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Treatment of Neonatal Unconjugated Hyperbilirubinemia: A Brief Review

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Abstract

Neonatal unconjugated hyperbilirubinemia is a highly prevalent condition in newborns, resulting from elevated levels of bilirubin, a breakdown product of hemoglobin. While often self-limited and benign, excessive bilirubin can accumulate in the central nervous system, potentially leading to kernicterus spectrum disorders and long-term neurological damage. Bilirubin levels rise due to increased red blood cell breakdown, immature hepatic conjugation, and enhanced enterohepatic circulation in neonates, particularly in preterm or at-risk infants. Clinical recognition relies on monitoring for jaundice, scleral icterus, and laboratory assessment of serum bilirubin levels, with timely intervention essential to prevent adverse outcomes. Phototherapy remains the cornerstone of treatment, effectively converting toxic bilirubin into water-soluble forms for excretion, while exchange transfusion is reserved for severe cases unresponsive to light therapy. Adjunctive pharmacological approaches, including fibrates, zinc, probiotics, metalloporphyrins, and intravenous immunoglobulin, are under investigation, though efficacy and safety remain variable. Understanding the underlying mechanisms of bilirubin metabolism, identifying infants at risk, and evaluating treatment strategies are critical to minimizing complications. This review emphasizes the importance of optimizing management of neonatal unconjugated hyperbilirubinemia, balancing therapeutic efficacy with safety, and highlights the need for ongoing research to refine current treatments research to refine current treatments and develop new interventions to improve outcomes for vulnerable neonates.

Keywords: Unconjugated Hyperbilirubinemia; Phototherapy; Kernicterus; Bilirubin Metabolism; Enterohepatic Circulation

Abbreviations: UHB: Unconjugated Hyperbilirubinemia; AAP: American Academy of Pediatric; μW/cm2/NM: Microwatts Per Square Centimeter Per Nanometer; BSA: Body Surface Area; PDA: Patent Ductus Arteriosus; DNA; Deoxyribonucleic Acid; RBCs: Red Blood Cells; GI: Gastrointestinal; IVIG: Intravenous Immunoglobulin

Introduction

Neonatal unconjugated hyperbilirubinemia (UHB) is an extremely prevalent condition in newborns that results from deposition of elevated levels of bilirubin (a yellow pigment derived from the breakdown of hemoglobin) within their skin [1,2]. This condition is often self-limited or benign, and often clinically presents with yellowish skin, sclerae, and mucous membranes [3-5]. However, certain infants who are exposed to high levels of bilirubin may be at risk for kernicterus spectrum disorders due to bilirubin induced brain damage [6-9]. It is thus extremely important to understand the etiology of UHB to prevent such complications by evaluating risk factors, regular examinations and obtaining screening bilirubin values. The American Academy of Pediatrics (AAP) has provided clinical practice guidelines to assist providers in the management of UHB in neonates [10]. These guidelines mainly pertain to phototherapy treatment which is the goal standard for treating neonatal UHB but other interventions may also be considered. This brief review will attempt to provide an overview and fundamental understanding of the different modalities in managing neonatal UHB.

Discussion

Phototherapy

About 80% of bilirubin is derived from heme released from senescent red blood cells with the remainder originating from various heme-containing proteins found in other tissues, notably the liver and muscles [11]. After a two-stage reaction, bilirubin's final structure (bilirubin IX-alpha-ZZ) is essentially insoluble in aqueous solutions due to compaction from hydrogen bonding [12]. The therapeutic potential of light exposure to modify these bilirubin properties was first hypothesized in the early 1950s, following observations of decreased bilirubin concentrations in jaundiced infants exposed to sunlight. Further investigation demonstrated that light exposure triggered configurational photoisomerization, resulting in the conversion of insoluble, toxic bilirubin into water-soluble isomers and structural isomerization forming lumirubin which are efficiently eliminated through biliary and urinary excretion [13,14].

