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Review

Perspective on Neonatal Hyperbilirubinemia

Prof. Dhastagir Sultan Sheriff[Ψ] PhD and Dr. Abdalla M. Jarari PhD

Department of Biochemistry, Al Arab Medical University, Benghazi, Libya

ABSTRACT: Jaundice in newborns provides a different response from the parents when compared to jaundice in older children and adults. Physiologic hyperbilirubinemia occurs commonly in term newborn infants in the absence of any underlying pathologic cause. Yet, the jaundice itself is commonly regarded as a problem in the transition to extrauterine life. In Neonatal hyperbilirubinemia (NHB) the total bilirubin level is greater than 15mg/dL in 15 day or less old neonates and 2mg/dL in neonates above 15 days of age. Estimation of total bilirubin is preferred in the routine analyses for NHB compared to measurement of direct bilirubin. If certain conditions like sepsis, hepatic infections and other liver diseases are present it may be prudent to use direct bilirubin measurement. Yet contrary to the usual assumption of pathology, there are several lines of evidence supporting an adaptive role for neonatal hyperbilirubinemia. First, experimental and clinical evidence indicate that neonatal enzyme systems are not yet mature at birth; bilirubin has been demonstrated to scavenge potentially toxic oxygen free radicals that in later life are removed by the mature antioxidant enzyme system. Second, presence of bilirubin in mammals, similar patterns of expression of neonatal hyperbilirubinemia in nonhuman primates, and significant inter population variation in newborn serum bilirubin levels among humans all suggest that bilirubin production, metabolism, and excretion are under genetic control. Therefore bilirubin metabolism and its understanding may help improve its diagnosis and prognosis.

KEY WORDS: *Jaundice; Neonatal Hyperbilirubinemia (NHB); Direct Bilirubin*

INTRODUCTION

Neonatal hyperbilirubinemia (NHB), one of the most common problems pediatricians encounter in their clinical practice, remains a topic of interest and debate[1,2].

Although the majority of neonatal jaundice is benign, a small number of hyperbilirubinemia poses a major health problem in term of bilirubin encephalopathy or kernicterus[3]. Factors such as inadequate breast milk intake, imbalance between bilirubin production and conjugation and mutation of the gene encoding bilirubin conjugation have been identified to be associated with hyperbilirubinemia[4-6]. Measurement of serum bilirubin in infants at risk and prompt intervention are the important steps in preventing hyperbilirubinemia and kernicterus. But identifying infants at risk and to obtain serum for bilirubin estimation are still a cause for concern. The American Academy of Pediatrics (AAP) published a practice parameter on the management of hyperbilirubinemia in healthy term newborn in 1994[7]. These guidelines provide a framework for the prevention and management of hyperbilirubinemia in newborn infants of 35 or more weeks of gestation. In every infant, we recommend that clinicians - 1) promote and support successful breastfeeding; 2) perform a systematic assessment before discharge for the risk of severe hyperbilirubinemia; 3) provide early and focused follow-up based on the risk assessment; and 4) when indicated, treat newborns with phototherapy or exchange transfusion to prevent the development of severe hyperbilirubinemia and, possibly, bilirubin encephalopathy (kernicterus)[8,9]. Resurgence of kernicterus, reported in the following years, partly questioned the adequacy of this parameter.).

However, there were also comorbid factors, inappopriate application of the guidelines, lack of adherence and less concerned attitude that might

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[Ψ]**Correspondence at:** Department of Biochemistry, Al Arab Medical University, Benghazi, Libya; Email: dhastagir@yahoo.ca

play roles in it[3,8,9]. In 2004, AAP issued a clinical practice guideline focused on reducing the frequency of severe hyperbilirubinemia and bilirubin encephalopathy[10]. This review offers a perspective on neonatal jaundice by examining bilirubin metabolism, bilirubin neurotoxicity, the management of neonatal hyperbilirubinemia, and methods for the clinical assessment of neonatal jaundice.

