by dystonia, athetosis, auditory neuropathy spectrum disorder, paresis of vertical gaze, and dental enamel dysplasia.[7,10] The prevention of kernicterus remains a serious Newborn jaundice occurs when a baby has a high level of bilirubin in the blood. Bilirubin is a yellow substance that the body creates when it replaces old red blood cells. The liver helps break down the substance so it can be removed from the body in the stool.

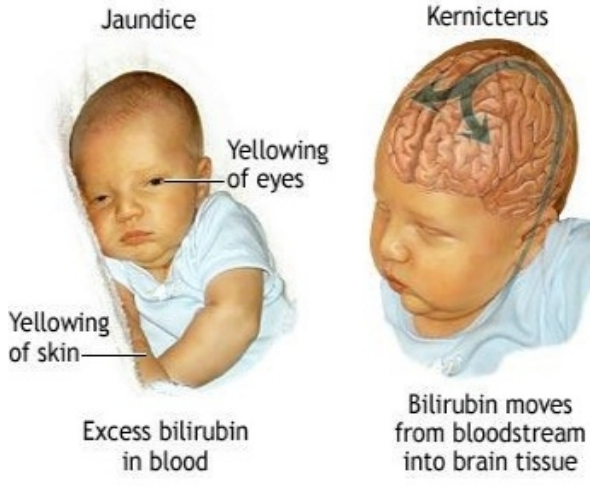
INTRODUCTION:

A high level of bilirubin makes a baby's skin and whites of the eyes look yellow. This is called jaundice.It is normal for a baby's bilirubin level to be a bit high after birth.When the baby is growing in the mother's womb, the placenta removes bilirubin from the baby's body. The placenta is the organ that grows during pregnancy to feed the baby. After birth, the baby's liver starts doing this job. It may take some time for the baby's liver to be able to do this efficiently[4].Most newborns have some yellowing of the skin, or jaundice. This is called physiological jaundice. It is often most noticeable when the baby is 2 to 4 days old. Most of the time, it does not cause problems and goes away within 2 weeks.Two types of jaundice may occur in newborns who are breastfed[5]. Both types are usually harmless.Breastfeeding jaundice is seen in breastfed babies during the first week of life. It is more likely to occur when babies do not nurse well or the mother's milk is slow to come in.Breast milk jaundice may appear in some healthy, breastfed babies after day 7 of life. It is likely to peak during weeks 2 and 3, but may last at low levels for a month or more. The problem may be due to how substances in the breast milk affect the breakdown of bilirubin in the liver[6]. Breast milk jaundice is different than breastfeeding jaundice.Severe newborn jaundice may occur if the baby has a condition that increases the number of red blood cells that need to be replaced in the body, such as:Abnormal blood cell shapes (such as sickle cell anemia),Blood type mismatch between the mother and baby (Rh incompatibility),Bleeding underneath the scalp (cephalohematoma) caused by a difficult delivery Higher levels of red blood cells, which is more common in small-for-gestational age (SGA) babies and some twins.Lack of certain important proteins, called enzymes Things that make it harder for the baby's body to remove bilirubin may also lead to more severe jaundice, including: Infections present at birth, such as rubella, syphilis, and others Diseases that affect the liver or biliary tract, such as cystic fibrosis or hepatitis Low oxygen level (hypoxia) [7]Infections (sepsis) Many different genetic or inherited disorders Babies who are born too early (premature) are more likely to develop jaundice than full-term babies.clinical concern for neonatal caregivers worldwide.9,14,15 Bilirubin is not merely a nuisance molecule that has dire consequences, but bilirubin such as uric acid is an important antioxidant circulating in biologic system of neonate (9–11). However, high bilirubin levels can be toxic for central nervous system development and may cause behavioral and neurological impairment (Neurotoxicity or Kernicterus) even in term newborns (12–14)[8]. Five to ten percent of newborns developed jaundice required the management of hyperbilirubinemia [(1,5).] Neonatal jaundice may be on account of different parameters such as birth weight, gestational age, premature rupture of membranes, maternal infectious diseases or other illness during pregnancy, having different sources of origin, hence having different types [(1,6).] This has been followed at molecular level intensibly[9]. The main causes of increased bilirubin mostly are: race, genetic polymorphisms; inherited and acquired defects e.g. spherocytosis, Gilbert's syndrome, Najjar 1 and 2 Molecular genetics studies have shown the correlations between neonate's hyperbilirubinemia and different genetic variations which can change in enzyme activity. For example, variations in the uridine 5′-diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene may cause decreased enzyme activity in neonates and adults which leads to the unconjugated bilirubin accumulation[10].

