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Review Articles

An Overview of Neonatal Unconjugated Hyperbilirubinemia and It's Management

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Abstract

Neonatal hyperbilirubinemia is the most common clinical condition in the newborn requiring hospital readmission. About 60% of term and 80% of preterm infants develop jaundice during 1st week of life. Unconjugated hyperbilirubinemia occurs mostly due to increased hemolysis, decreased hepatic clearance, enterohepatic circulation, immaturity, blood group incompatibility and infections. Evaluation of neonatal jaundice is done based on history, age of onset of jaundice and physical examination findings which is necessary for proper management. Otherwise significant hyperbilirubinemia may endanger life of the baby and may lead to acute and subsequently chronic bilirubin encephalopathy. There are many diagnostic tools those help to detect jaundice such as Kramer's rule, transcutaneous bilirubinometer, Bilichecker apps and smartphone apps. Besides these BIND score added a new dimension in diagnosis of acute bilirubin encephalopathy which can be confirmed by measuring bilirubin – albumin ratio in blood. Management of unconjugated hyperbilirubinemia includes: Phototherepy, Exchange transfusion are two major effective therapeutic modalities available today. Additional options include Pharmacotherapy in the form of phenobarbital and intravenous immunoglobulin. Each therapy has its pros and cons. Even there is dilemma in many therapeutic conditions like role of prophylactic phototherapy in preterm neonates, role of sunlight etc. As pediatricians have to deal cases with unconjugated hyperbilirubinemia frequently, so an updated knowledge is required. From this concern we reviewed issues on neonatal unconjugated hyperbilirubinemia and compiled for better understanding of the condition.

Keywords: *Neonatal jaundice, phototherapy, exchange transfusion, bilirubin, kernicterus.*

Introduction:

Neonatal jaundice is a commonly encountered problem. It is observed during the first week of life in approximately 60% in term and 80% in preterm infants. The discoloration is caused by accumulation of a yellow substance called bilirubin.[1] In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However high bilirubin levels may be toxic to the developing central nervous system and may cause neurological impairment even in term newborns. In most of the cases jaundice is a benign condition and no intervention is required. But in 10-15% of the jaundiced newborns have clinically significant jaundice and then phototherapy or other therapeutic options are required.[2] Though neonatal hyperbilirubinemia is not a major cause of neonatal mortality in our country but its morbidity during the neonatal period and later on is often severe enough to necessitate its early recognition and adequate management.[3] Moreover there is controversy in different diagnostic and management tools. There is no uniform protocol for assessing need of phototherapy or exchange transfusion. So, an updated knowledge is required for dealing neonatal jaundice in our daily practice.

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Incidence:

The overall incidence of neonatal jaundice in our country is about 33% and reported by various Indian workers varies from 4.6% to 77%.[3,4] Incidence is higher in East Asians and American Indians and lower in Africans. Incidence of severe hyperbilirubinemia in High Income Countries (HIC) is currently estimated to be about 31.6/100,000 live births, while the incidences of acute and

chronic bilirubin encephalopathy have been estimated as being in the range of 1.0–3.7 and 0.4–2.7/100,000 live births, respectively. The situation is completely different in Low- and Mid Income Countries (LMICs).[5-10] Severe neonatal jaundice is 100-fold more frequent in Nigeria than industrialized countries. Ethnic variability in the incidence and severity of neonatal jaundice may be related to differences in the distribution of the genetic variants in bilirubin metabolism.[11]

Pathophysiology:

Jaundice is the yellow discoloration of skin, sclera and mucous membrane which occurs due to accumulation of unconjugated, lipid soluble bilirubin pigment in the skin. In neonates it is due to increased break down of fetal erythrocytes which has shortened life span. Hepatic excretory capacity is also low in newborns. These occur more in premature babies than term infants. Another commonly found variety is breast milk jaundice which occurs due to presence of certain factors in mother's breast milk that increases enterohepatic circulation and thus increased bilirubin production. Besides these causes often jaundice becomes more pronounced due to blood group incompatibility and sepsis which cause increased hemolysis as a result there is increased bilirubin production.[11]So the increased bilirubin production, reduced hepatic clearance and enhanced enterohepatic circulation are the sole cause of increased prevalence of jaundice in newborn.

