Review Article

Evaluation of Neonatal Jaundice and its Management, Review Article

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Abstract

Among the most prevalent medical problems is hyperbilirubinemia. Newborn hyperbilirubinemia is a prevalent clinical issue in the newborn era, particularly in the first week of life. Hyperbilirubinemia affects 8% to 11% of newborns. The yellowing of a newborn's skin and sclera brought on by bilirubin is known as neonatal jaundice. Normal neonatal jaundice is benign and self-limiting; however, kernicterus, a condition where there is permanent damage to the brain due to abnormally high bilirubin levels, can occur. As a result, it is critical to correctly detect and treat newborn jaundice. This study aimed to provide an overview of jaundice, its types, and etiology, as well as to review various preventive precautions for parents of newborns with hyperbilirubinemia and therapeutic methods. The following keywords were employed in the mesh ((("neonatal jaundice"[Mesh]) AND ("hyperbilirubinemia"[Mesh]) OR ("phototherapy"[Mesh])) when selecting articles from the PubMed database. For patients with unconjugated hyperbilirubinemia, exchange transfusion and phototherapy are the cornerstones of treatment. Phototherapy continues to be the initial therapy for pathological unconjugated hyperbilirubinemia. The treatment of conjugated hyperbilirubinemia is customized to the underlying cause. Regarding prevention, exclusive breastfeeding is suggested throughout the first 6 months of life because exclusively breastfed neonates had the lowest rate of mortality.

Keywords: Neonatal jaundice, Management, Diagnosis, Evaluation

Introduction

Clinical problems that are most frequent include hyperbilirubinemia. A common clinical problem in the neonatal period, especially during the first week of life, is newborn hyperbilirubinemia [1]. In neonates, hyperbilirubinemia impacts 8% to 11%. Hyperbilirubinemia happens when total serum bilirubin (TSB) levels reach the 95th percentile for age (high-risk zone) within the first week of delivery [2]. 60% to 80% of healthy newborns are expected to experience idiopathic neonatal jaundice. The darkening of a newborn's skin and sclera due to bilirubin is known as neonatal jaundice [3]. In-hospital live deliveries had a 3.3% incidence of newborn hyperbilirubinemia, whereas extramural hospitalizations had a 22.1% morbidity rate owing to hyperbilirubinemia. When bilirubin levels rise, dermal icterus is initially observed in the faces of neonates before spreading to the torso and then the limbs. Within the first week of life, 50%–60% of neonates are affected by this condition [4].

Like uric acid, bilirubin is a necessary antioxidant that circulates in the biological system of newborns and is not just an unpleasant molecule with negative repercussions [5]. Nevertheless, high bilirubin levels can cause neurological and behavioral dysfunction as well as be toxic to the central nervous system in newborns [6]. Five to ten percent of infants experience jaundice, which calls for the management of hyperbilirubinemia [7]. There are several causes of neonatal jaundice, each with its own variations in manifestation. These include birth weight, gestational age, early rupture of the membranes, maternal infectious diseases, and other illnesses throughout pregnancy [8]. As a result, it could worry the medical professional and make the parents anxious. While jaundice in newborns is often benign and self-limiting,

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exceptionally high bilirubin levels have the potential to induce kernicterus, a condition that causes permanent brain damage [1]. As a result, it is critical to correctly detect and treat newborn jaundice. In this review article, we aim to provide an overview of jaundice, its types, and etiology, as well as to review various preventive precautions for parents of newborns with hyperbilirubinemia and therapeutic methods.

Materials and Methods

The following keys were utilized in the mesh (("neonatal jaundice"[Mesh]) AND ("hyperbilirubinemia"[Mesh]) OR ("phototherapy"[Mesh])) for the purpose of selecting articles from the PubMed database.

The articles were chosen according to the inclusion criteria if they included any of the following topics: prevention, management, and neonatal jaundice. All other articles that did not have one of these themes as their major destination were excluded.

Out of 1159 papers indexed in the recent decade, 473 were chosen as the most therapeutically relevant, and their entire texts were reviewed. Following a careful assessment, 20 of the 473 were included. Using reference lists from recognized and related papers, further research and publications were discovered. Expert consensus guidelines and commentary were given where appropriate to assist practicing doctors in assessing neonatal jaundice most straightforwardly and practically feasible.