BILIRUBIN TOXICITY

"Kernicterus" refers to the neurologic consequences of the deposition of unconjugated bilirubin in brain tissue. Subsequent damage and scarring of the basal ganglia and brainstem nuclei may occur.5 The precise role of bilirubin in the development of kernicterus is not completely understood. If the serum unconjugated bilirubin level exceeds the binding capacity of albumin, unbound lipid-soluble bilirubin crosses the blood-brain barrier. Albumin-bound bilirubin may also cross the blood-brain barrier if damage has occurred because of asphyxia, acidosis, hypoxia, hypoperfusion, hyperosmolality, or sepsis in the newborn.[3,8] The exact bilirubin concentration associated with kernicterus in the healthy term infant is unpredictable.[1] Toxicity levels may vary among

ethnic groups, with maturation of an infant, and in the presence of hemolytic disease. Although the risk of bilirubin toxicity is probably negligible in a healthy term newborn without hemolysis,[9] the physician should become concerned if the bilirubin level is above 25 mg per dL (428 μ mol per L).[1,3,10] In the term newborn with hemolysis, a bilirubin level above 20 mg per dL (342 μ mol per L) is a concern.[1,3]



Kernicterus Fig:1

The effects of bilirubin toxicity are often devastating and irreversible [3,9] Early signs of kernicterus are subtle and nonspecific, typically appearing three to four days after birth. However, hyperbilirubinemia may lead to kernicterus at any time during the neonatal period.[2] After the first week of life, the affected newborn begins to demonstrate late effects of bilirubin toxicity. If the infant survives the initial severe neurologic insult, chronic bilirubin encephalopathy (evident by three years of age) leads to developmental and motor delays, sensorineural deafness, and mild mental retardation.Also the variation in the organic anion transporter 2 (OATP2) gene may result in severe hyperbilirubinemia in neonates (17, 18). Variations of 388 G>A (Asp130Asn, rs2306283), 521 T>C (Val174Ala, rs4149056), 463 C>A(Pro155Thr, rs11045819) of the solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene which encodes the hepatic solute carrier organic anion transporter 1B1, a putative bilirubin transporter, may dispose subjects to newborns hyperbilirubinemia by the limitation of hepatic bilirubin uptake (19–21). Furthermore, in a genome wide association study, two polymorphisms of SLCO1B3 gene (rs17680137 C>G and rs2117032 C>T) were observed to have a strong association with serum bilirubin levels and to contribute to idiopathic mild unconjugated hyperbilirubinemia in healthy adults [(2,3).]

DISCUSSION

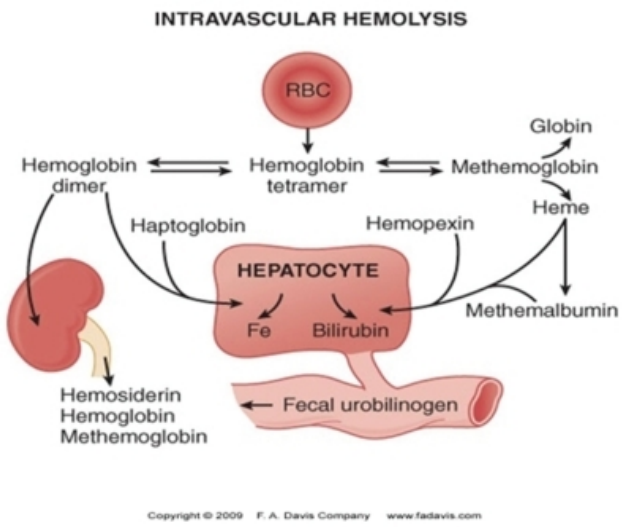
Types of Hyperbilirubinemia

Several types of Bilirubinemia have been reported in neonates including physiological jaundice, pathological jaundice, jaundice due to breastfeeding or breast milk and hemolytic jaundice including three subtypes due to Rh factor incompatibility, ABO blood group incompatibility and Jaundice associated with Glucose-6-phosphate dehydrogenase (G6PD) deficiency [(2,4).]

It is the most abundant type of newborn hyperbilirubinemia, having no serious consequences [(2,5).] Neurodevelopmental abnormalities including as athetosis, loss of hearing, and in rare cases intellectual deficits, may be related to high toxic level of bilirubin [(2,6)]. Jaundice attributable to physiological immaturity which usually appears between 24–72 h of age and between 4th and -5th days can be considered as its peak in term neonates and in preterm at 7th day, it disappears by 10–14 days of life [(2,7)]. Unconjugated bilirubin is the predominant form and usually its serum level is less than 15 mg/dl [(2,8)]. Based on the recent recommendations of the AAP, bilirubin levels up to 17–18 mg/dl may be accepted as normal in term of healthy newborns. [5]

Pathological Jaundice

Bilirubin levels with a deviation from the normal range and requiring intervention would be described as pathological jaundice [(2,5)]. Appearance of jaundice within 24 h due to increase in serum bilirubin beyond 5 mg/dl/day, peak levels higher than the expected normal range, presence of clinical jaundice more than 2 weeks and conjugated bilirubin (dark urine staining the clothes) would be categorized under this type of jaundice.