To optimize this process, phototherapy must be delivered at an effective dose, which is determined by several key factors. The first factor is spectral quality, as effective bilirubin degradation depends on light emission within the 460-490 nm wavelength range [15]. Blue, green, and turquoise wavelengths within the blue-green spectrum are regarded as optimal because of their enhanced skin penetration and maximal bilirubin absorption. Blue light phototherapy has become the standard light source for most therapeutic devices due to higher bilirubin affinity when compared with other lights in the blue-green spectrum [16,17]. The second factor, irradiance, is defined as the intensity of light energy delivered to the skin per unit surface area, typically quantified in microwatts per square centimeter per nanometer ($\mu W/cm^2/nm$) [18]. Higher irradiance doses have been associated with significant declines in bilirubin values and the AAP has recommended that for intensive phototherapy, an irradiance of 30 $\mu W/cm^2/nm$ (range 25 to 35) of blue-green light in the range 460 to 490 nm be applied [19]. Irradiance doses greater than 35 $\mu W/cm^2/nm$ have not demonstrated further efficacy in lowering bilirubin concentrations and may be associated with potential adverse effects on tissues and organs [20].

Measurement of irradiance across a defined wavelength range can be performed using a radiometer or spectroradiometer. Manufacturer-recommended devices should be employed, as inter-instrument variability result in differing measurements for identical light sources. Irradiance exhibits an inverse relationship with the distance from the light source to the body surface, increasing as the light source is positioned closer to the infant [21-24]. Body surface area (BSA) exposure is also directly related to bilirubin values with greater exposure allowing for a greater decline in bilirubin [15]. Phototherapy efficacy is primarily determined by the percent of exposed BSA using the most appropriate light source rather than the number of devices [19,25]. Yet utilization of multiple devices, either placed overhead or below the infant, can improve effectiveness if it allows for greater skin surface illumination.

The type of phototherapy device utilized in managing neonatal UHB is also a crucial point to be considered. Initially, conventional phototherapy was standard of care to treat neonatal UHB and employed the use of compact fluorescent lamps or halogen lamps. However, recent research has demonstrated that Light Emitting Diode compared to conventional phototherapy reduces bilirubin faster with decreased hospital stays, emits less heat, requires less energy, is more convenient to use and has a lower risk profile [26]. Also now in wide use are fiber optic pads that is a portable device that consists of an illuminator that directly administers blue or white light directly onto an infant's skin. Studies have demonstrated that fiber optic phototherapy is superior to conventional phototherapy with less risk of overheating infants, allows for infant and caregiver holding and bonding and avoids environmental contamination [27].

Phototherapy was initially thought to be a non-invasive and benign form of treatment yet recent data has shown that it is associated with certain adverse risks. Enacting phototherapy treatment for severe neonatal UHB often requires separating infants from their mothers and limiting breastfeeding and time away from the lights [28-30]. Studies have also demonstrated that phototherapy treatment may alter genes regulating an infant's circadian rhythm potentially affecting their sleep wake cycles [31,32]. Dehydration and hypocalcemia are also often noted especially in preterm infants after phototherapy treatment [33,34]. Depending on the particular light modality, there may be significant water loss and increased excretion of calcium in the urine. Hypocalcemia may also be due to phototherapy's inhibitory effect on the pineal gland decreasing melatonin and cortisol levels subsequently lowering calcium levels [35,36]. Infants undergoing treatment have also been noted to have an increase in petechiae, rash and an irregular pigmentation known as bronze baby syndrome. Phototherapy has also been linked to more severe long-term complications. One study found an increased incidence in patent ductus arteriosus (PDA) in lower birth weight infants exposed to phototherapy [37]. Bender et al. observed comparable results, hypothesizing that blue light penetration through translucent skin may induce vasodilation and subsequent reopening of a constricted PDA [38]. Phototherapy has also been associated with myocardial dysfunction, with several studies reporting significant reductions in systolic and diastolic blood pressure, stroke volume, and left ventricular output, alongside an increase in heart rate compared with pretreatment values [39]. While permanent eye damage has not been reported in children receiving phototherapy, concerns persist given evidence that blue light irradiation can impair retinal function. There is also consideration, based on recent evidence, that phototherapy can damage the Deoxyribonucleic Acid (DNA) of neonates and induce apoptosis of peripheral blood lymphocytes by inducing the generation of free oxygen radicals and altering tumor suppressor genes. These effects may partially account for observations from recent studies suggesting a potential increase in cancer later in life among newborns treated with phototherapy [40-45]. While the majority of reported complications have involved term infants, preterm infants may experience greater prevalence and severity owing to increased susceptibility related to their immature physiological systems. Findings from a large study by Morris et al. further heighten this concern, demonstrating increased mortality specifically associated with aggressive phototherapy in preterm infants weighing less than 750 grams [46]. In light of evidence that phototherapy duration may be significantly associated with adverse effects, the AAP recently updated its bilirubin guidelines