Results and Discussion

Given the present period of early postnatal release and community assistance in the NHS, risk factors for severe jaundice must be addressed before discharge. A second clinical assessment should be performed before 48 hours of age, according to the NICE guidelines [9]. In all newborns with jaundice, a complete family history and clinical examination are critical for determining the probable etiopathophysiology. Appropriate examinations can detect reversible conditions (e.g., isoimmunization, infection, biliary atresia) early and enhance outcomes [9, 10].

Early Jaundice

Clinical jaundice in the first 24 hours of life is most commonly pathogenic and occurs by isoimmunization (most commonly ABO or rhesus incompatibility) or different types of severe hemolysis. Both the mother and the infant must have a direct agglutination test (DAT), as well as know their blood type and rhesus status. In women who do not have rhesus, anti-D prophylaxis may cause a marginally positive DAT test due to passive antibody transfer. The degree of jaundice may not always be reflected by a positive DAT test [11]. When it comes to identifying hemolysis in newborn neonates, the reticulocyte count and blood film have restricted sensitivity and specificity [12]. A review of the maternal prenatal notes can frequently provide important information concerning additional blood group incompatibilities or the existence of other antibodies. In unwell neonates with early jaundice, infection should always be ruled out. Although G6PD deficiency-related jaundice emerges after 48 hours, it should be evaluated in neonates whose parents are of Mediterranean, Asian, or African heritage. Crigler-Najjar syndrome should be explored if hemolysis is ruled out. Although uncommon, it is possible to develop quickly worsening non-hemolytic unconjugated jaundice early in infancy. Infants with G6PD deficiency can also appear with newborn non-hemolytic jaundice [1, 10].

Prolonged Jaundice

Prolonged jaundice is defined as persistent clinical jaundice in term newborns at 2 weeks and preterm infants at 3 weeks of age. This is a frequent community referral that often manifests as unconjugated jaundice in breastfeeding newborns. Pathological reasons can be ruled out with a feeding history, stool and urine color, and clinical examination. The investigations should be carried out in stages based on the findings of the preliminary investigations. Checking the color of the stool (whether yellow or pale chalky stool), checking the urine (whether it is dark and easily stains the nappy), measuring total and split bilirubin, full blood count, blood group and DAT, liver function test, urine culture and sensitivity, ensuring the Guthrie card is sent for routine metabolic screening, thyroid function test, and G6PD level are all preliminary tests for infants with prolonged jaundice [1, 9, 10].

Conjugated Jaundice

Conjugated jaundice is defined as a serum-conjugated bilirubin level of more than 25 mmol/liter. Although a 10% cut-off number for total blood bilirubin level is commonly utilized in clinical practice, this might provide false confidence in cases with high total bilirubin levels. Pale chalky stool and dark urine might be significant indicators. A liver function test should be performed to rule out any clotting abnormalities. In situations of suspected obstructive jaundice, a liver ultrasound might give further information. Congenital infections, sepsis, galactosemia, and aminoacidurias can all be ruled out with further testing. Preterm newborns receiving total parenteral nourishment frequently show a significant rise in conjugated bilirubin fraction, which gradually improves once whole parenteral nutrition is discontinued [13].

The term 'jaundice' refers to the yellow-orange coloring of the skin and sclera caused by an excess of bilirubin in the skin and mucous membranes. Jaundice is not a sickness in and of itself, but rather a symptom or indicator of another [14]. Bilirubin is primarily generated in the spleen when the haem component of red blood cells is broken down to biliverdin and subsequently unconjugated bilirubin. Because bilirubin is not water soluble, it travels from the spleen to the liver via the circulation, coupled with the plasma protein albumin. It is

known as conjugated bilirubin in this state, which is subsequently released into the gallbladder. It is further converted in the intestines to other gall pigments and eliminated in the stool [14, 15].

The mechanism of newborn jaundice is a bilirubin production and conjugation imbalance, which results in elevated bilirubin levels. This imbalance is caused primarily by the neonate's underdeveloped liver and the fast breakdown of red blood cells, which may be multifactorial [16].

Clinically, newborn jaundice can be identified at bilirubin levels ranging from 85 to 120 mol/L. According to Moyer *et al*., the clinical diagnosis of newborn jaundice is "neither reliable nor accurate." [17].

Neonatal jaundice is quite frequent, affecting 60% of term newborns and up to 80% of preterm neonates. Prematurity and newborn sepsis have been recognized as major risk factors for neonatal jaundice [16, 18]. Only unconjugated bilirubin levels are elevated in physiological jaundice due to liver immaturity in the absence of any other sickness. Pathological jaundice is caused by underlying diseases that either increase or reduce bilirubin excretion. The underlying problems must be addressed to treat pathological jaundice [14, 16].