Diagrammatic Approach Fig:2

Breast Milk Jaundice

Jaundice in breast fed babies usually appears between 24–72 h of age, peaks by 5–15 days of life and disappears by the third week of life. Higher bilirubin levels have been reported in these infants [2,9]. In case of breastfed newborns, mild jaundice may take 10–14 days after birth or may reoccur during the breast-feeding period (30). Very large amounts of bilirubin rarely accumulate in the blood and cause cerebral lesions, a situation known as nuclear jaundice (31). These cuts may be followed by hearing loss, mental retardation, and behavioral disorders. A mild clinical jaundice has been observed in one third of all breastfed babies in the third week of life, which may persist for 2 to 3 months after birth in a few babies [3,2]. Decreased frequency of breastfeeding is associated with exaggeration of physiological jaundice. One of the significant procedures to manage the jaundice in a term healthy baby is the mothers' encouragement to breastfeed their babies at least 10–12 times per day [3].

Breast feeding jaundice

Hyperbilirubinemia is also associated with breast milk of mother in neonates (34). About 2%–4% of exclusively breastfed babies have jaundice in excess of 10 mg/deal in the third week of life. These babies in the third week of life with bilirubin serum levels higher than 10mg/dl should be considered for prolonged jaundice [3,5]. A diagnosis of breast milk jaundice should be investigated if the serum bilirubin is predominantly unconjugated, other causes of prolonged jaundice have been eliminated and the infant is in good health, vigorous and feeding well and gaining weight adequately [3,6]. Mothers should be advised to continue breastfeeding at more frequent intervals and bilirubin levels usually diminish gradually. Discontinuity of breastfeeding is not recommended unless levels exceed 20 mg/dl [3,7].

HAEMOLYIC JAUNDICE

Rh Incompatibility

Rhesus hemolytic disease of the newborns (RHDN) results from maternal red-cell alloimmunization [3,8]. Maternal antibodies are produced against the fetal red blood cells, when fetal red blood cells are positive for a certain antigen, usually at what time a baby having Rh positive born to an Rh-negative mother [2] (and Rh-positive father), then maternal immunoglobulin (IgG) antibodies might cross the placenta into the fetal circulation and cause a wide variety of symptoms in the fetus, ranging from mild to severe hemolytic anaemia and fetal hydrops [3]. To facilitate early treatment in neonates who are dubitable to have Rh factor, a blood group and Rh typing, DCT, PCV (packed cell volume) and serum bilirubin on cord blood should be performed. A reticulocyte count should be sent before the first exchange transfusion (ET). Vigorous phototherapy is required immediately after the birth and it should be continued until a level, which is 5 mg/dl less than the level estimated for exchange blood transfusion [4].

ABO Incompatibility

The incidence of the incompatibility of the ABO blood groups of the mother and fetus, when the mother has the blood group O and the newborn has the A or B blood group, is 15–20% of all pregnancies (2). Babies with O-blood group mothers should be closely checked for and discharged after 72 h. Routine cord blood screening is not recommended for newborns with O-group mothers [3]. Jaundice owing to ABO incompatibility usually appears 24 h after the birth. In the presence of significant jaundice or jaundice

appearing within 24 h, the work up for pathological jaundice should be done (44). Intensive phototherapy is advised at SB 12–17 mg/dl depending upon postnatal age of the baby. Exchange blood transfusion is indicated at TSB. The weight at birth as a criterion for phototherapy and ET may be used for preterm newborns [4,5].

G6PD Deficiency

Deficiency, hereditary spherocytosis, and minor group incompatibilities should be managed similar to ABO incompatibility. G6PD, most common enzymopathy, is the deficiency of an enzyme in RBCs (4,6). It is the most vital disease of the pathway of hexose monophosphate ,7.

Clinical examination of Jaundice

Originally described by Kramer [3], dermal staining of bilirubin may be used as a clinical guide to the level of jaundice. Dermal staining in newborns progresses in a cephalo-caudal direction [5]. The newborn should be examined in good daylight. The physician should pale the skin by digital pressure and the underlying color of skin and subcutaneous tissue should be noted. Newborns who are detected the yellow skin beyond the thighs should have an urgent laboratory confirmation for bilirubin levels[9]. Clinical assessment is unreliable if a newborn has been receiving phototherapy and has dark skin.

Measurement of Bilirubin

I. Bilirubin level can be checked through biochemical method, Bilimeter or transcutaneous bilirubinometer [2,6].

II. Most Important method for bilirubin estimation is the total and conjugated bilirubin assessment based on the van den Bergh reaction.