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to minimize overtreatment in infants >35 weeks' gestational age [10]. In preterm infants, intermittent or cycled phototherapy has been proposed as an alternative to continuous phototherapy to minimize treatment duration while maintaining effective bilirubin clearance. A recent study by Arnold et al. found that cycled phototherapy substantially decreased phototherapy time with little effect on bilirubin values in extremely low birth weight infants [8]. Further large-scale studies are required to assess the impact of cycled phototherapy on survival and long-term outcomes in this infant population.

Exchange Transfusion

Exchange transfusion, once the standard first-line treatment for neonatal UHB, is now limited to severe cases unresponsive to phototherapy [10,19]. The procedure involves insertion of a vascular catheter to allow the gradual withdrawal of aliquots of the infant's blood while donor blood is simultaneously infused, thereby facilitating removal of bilirubin and antibody-coated red blood cells (RBCs). It is estimated that this procedure reduces serum bilirubin levels by 50-60%, significantly decreasing the risk of chronic bilirubin encephalopathy, or kernicterus. Yet this procedure has been associated with significant risks such as infection, thrombocytopenia, electrolyte imbalance, metabolic acidosis, hemolysis, sepsis, necrotizing enterocolitis, or even death [10,19]. The decision to perform this procedure should incorporate assessment of the infant's risk factors in conjunction with guidance from AAP exchange transfusion guidelines.

Pharmacotherapy

In light of the substantial risk of encephalopathy and kernicterus and the potential adverse effects of existing therapies, pharmacological adjuvant treatments have been suggested. One such medication is fibrates, which have been proposed to induce hepatic uptake and conjugation of bilirubin. Evidence from multiple studies indicates that fenofibrate significantly lowers serum bilirubin concentrations, reduces phototherapy duration, and shortens hospitalization; however, larger randomized controlled trials are necessary prior to its integration into standard care [47-50]. Probiotics have also been suggested due to their ability to modify intestinal flora, improve gastrointestinal (GI) immunity, reduce enterohepatic circulation and degradation of conjugated bilirubin as well as improve GI mobility and stool viscosity. However, studies evaluating probiotic use for UHB have yielded inconsistent results, and concerns regarding invasive infection from contaminated products have prompted U.S. Food and Drug Administration warnings and AAP recommendations against routine use because of limited regulation and potential harm [51-57].

Zinc has also been suggested as an alternative treatment due to its potential ability to prevent lysis of RBCs and reduce enterohepatic circulation of bilirubin. Evidence from multiple studies suggests potential benefit; however, outcomes have been variable, and safety concerns related to zinc toxicity persist [58-64]. With its ability to inhibit the activity of heme oxygenase, Metalloporphyrins have also been proposed to prevent neonatal UHB. While some studies have reported favorable outcomes, these therapies are currently being assessed in phase II clinical trials, thereby restricting their routine clinical use [65-68]. Intravenous immunoglobulin (IVIG) has been used in conjunction with phototherapy for alloimmune hemolytic diseases due to its ability to block RBC receptors and prevent antigen antibody interactions and hemolysis [69,70]. Although frequently used in clinical practice based on the belief that it reduces bilirubin levels, phototherapy duration, and the need for exchange transfusion, published studies have demonstrated variable efficacy. Ongoing investigation is necessary to identify the formulations and conditions under which IVIG is efficacious; until such evidence is available, its use should be limited due to the risk of multiple side effects [71-75].

Conclusion

Neonatal unconjugated hyperbilirubinemia is a common condition that is often self-limiting but can result in serious neurological complications if bilirubin levels become excessive. Effective management requires early recognition, careful monitoring, and assessment of risk factors to prevent adverse outcomes. While several treatment approaches are available, their use must balance potential benefits with associated risks. Continued research is essential to better understand the condition, refine management strategies, and ensure safe, evidence-based care. Ultimately, a thorough understanding of neonatal hyperbilirubinemia and adherence to clinical guidelines are critical to safeguarding infant health and optimizing long-term outcomes.

Conflict of Interest

The authors report that they have no financial or personal relationships that could inappropriately influence or bias the content of this article.

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