BILIRUBIN METABOLISM

Bilirubin is the end product of heme degradation. The majority of bilirubin is derived from erythrocytes normally removed from the circulation and destroyed in the reticuloendothelial system. Heme oxygenase is the rate-limiting enzyme that catalyzes the alpha-specific oxidative cleavage of the heme molecule to form equimolar amounts of biliverdin and carbon monoxide. Biliverdin undergoes reduction via NADPH-dependent biliverdin reductase to form bilirubin. Bilirubin, after formation, is released into the circulation, where it is reversibly bound to albumin. Albumin in the circulation provides a vast bilirubin binding source, so that unbound bilirubin in plasma is generally low. Albumin transports bilirubin to its specific metabolic pathway in the liver, where bilirubin uptake is rapid. Intracellular transport of bilirubin from the hepatic plasma membrane to the endoplasmic reticulum, where conjugation occurs, is not well understood; however, cytosolic proteins (Y or ligandin Z or fatty-acid-binding protein) account for most of the intracellular bilirubin binding capacity. The conversion of bilirubin to mono- and di-glucuronide conjugates occurs in the endoplasmic reticulum. A stepwise addition of D-glucuronic acid from UDP-D-glucuronic acid to bilirubin, takes place with the help of the enzyme UDP-glucuronate-bilirubin glucuronyltransferase. The addition of glucuronide makes conjugated bilirubin water soluble and capable of canalicular transport into the bile. In the small bowel, bilirubin may be transiently deconjugated by bacterial and brush border enzymes before being further metabolized to other heme derived products. Because bilirubin P-glucuronidase is indigenous to the small bowel brush border, some bilirubin in the small bowel is deconjugated by this enzyme, reabsorbed at the brush border, and recirculated to the blood; this is known as the enterohepatic recirculation of bilirubin[11,12].

Transient unconjugated hyperbilirubinemia develops in all newborns during the first week of life while they are adapting to the extrauterine environment. The interaction of several factors not present in adults contributes to this development, including a shorter mean red blood cell life span, a higher circulating red blood cell volume, a greater enterohepatic recirculation, and a hepatic system

for uptake, enzymatic conjugation, and biliary excretion of bilirubin that is not yet fully functioning.

TOXICITY OF UNCONJUGATED BILIRUBIN

It is widely held, based on both laboratory investigations and epidemiologic studies, that unconjugated bilirubin is toxic to the central nervous system. "Kernicterus" was originally a term describing the typical autopsy findings of the brain in infants who died during severe jaundice, often caused by Rh isoimmunization or by infection. The term has also been used to identify the acute clinical, often fatal, condition in the severely jaundiced newborn characterized by convulsions, opisthotonos, hypotonia, high-pitched cry, and fever. Kernicterus has also been used to refer to the neurologic sequelae in survivors, including choreoathetosis, asymmetric spasticity, paresis of upward gaze, and neurogenic hearing loss[13-15]. The term "bilirubin encephalopathy" is, in fact, more appropriate for the acute clinical findings.

Hyperbilirubinemia in full-term infants has become an uncommon event in the last 30 years, as the result of the recognition of and early prenatal intervention in Rh-negative mothers and the widespread use of Rho (D) immune globulin (RhoGAM), exchange transfusions, and phototherapy. After 1970, postmortem findings consistent with kernicterus were described in a new population of babies. With the improved survival of low-birth-weight (under 1500 grams) infants, pathologic changes were described even in the presence of low bilirubin levels and without the typical symptoms.[16,17]

Several clinical situations may increase the risk of bilirubin entry into and toxicity to the brain. These include concentration of unconjugated bilirubin high enough to exceed the bilirubin-binding capacity of albumin, due to severe hemolysis from Rh isoimmunization[18]; bilirubin displacement from albumin by competing or affinity-altering molecules such as sulfisoxazole[19] or free fatty acids[20]; and disruptions of the blood-brain barrier that allow bilirubin-protein complexes to enter the brain. In the newborn, the latter is most often caused by hypoxemia, hypercarbia, and hyperosmolar conditions[21,22].