III. Spectrophotometry is the base of Bilimeter and it assesses total bilirubin in the serum.

IV. Clinical Approach

a. The initial step in evaluation of any newborn for jaundice is to differentiate between physiological and pathological jaundice.

b. Onset of jaundice within 24 h, presence of pallor and hydrops, presence of hepatosplenomegaly, presence of hemolysis on the smear of peripheral blood, increased count of reticulocyte (>8%), rapid rise of bilirubin (>5 mg/dl in 24 h or >0.5 mg/dl/hr) or a family history of considerable jaundice should create a suspicion of hemolytic jaundice [5].

c. The mother should be encouraged to breast-feed her baby frequently and exclusively, at least eight to twelve times per day for initial several days, with no top feeds or glucose water whatsoever [1]. Mother should be told to bring the baby to the hospital if the color on the legs looks as yellow as the face.

Management of Pathological Jaundice

1. Hyperbilirubinemia can be treated easily without or with a minimal adverse effect with phototherapy. The efficacy of phototherapy depends on surface area exposed to phototherapy: Double surface phototherapy may be more effective than single surface phototherapy

2. **Conventional** or fiber-optic phototherapy units provided jaundice is non-hemolytic or its progression is slow.

3. Intensive Phototherapy

4. In the circumstances including hemolytic jaundice, rapidly increasing bilirubin, or ineffectiveness of a conventional unit, using of intensive phototherapy is warranted. Placing the baby on the bili-blanket and using additional overhead phototherapy units contain blue lights and then lowering the phototherapy units to within a distance of 15–20 cm are two significant remedies [1].

5. Exchange Transfusion

6. Always, Blood using for exchange transfusion

should be negative Rh isoimmunization, negative for Rh factor. O (Rh) negative packed cells suspended in AB plasma will be the best choice.

7. Only **O-blood group** should be used for exchange transfusion in newborns with ABO incompatibility.

8. **Blood Volume Used**: Partial exchange is done at birth in Rh hemolytic disease: 50-ml/kg of packed cells.

9. **Double Volume Exchange**: 2 Pts (80–100 ml/kg) &times birth weight (kg)

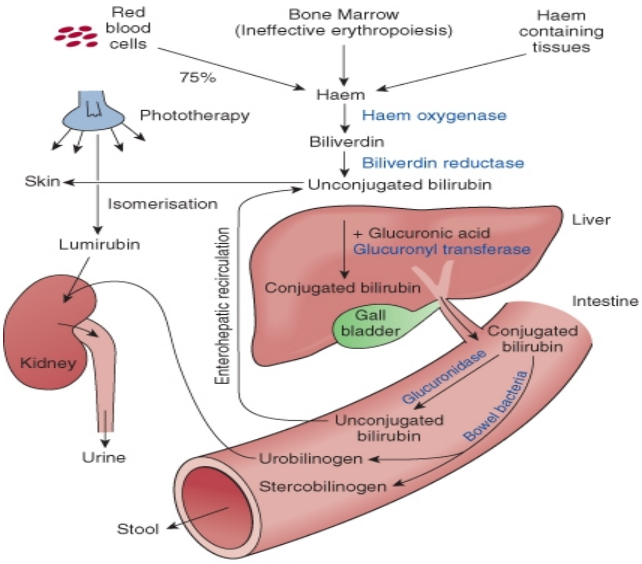
10. **Bilirubin processing** including hepatic uptake, conjugation and its excretion are ameliorated by this agent thus helps in decreasing level of bilirubin. However the effect of phenobarbitone is not rapid and takes time to show.

11. Intravenous Immunoglobulin (IVIG)

12. **High dose IVIG** (0.5–1 gr/kg) has shown to be effective in decreasing the needs of exchange transfusion and phototherapy in babies with Rh hemolytic disease.

13. **Metalloporphyrins; These** compounds are still experimental but showing promising results in various hemolytic and non-hemolytic settings without significant side effects (88, 103–107).

14. **Recently** Hour-specific bilirubin nomograms have been constructed based on routine pre-discharge bilirubin assessment [8,10]. These charts are useful in predicting hyperbilirubinemia based on a bilirubin level done after 24 h of age. However, the mentioned charts are prepared based on infants born in the West and probable need to be assessed and validated on Asian infants or on regional basis before they can be used for routine newborn care.



How Bilirubin IS Metabolized Fig: 3

CONCLUSION

Hyperbilirubinemia is more severe in newborns. Therefore, precautionary measure should be adopted by both parents, and clinicians to diagnose and treat the disease properly. Government and public health organizations should arrange seminars, workshops and trainings for mothers regarding neonatal jaundice. Medical scientists should search for new treatments and preventive measures having no side effects and capable of recovering babies more speedily. Partners should screen their ABO blood groups as well as Rh factor before marriage. Consanguineous marriages should be avoided.

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