Treatment of Unconjugated Hyperbilirubinemia

The cornerstone treatments for patients with unconjugated hyperbilirubinemia are phototherapy and exchange transfusion.

Phototherapy

The first line of treatment for pathological, unconjugated hyperbilirubinemia is phototherapy. When it comes to bringing TSB down to levels that are manageable, phototherapy is incredibly effective in reducing the likelihood of bilirubin toxicity and the need for exchange transfusions. On the bilirubin nomogram [19], phototherapy is started in response to risk variables and TSB levels. However, due to a paucity of information, recommendations on the indications for phototherapy in preterm newborns are inadequate, notably in the US. Because of this, based on birth weight or gestational age, the majority of US hospitals have established procedures for phototherapy and exchange transfusions in preterm newborns [20].

The effectiveness of phototherapy is dependent on the amount and wavelength of light used, as well as the surface area of the baby's body exposed to it. Place phototherapy units as close to the baby as you can while using more units to increase the dose of PT. Strong blue-green light absorption is seen in bilirubin (460–490 nm). Phototherapy produces bilirubin photoisomerization and the conversion of bilirubin to lumirubin, which is the rate-limiting stage in the elimination of bilirubin [21].

To avoid retinal damage, the newborn's eyes must be covered during phototherapy. Measures must be taken to expose the largest amount of body surface area to light while avoiding disruptions in PT. Because most bilirubin is removed from the urine as lumirubin, it is vital to maintain proper hydration and regular production of urine. An increase in total blood bilirubin levels occurs after phototherapy is stopped; this is referred to as "rebound bilirubin." Resuming phototherapy is not necessary when the "rebound bilirubin" level is less than it was at the beginning of the treatment [22].

Despite the generally accepted belief that phototherapy is safe, recent research indicates that there may be long-term risks. According to reports, using phototherapy can have negative consequences such as rashes, dehydration, hypocalcemia, retinal damage, hemolysis due to oxidative damage, delayed PDA closure in preterm babies, and allergic reactions [23]. Moreover, a few studies have found that children who have had phototherapy are more likely to develop solid organ cancers and non-lymphocytic leukemias [24]. The bronze newborn syndrome is another commonly reported problem associated with phototherapy that results in uneven skin, mucous membranes, and urine coloration. It most frequently occurs in newborns with elevated levels of blood-conjugated bilirubin. Although the exact process is uncertain, bilirubin photoisomer buildup and biliverdin deposition seem to be related [25].

Biliblankets made of fiber optics are an excellent approach to lower bilirubin levels. They aid in the continuance of phototherapy during cuddles with parents and, when mixed with an overhead unit, can be an ideal method to deliver 'double' phototherapy. As a result of their low heat emissions, they can be placed directly in contact with the infant. Transforming bilirubin into lumirubin, a water-soluble molecule secreted along with bile and urine, by an irreversible photochemical process is the most popular method of removing bilirubin from the body. Two further important processes of bilirubin photo-modification are configurational isomerization of the bilirubin isomer to more water-soluble and less toxic isomers and photo-oxidation of bilirubin to colorless polar molecules excreted in urine [26]. Even though phototherapy is normally safe, some people have skin discoloration, increased fluid loss, diarrhea, and an erythematous rash. Over the last decade, advances in phototherapy devices have significantly minimized these negative effects.

Exchange Transfusion

Therapy for severe unconjugated hyperbilirubinemia now available is exchange transfusion, which was the first effective therapy for jaundice. In cases where phototherapy is ineffective or the initial TSB levels fall within the exchange range of the nomogram, it is suggested. Exchange transfusion rapidly removes bilirubin and hemolysis, resulting in the removal of antibodies from circulation. In a double-volume exchange blood transfusion, the neonate's blood is substituted

with aliquots of crossed-matched blood. Because a significant number of total body bilirubin is located in the extravascular compartment, TSB levels soon after an exchange transfusion are around 60% of pre-exchange levels, enhancing to 70 to 80% of pre-exchange levels as an outcome of equilibrium with an extravascular moiety of bilirubin. Vital signs must be constantly watched during the exchange transfusion, and after the treatment, measurements of TSB, CBC, serum calcium, glucose, and electrolytes need to be made. Exchange transfusion complications might include thrombocytopenia, heart arrhythmias, blood-borne infections, graft versus host disease, necrotizing enterocolitis, and electrolyte abnormalities including hypocalcemia and hyperkalemia [27].