Etiological Consideration:

Based on age of onset, unconjugated hyperbilirubinemia can be divided into three broad groups. Neonates developing jaundice within first 24 hours is always pathological and commonest causes are- Rh incompatibility, ABO incompatibility, G-6PD Deficiency and Hereditary spherocytosis. Jaundice due to physiological factors, prematurity, inadequate breast feeding and infections occur between two days to fourteen days of life. Indirect hyperbilirubinemia which develop after 2 weeks are mostly due to infection, breast milk factors and hypothyroidism.[12]Among all these varieties, physiological jaundice is a normal response which appears on 2nd/3rd day of life and peaks on 3rd/4th day of life in term, 5th-6th days in preterm. Gradually disappears spontaneously. Baby is otherwise healthy. Sometimes exaggerated physiologic jaundice can occur where higher bilirubin levels occur earlier and last longer. Prematurity, severe weight loss, maternal diabetes and bruising in infants are the factors behind this condition.[13] Breast milk jaundice is found in66% of breastfed babies from 3rd week of life and may persist up to 3 months. Another similar term is breast feeding jaundice that develops in the 1st week of life. It is due to decreased milk or calorie intake.This necessitatesto increase breast feeding or to improvehydration. Blood group incompatibilities are found within first 24 hours of life usually.Severity of Rh incompatibility increases with increased number of pregnancy. It presents with jaundice, anaemia, hepatosplenomegaly and in severe case hydropsfoetalis. ABO incompatibility is usually less severe and first baby is affected in 50% cases. Currently G6PD Deficiency is possible to diagnose in our country.It is indirect hyperbilirubinemia with ethnic origin. It presents with features of hemolysis with male predominance. Another rare Autosomal recessive disorder affecting bilirubin metabolism is CriglerNajjar Syndrome. It is due to complete or partial deficiency of hepatic enzyme (UGT) activity.It is of two types –I and II. Bilirubin is commonly >20 mg/dl in type I, unresponsive to phenobarbitone therapy and require exchange transfusion.[13]In developed countries blood group incompatibility is the major causes of jaundice whereas in developing countries prematurity, sepsis is the main causes. In most of the studies like in India and Bangladesh, they found blood group incompatibility and sepsis are the commonest causes of neonatal hyperbilirubinemia.[3,14,15]

Evaluation of jaundice in newborn:

The evaluation of the jaundiced infant must include a thorough history and physical examination with particular emphasis on the state of hydration and consideration of the possibility of an acute hemolytic process and / or infection. First we have to assess **whether the baby is term or preterm** as basic pathology of jaundice is same in both but premature babies are at a higher risk of developing brain damage at lower level. Then features of hemolysis like presence of pallor, hepatosplenomegaly should be excluded. It is commonly evaluated if mother and baby have blood group incompatibility. Thirdly we have to differentiate a well-baby from sick neonates. Baby's general condition, feeding and hydration status, activity will guide us to detect features of sick baby and eventually the cause (sepsis or asphyxia). Along with these, certain features of bilirubin induced encephalopathy need to be searched like seizures, retrocolis, shrill cry etc.[2,16] (Figure -1) Besides these we also assess jaundice by using Kramer's rule. Kramer drew attention to the observation that jaundice starts on the head, and extends towards the feet as the level rises. This is useful in deciding whether or not a baby needs serum bilirubin measurement.[17] Regarding investigations along with serum bilirubin, other investigations are often sent based on clinical suspicion of cause like blood grouping and Rh typing, complete blood count with peripheral blood film, reticulocyte count, Coomb's test, sepsis work up, G-6PD level etc.