Clinical and experimental studies of bilirubin toxicity have provided mixed results and have not yielded a definitive model for the reactions that bilirubin undergoes after it enters the central nervous system or for the mechanism underlying its toxicity.

In the newborn, the auditory pathway is vulnerable to damage from moderate to severe hyperbilirubinemia, resulting in sensorineural

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hearing loss[23]. Birth weight less than 1500 grams, prolonged duration of hyperbilirubinemia, and acidotic episodes have been associated with sensorineural hearing loss. A direct correlation between increasing bilirubin concentration and changes in the amplitude and latency of auditory-evoked brainstem potentials has been demonstrated in studies of infants[24,25]. Acute changes in conduction time may be reversed by therapeutic intervention[26]. However, a well defined threshold for neurologic change has not been identified. In the healthy full-term infant, without hemolysis, detailed analyses, of a multitude of studies have failed to show any consistent effect of bilirubin (within a wide range of concentrations) on IQ, neurologic parameters, or hearing [27].

The current management of low-birth-weight infants, with prompt cardio respiratory stabilization and avoidance of drugs (including benzyl alcohol preservatives) believed to affect bilirubin metabolism and transport seems to have contributed to a decrease in the incidence of identifiable bilirubin toxicity[28]. Unfortunately, the lack of detailed understanding of all the physiologic mechanisms accounting for bilirubin toxicity has prevented us from knowing when not to treat smaller infants for hyperbilirubinemia. Thus, early and aggressive use of phototherapy and occasional exchange transfusions remain part of routine care.

THERAPY FOR NEONATAL HYPERBILIRUBINEMIA

Phototherapy

When bilirubin absorbs a photon of light, one of three possible photochemical reactions can occur: photo-oxidation, configurational isomerization, and structural isomerization. Photo-oxidation results in the formation of colorless water-soluble molecules. Although originally thought to be the main pathway of bilirubin elimination during phototherapy, the reaction now appears to occur too slowly to be of clinical importance. Configurational isomerization is the conversion of the 4Z, 15Z-bilirubin molecule to the 4Z, 15E-isomer a more water soluble form. Although formation of the Z, E-isomer is the most rapid of the photochemical reactions, this isomer is excreted slowly, if at all, in icteric infants. Structural isomerization produces lumirubin, a molecule that is formed relatively slowly but appears to be excreted fairly efficiently; it is thought to account for most or all of pigment elimination during phototherapy. Lumirubin has been identified as the major bilirubin species in urine and in aspirates of duodenal bile in infants undergoing phototherapy[29, 30].

The color of light used in phototherapy is critical for its therapeutic success. As a yellow pigment, bilirubin can only absorb in the blue, violet, and green spectra. In vitro, 450 nm blue light is best absorbed; however, in vivo, light of longer wavelengths such as green light is thought to penetrate infant skin more deeply[28].

Fluorescent daylight, blue light, and green light have been compared for efficacy in the management of non-hemolytic hyperbilirubinemia. The decrease in serum bilirubin concentration was fastest, and the required duration of phototherapy exposure was briefest, in the group of infants treated with blue light, which was twice as effective as green light[29-31]. Recently, a controlled trial compared fiberoptic phototherapy with conventional phototherapy. Healthy newborns weighing less than 2500 grams with nonhemolytic hyperbilirubinemia were randomized either to wear a fiberoptic light source as a cummerbund around the torso or to receive phototherapy using standard equipment[32]. Although fiberoptic phototherapy eliminated the need for eye protection and Isolette use and therefore promoted better infant-parent bonding, it was less effective than conventional phototherapy in decreasing serum bilirubin levels, presumably because of decreased irradiance. In general, phototherapy has no significant toxicity and its side effects are few (i.e. increased insensible water loss, diarrhea, skin rash, hypocalcemia, etc.) and are reversible with removal of the lights.