After the exchange transfusion, phototherapy should be resumed until the bilirubin level drops to a safe level.

Intravenous Immunoglobulin (IVIG)

When immune-mediated hemolysis is the source of unconjugated hyperbilirubinemia jaundice, IVIG is administered to inhibit RBC hemolysis by covering Fc receptors on RBCs. If TSB remains within 2 to 3 mg/dl of the exchange level after intense phototherapy, IVIG infusion is recommended [28]. However, there is little evidence that IVIG usage lessens the requirement for exchange transfusion. Despite this, IVIG is often used in clinical practice to treat unconjugated hyperbilirubinemia.

Treatment of Conjugated Hyperbilirubinemia

Treatment for conjugated hyperbilirubinemia is individualized based on the underlying cause. In this age bracket, one-fifth of all newborns transferred to a UK hepatobiliary referral center have biliary atresia, the most frequent surgically correctable liver problem. One-third of children with biliary atresia initially have colorful stools because the intra- and extrahepatic bile ducts may stay open in the first few weeks of life. When they reach the atretic, the bile stops flowing and the stool takes on a chalky, white look. Patients with biliary atresia should have a hepatic portoenterostomy, or Kasai procedure, within the first two months of their lives for the greatest results [29]. To construct a different conduit for biliary drainage, the Kasai operation involves excising the fibrous plate and atretic biliary ducts, followed by a Roux-en-Y anastomosis of the jejunum with the remaining ducts [30].

Antimicrobials would be used to treat infectious causes of cholestasis; however, many BASDs are often cured with cholic acid and chenodeoxycholic acid. Generally, metabolic reasons for cholestasis would respond to the primary illness getting better and the liver working again. For individuals with GALD, IVIG and double-volume exchange transfusions seem to be beneficial treatments. Liver transplantation is curative when available, but in this age group, it is technically challenging [31]. Cyclic parenteral nutrition (PN) shortens the duration of exposure and initiates enteral feedings as soon as practical to cure cholestasis caused by parenteral nutrition. Lowering the PN's manganese and copper levels will prevent liver damage.

Prevention

It is advised to nurse an infant exclusively for the first six months of life due to the lower all-cause death rate. Hyperbilirubinemia is related to exclusive breastfeeding, although inadequate nursing appears to be the main reason for hyperbilirubinemia [32, 33]. If difficulties with lactation are found, assistance with the process should start in the hospital and continue in the doctor's office and at home. At UMHS, patient education materials like Feeding the Baby Born Before 38 Weeks are available to assist with this process. To lessen the risk of dehydration, the American Academy of Pediatrics advises urging all term babies to breastfeed at least 8 to 12 times daily during the first few days of life. Breastfeeding mothers who notice jaundice in their babies are more likely to terminate nursing prematurely [19].

Unless the amount is near the threshold for exchange transfusion, mothers should be supported to breastfeed and provided lactation help if they are experiencing difficulties [34]. If phototherapy can be administered during nursing, that should be encouraged. Formula supplementation may be investigated if the newborn seems dehydrated, if weight loss surpasses the 95th percentile per NEWT, if the infant's intake is inadequate, or if the infant's jaundice is severe. Signs of normal intake in breastfed neonates include four to six totally wet diapers each day, three to four stools daily by the fourth day of life, and the possibility of seedy, mustard-colored stools by the 3rd or 4th day of life [19]. It is suggested that all babies be breastfed at least eight times per day beginning soon after delivery [35]. Newborns should be kept skin-to-skin and fed at least every three hours, depending on eating signals. In the first 24 to 48 hours after birth, NEWT advises against feeding supplements unless there is a noticeable sign of dehydration or weight loss that exceeds the 95th percentile [19]. Below are the UMHS augmenting recommendations for term infants who are difficult to latch for the first four days. The normal breast milk consumption of healthy breastfed newborns [20] is the basis for this advice.

Conclusion

Exchange transfusions and phototherapy are the mainstay therapies for individuals with unconjugated hyperbilirubinemia. Phototherapy continues to be the initial therapy for pathological unconjugated hyperbilirubinemia. The treatment of conjugated hyperbilirubinemia is customized to the underlying cause. Regarding prevention, exclusive breastfeeding is suggested throughout the first 6 months of life because exclusively breastfed neonates had the lowest all-cause mortality.

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