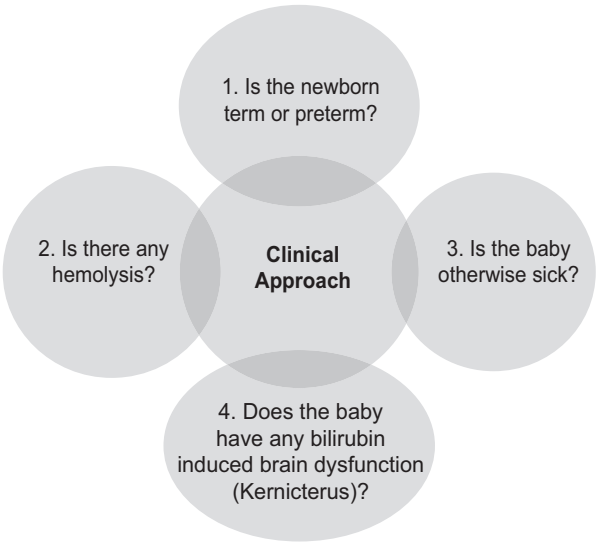

Fig.-1: *Steps of Clinical Approach in a newborn with jaundice*

Assessment of Bilirubin Induced Neurotoxicity: Marked hyperbilirubinemia can lead to acute bilirubin encephalopathy (ABE) and evolve into chronic bilirubin encephalopathy (CBE), a devastating, permanently disabling neurologic disorder[18]. As neurotoxicity is a risk in hyperbilirubinemia, physicians have to be cautious to detect it early. There are some neurotoxicity risk factors which will guide us for timely and early intervention such as presence of isoimmune hemolytic disease, G6PDdeficiency, asphyxia, sepsis, acidosis and albumin levels lower than 3.0 g/dl.[19] Hemolytic conditions remain prevalent contribu-tors to both hyperbilirubinemia and bilirubin neurotoxicity risk. Although mechanisms underlying the neurotoxicity-intensifying effect is unclear, recent data provide strong corroboration that hemolysis aug-ments bilirubin neurotoxicity in neonates, with Rh hemolytic disease and G6PD deficiency playing particularly prominent etiologic roles. The presence of Rh hemolytic disease alone greatly increased the risk for bilirubin encephalopathy[20]. So we have to find out the cause timely and judiciously to reduce adverse outcome. Forneurotoxicity assessment, Clinical Bilirubin Induced Neurological Dysfunction (BIND) score has gained much popularity now a day (Table -1). This scoring system may prove to be a useful clinical tool in identifying infants with intermediate to advanced ABE, conditions that pose significant risk for CBE and are an indication

Table-I

Clinical bilirubin induced neurological dysfunction (BIND) score of onset, severity and progression of acute bilirubin encephalopathy, as elicited by history and physical examination

Clinical signs	Bilirubin-induced neurological dysfunction score	Acute bilirubin encephalopathy
Mental Status		
Normal	0	None
Sleepy but able to be aroused; decreased feeding	1	Subtle
Lethargy, poor suck, and/or irritable/jittery with strong suck	2	Moderate
Semicoma, apnea, unable to feed, seizures, coma	3	Advanced
Muscle tone		
Normal	0	None
Persistent mild to moderate hypotonia	1	Subtle
Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation	2	Moderate
Persistent retrocollis and opisthotonos, bicycling or twitching of hands and feet	3	Advanced
Cry pattern		
Normal	0	None
High-pitched when aroused	1	Subtle
Shrill, difficult to console	2	Moderate
Inconsolable crying or weak or absent cry	3	Advanced

Notes: Total BIND (acute bilirubin encephalopathy score) Scores of 1–3 are consistent with subtle signs of acute bilirubin encephalopathy in infants with hyperbilirubinemia. Scores of 4–6 represent moderate acute bilirubin encephalopathy and are likely reversible with urgent and prompt bilirubin reduction strategies. Scores of 7–9 represent advanced acute bilirubin encephalopathy; urgent, prompt, and individualized intervention are recommended to prevent further brain damage, minimize severity of sequelae, and possibly reverse acute damage.

for the urgent application of bilirubin reduction strategies.[18]

Newer Diagnostic Tools for Neonatal Jaundice:
With time many newer easy techniques have been invented for diagnosing jaundice. Among them Transcutaneous bilirubinometer (TcB) has become popular. It is a noninvasive procedure which detects the level of bilirubin and it also decreases unnecessary blood sampling(Figure-2). But the correlation of Transcutaneous bilirubin (TcB) and total serum bilirubin (TSB) is not accurate in all gestational age groups. In a study conducted in 2017 with 588 pairs of measurements were recorded in 86 premature infants of 26–34 weeks and weighing 618–2400 grams. The overall correlation coefficient between TcB and TSB was 0.8 (p=0.001). Subset analysis revealed lower correlation in infants born before 30 weeks. TcB was consistently estimated around 1mg% lower than TSB.[19] The RCOG's BiliChecker app is another tool that will help us to choose the safest management option for a baby with neonatal jaundice in less than 1 minute based on the recommendations of the NICE guideline. It calculates phototherapy threshold for newborns that are not in a neonatal intensive care unit, displays values on phototherapy nomogram and then directly links to source guideline.[21] Other recent diagnostic tool includes assessment of the accuracy of a technology based on the analysis of digital images of newborns obtained using a smartphone application called Bilicam.[22] The measurement of free serum bilirubin and albumin ratio is also a newer way to assess the risk of neurotoxicity in a jaundiced infant.[23]

Fig.-2: *Transcutaneous Bilirubinometer*

Management:
There is dilemma in managing jaundiced newborn as it is a common outdoor problem and parents have social belief in other non-therapeutic measures. But activities are going on to increase awareness among people. Currently, phototherapy and exchange transfusion are two major effective therapeutic modalities.[2] Additional options include pharmacotherapy in the form of Phenobarbital, IVIG, metalloporphyrin, zinc sulfate etc.