Metalloporphyrins

An alternative to treating neonatal hyperbilirubinemia by increasing bilirubin excretion, as in phototherapy, is to prevent the formation of bilirubin. Tin-protoporphyrin (Sn-PP) is a competitive inhibitor of heme oxygenase and thus can block the catabolism of heme and the production of bilirubin. In a study of SN-PP use in full-term newborns with Coombs-positive ABO incompatibility, infants who received a large dose of SN-PP (0.75 VL mol/kg per 24 hrs for 2-3 days) had lower serum bilirubin concentrations than control patients[31-33]. Also, fewer patients in the SN-PP treated group than in the control group required adjuvant phototherapy. From these data, it is unclear whether the primary effect of metalloporphyrin therapy is decreased bilirubin formation or increased photosensitivity of bilirubin resulting in increased excretion. Furthermore, the decrease in serum bilirubin concentration, although statistically significant was not clinically impressive. In addition, significant cutaneous side effects were noted including erythema and pruritis followed by edema and even tissue necrosis, thought to be a result of membrane damage from the formation of singlet oxygen. Other reported side effects include altered glutathione metabolism in the brain[34]. Additional potential effects, as yet unreported, include altered heme homeostasis,

leading to changes in hemoproteins such as P450 and thus to alterations in drug metabolism. At this time, caution in the use of SN-PP in the treatment of neonatal hyperbilirubinemia seems prudent until further data are available about its potentially toxic effects in the newborn[35,36].

Pharmacologic agents used in the management of hyperbilirubinemia can accelerate bilirubin clearance via the normal metabolic pathways, inhibit the enterohepatic circulation of bilirubin or interfere with bilirubin formation by either blocking the degradation of heme or inhibiting hemolysis. Clofibrate as a hypolipidemic drug is a glucuronosyltransferase inducer which accelerates bilirubin elimination. In one of the studies Clofibrate is reported to be an effective adjunctive drug in neonatal hyperbilirubinemia, which results in decreased TSB level and reduced duration of phototherapy in late pre-term newborns[37].

NONINVASIVE BILIRUBIN MEASUREMENT

Although the major foci of research on neonatal jaundice have been toxicity and treatment, accurate and rapid measurement of elevated bilirubin concentration has also intrigued investigators. The standard clinical management of infants with jaundice includes visual estimation of extent and serial estimation of serum bilirubin concentration[35]. Blood is obtained by repetitive venous, arterial, or capillary puncture. Any mode of obtaining blood is a source of discomfort and infection. Transcutaneous bilirubinometry is a noninvasive and cost-effective alternative. It is currently being investigated as a replacement for serum bilirubin testing or as a screening device to assess the need for serum bilirubin testing.

VISUAL ESTIMATION OF BILIRIBIN

Simple visual estimates for the presence or absence of jaundice are made daily by pediatricians to aid in the decision to test serum bilirubin levels. The visual estimate is refined by classifying the dermal zone of jaundice based on the phenomenon of cephalo-caudal progression. Jaundice in zone I (from head to neck and the level of the clavicle) translates approximately to a serum bilirubin concentration of 5 mg/dL; in zone 2 (from the clavicle to the umbilicus) to 6-8 mg/dL; in zone 3 (from the umbilicus to the knees) to 9-12 mg/dL; in zone 4 (from the knees to the ankles) to 13-15 mg/dL; and in zone 5 (the palms and soles) to over 15 mg/dL. A second refinement of the visual estimate is the use of a "Tintometer" and "Ingram Icterometer" to gauge the depth of jaundice in newborns[38,39]

TRANSCUTANEOUS ESTIMATES

A more sophisticated device is the Minolta/Air Shields Jaundice Meter[38]. It works via the principle of skin reflectance, which assumes that subcutaneous bilirubin is correlated in a linear fashion to serum bilirubin. The ability to estimate serum bilirubin values can be simplified by using the compartmental model[40]. The relationship between the concentrations of bilirubin in the subcutaneous tissue compartment and the blood compartment is governed by rate constants that describe the rate of entry and exit of bilirubin from one compartment to another. To obtain a satisfactory correlation between these two values, the serum bilirubin and; the cutaneous bilirubin measurement must be accurate; and the two compartments and the kinetics of the transfer of bilirubin to and from each compartment must be similar for every infant[41].