Phototherapy: Phototherapy is the mainstay of unconjugated hyperbilirubinemia treatment in neonates. In widespread application since the 1970s, phototherapy has resulted in a marked reduction in the need to perform exchange transfu-sions to prevent hazardous hyperbilirubinemia and bilirubin encephalopathy.[24,25,26]There are several guidelines of phototherapy available in this regard but AAP guidelines are well accepted in many countries including Bangladesh which distinguish between 3 risk categories: low, intermediate and high. The 2004 AAP guidelines provided management for the jaundiced newborn at ≥ 35 weeks.[19](Figure:3) There is another direction for management of jaundicein preterm infant.[27] Also NICE guideline is another easy way to assess therapeutic need in jaundice according to gestational age of baby which is a very cost effective method and based on evidence.[28] As there are limited data for evidence-based recommendations in preterm neonates, these guidelines are, of necessity, consensus-based and provided by differ-ent experts, none of whom would make any claim for the greater validity of one approach over another.[29,30]

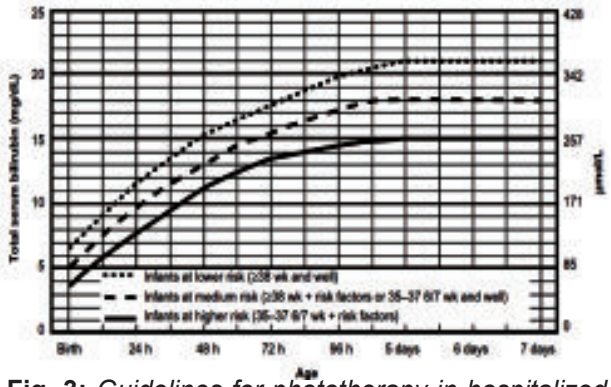

Fig.-3: *Guidelines for phototherapy in hospitalized infants e"35 weeks' gestation. Risk factors are isoimmune hemolytic disease, glucose-6 phosphate dehydrogenase deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis or an albumin level of less than 3.0 g/dl (if measured). Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin.*

The effectiveness of phototherapy is determined by the irradiance, the surface area of exposure, and the light spectrum used. Regarding light source for phototherapy, there are variable lights are being used such as blue fluorescent tubes followed by green and white light; Fibreoptics have a lower risk of overheating the infant. LED lights are found in most new phototherapy units. There is no significant difference in STB rate of decrease was detected between LED and other types of phototherapy[31]. The benefit of timely phototherapy application in infants is clearthat configurational photoisomerization of bilirubin occurs almost instantaneously and is detectable in appreciable amounts in the blood of newborns within 15 minutes of initiat-ing intensive phototherapy.[32] These photoisomers can account for up to 20%–30% of the total unconjugated bilirubin and are less lipophilic than native bilirubin, and therefore are less likely to cross the blood–brain barrier.So the immediate detoxification of some bilirubin, even before it is excreted, is a possible additional benefit of phototherapy.[32] Although phototherapy has some complications such as skin rashes, dehydration, loose watery stool, hypocalcemia, hypomagnesemia, retinal damage etc.[31] Most of them are benign and resolved as soon as phototherapy is stopped. Phototherapy can lead to decreased total and ionized calcium levels of neonates, especially in preterm neonates that can be prevented by covering the head during phototherapy with no need for prophylactic administration of calcium.[33]Further studies are needed to conclude in this regard.

Exchange transfusion: Exchange transfusion remains an important, if infrequently required, clinical intervention to prevent or reduce the risk for kernicterus.[18] The prevention of Rh (D) hemolytic disease with Rh (D) immunoglobulin and the more effective use of intensive phototherapy have led to a dramatic decline in the number of exchange transfusions performed.[25]Moreover data have shown that treatment with IVIG in infants with Rh or ABO isoimmunization can significantly reduce the need for exchange transfusion.[34]

Intravenous immunoglobulin: IVIG can reduce the need of exchange transfusion in hemolytic diseases that is evidence based.[35] The mechanism of action of IVIG is unknown, but it is possible that it might alter the course of immune-mediated hemolytic disease by blocking Fc receptors, thereby inhibiting hemolysis.The 2004 AAP guideline reserves the use of IVIG to direct Coombs-positive infants whose TSB continues to rise despite intensive phototherapy or whose TSB is within 2–3 mg/dL of the exchange level.[19]

Other Therapeutic Measures: In significant hyperbilirubinemia fluid therapy is a supportive measure to reduce jaundice and intravenous fluid supplementation may result in a faster decline of STB in first few hours of treatment.[36] Using clofibrate and phenobarbital were found supportive not only by decreasing the serum bilirubin level, but also by reducing the duration of hospitalization and phototherapy.[37] Some studies with prebiotics and probiotics havealso shown good outcome in reducing bilirubin level.[38,39] In the other hand zinc sulfate failed to reduce bilirubin significantly.[40]

Practical Aspects in Neonatal Jaundice Management: There are many practical issues we have to face during jaundice management in newborns. Mostly these are evidence based but practice is not uniform. These include:

Prophylactic versus threshold phototherapy: The efficacy and safety of prophylactic phototherapy in preventing jaundice in preterm infants were evaluated in a meta-analysis covering a total of nine clinical trials representing 3,449 infants. Prophylactic phototherapy initiated soon after birth (within 36 hours) prevents a significant rise in unconjugated hyperbilirubinaemia, reduces the need for exchange transfusion and may reduce long-term neurodevelopmental impairment. Although a recent study shows that prophylactic phototherapy is not associated with any improvement in neonatal outcomes.[41] Further well-designed studies are needed to determine the efficacy and safety of prophylactic phototherapy on long-term outcomes including neurodevelopmental outcomes.[42]

Is phototherapy a carcinogen? In previous years, several studies have been made to investigate a possible association between neonatal blue light phototherapy and the development of common melanocytic nevi and clinically atypical melanocytic nevi in childhood.While some studies could show an increasing incidence of common melanocytic nevi or clinically atypical melanocytic nevi after neonatal blue light phototherapy, others could not confirm these results and did not find higher numbers of melanocytic nevi or melanoma after neonatal blue light phototherapy.[31]

Any beneficial role of phototherapy other than jaundice reduction: Blue light, particularly in the wavelength range of 405-470 nm, exhibits a broad-spectrum antimicrobial effect against bacteria (either gram-positive or gram-negative bacteria).Moreover, blue light therapy is a clinically accepted approach for P. acnes infections.[31]

Role of sunlight in neonatal jaundice:
Using direct sunlight for phototherapy has a number of clinical and practical drawbacks that could make its use undesirable. Sunlight contains altitude-, seasonal-, and time-of-day-dependent levels of harmful ultraviolet A, B, and C radiation, which can cause a serious and permanent damage to human skin. It must be underlined that the use of sunlight, when filtered to exclude the harmful spectral radiation, is a novel, practical, and inexpensive method of phototherapy that potentially offers safe and efficacious treatment strategy for management of neonatal jaundice in tropical countries where conventional phototherapy treatment is not available.[31]There are many RCTs those stated that low cost filtered sunlight therapy is non inferior to conventional phototherapy in treating neonatal hyperbilirubinemia.[43]

Universal pre-discharge birth hospitalization bilirubin screening: The 2009 AAP update was notable for recommending universal pre-discharge birth hospitalization bilirubin screen-ing using TSB or transcutaneous (TcB) measurements to help assess the risk for subsequent severe hyperbilirubinemia. The pre-discharge bilirubin measurement combined with the gestational age of the infant make up a particularly robust predictor of subsequent severe hyperbilirubinemia that is consistent with the importance of immaturity as a risk fac-tor for jaundice. (Figure -4)

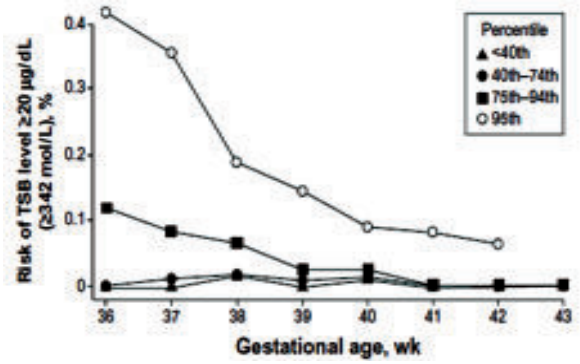

Fig.-4: *Gestational age impacts risk for severe hyperbilirubinemia*

Notes: Risk of developing a total serum bilirubin (TSB) level of 20 mg/dL (342 ¼mol/L) or higher as a function of gestational age and percentile of the first TSB measured at less than 48 hours on the Bhutani nomogram.

Conclusion:
Neonatal jaundice is of utmost concern for the pediatricians while dealing neonates. Advancements in diagnostic and management policy are going on day by day. So an updated knowledge is always required to give a better service to this population for ensuring a meaningful life.

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