The first prerequisite, serum bilirubin measurement in the laboratory, is not met; inaccuracies cause a substantial degree of error in attempts to correlate transcutaneous and serum values. The accuracy of the second prerequisite, transcutaneous bilirubin measurement is equally problematic. In studies of the precision of jaundice meters, several investigators[42,43] have found them less precise for low serum bilirubin levels, but others[44,45] have suggested that the accuracy of the jaundice meter may be compromised at higher serum bilirubin concentrations. Accuracy may also be compromised by the variability of individual meters[43], the influence of operator technique [41], and the presence of alcohol on the meter probe or the baby's skin[41]. The accuracy of jaundice meters is not only a function of precision, but also of the presence or absence of bias. It may be in the form of additional or interfering race-dependent skin chromogenes and the presence of bruising or birthmarks[46-50].

The third prerequisite for accurately correlating serum and subcutaneous bilirubin is that the two bilirubin compartments be stable in nature and that the kinetics of transfer between the two compartments be describable. Investigators who have examined this relationship between transcutaneous bilirubin values and serum bilirubin concentrations at various body sites generally have found the relationship to be linear and significant[31,42,51,52]. However, factors such as exchange transfusions, phototherapy, body site of measurement, serum albumin concentration, pH, and gestational and chronological age have the potential to alter either the intrinsic nature of the serum bilirubin compartment or the kinetics governing the relationship of the two compartments. Thus, meeting this prerequisite is questionable.

In homogeneous populations of full-term infants, investigators have found an excellent linear correlation between jaundice meters and serum bilirubin values, but in more heterogeneous populations and in non-steady-state conditions correlations are poor[44,53-55]. Therefore, there is a doubt[40] that transcutaneous bilirubin values can routinely replace serum bilirubin concentrations in clinical practice.

COMPUTERIZED PHOTOSENSOR

To avoid some of the known problems with transcutaneous devices, we are in the midst of evaluating a computerized photosensor (Chromatics) that takes advantage of a wealth of information on skin tone available to the cosmetics industry. Instead of registering the simple change in skin color caused by bilirubin, the Chromatics meter can measure minute alterations in any one of a vast array of human skin types. This patient-specific analysis takes account of race and skin perfusion and, in effect, allows the computer to "see bilirubin" below the surface. Some results[54] suggest a degree of accuracy and linearity not available in other devices. Surprisingly, phototherapy does not seem to interfere with the measurement, even though infants, while being treated, appear less jaundiced to the eye. This suggests that the depth of measurement by this new device exceeds that which influences the visual assessment of skin color.

The value of the Chromatics meter, or any other screening tool, ultimately rests on the clinician's need to measure bilirubin in the newborn. The trends toward extremely early discharge after delivery, cost containment, and decreases in medical interventions should increase our requirements for simple and safe methods of determining which infants have more than just "physiologic" jaundice. If we couple this with a rational use of phototherapy, and newer treatments to eliminate hyperbilirubinemia, the incidence of significant hyperbilirubinemia may be reduced. In selected cases, such as severe, unexplained familial hyperbilirubinemia, it may be appropriate to refer a family for genetic counseling and to obtain genotype analysis of the UGT 1A1 gene, a test that is now available in some clinical laboratories.[58,59] Prudent evaluation may facilitate prediction of severe jaundice and enable prevention of bilirubin encephalopathy in future siblings.[60]

CONCLUSION

Notwithstanding a number of advances in the understanding of hyperbilirubinemia and its treatment in the newborn, controversy continues.

The trend has been to decrease interventions and observe and manage infants with jaundice as outpatients. This trend will probably prove to be both medically and economically sound. In the absence of significant hemolysis or other underlying medical conditions such as infection, many physicians are now comfortable with expectant observation for those healthy full-term infants with serum bilirubin measurements of less than 18 mg/dL. New thinking about this condition and advances in treatment may transform hyperbilirubinemia in neonates into a medical curiosity.

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