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Review Article

Neonatal Jaundice and the Developing Brain: Pathophysiology, Clinical Management, and Long-Term Neurological Outcome

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Abstract

Neonatal jaundice, characterized by elevated serum bilirubin levels, is a common condition affecting newborns globally. While mild jaundice is often benign, severe hyperbilirubinemia poses a significant risk to neurological development. If left untreated, it can lead to irreversible brain damage, with lifelong implications for affected children. This review aims to examine the impact of neonatal jaundice on pediatric neurological outcomes, focusing on the pathophysiology, risk factors, clinical manifestations, and long-term consequences. A comprehensive analysis of current literature was conducted, including clinical studies and systematic reviews. Emphasis was placed on understanding the neurological sequelae of neonatal jaundice and evaluating the effectiveness of therapeutic interventions. Findings indicate that severe neonatal jaundice is associated with neurological complications such as acute bilirubin encephalopathy and kernicterus. These conditions can result in motor impairments, hearing loss, speech delays, and cognitive dysfunction. Early diagnosis and interventions, such as phototherapy and exchange transfusion, have significantly reduced the incidence of severe outcomes. However, in low-resource settings, delayed diagnosis and inadequate treatment remain substantial challenges, increasing the risk of permanent disability. Neonatal jaundice, if improperly managed, poses serious risks to pediatric neurological health. Timely intervention and improved screening protocols are essential to prevent long-term neurological damage. Further research is needed to explore the subtle neurodevelopmental effects and to enhance care strategies, especially in under-resourced regions. A multidisciplinary approach is crucial to mitigate these risks and improve outcomes for affected children.

Keywords: *Neonatal jaundice, Pediatric neurology, Neurodevelopmental outcomes, Kernicterus, Newborn health, Neonatal complications*

Introduction

Neonatal jaundice (NJ) is very common in newborns, affecting up to 60% of term to 80% of preterm babies usually in the first week of birth (1,2). The condition typically peaks within the first 3-5 days and resolves by the second week in most cases. Severe hyperbilirubinemia is defined as a serum bilirubin concentration approaching or exceeding the exchange transfusion threshold, based on the infant's postnatal age in hours and individual risk factors (3).

It is assessed using hour-specific bilirubin nomograms that consider gestational age, isoimmune hemolysis, G6PD deficiency, presence of sepsis, acidosis, and overall clinical status (4). It occurs in approximately 8-9% of neonates worldwide, posing a risk of bilirubin-induced neurological dysfunction (BIND) (a spectrum of neurological impairments caused by excessive unconjugated bilirubin) and kernicterus (5). Neonatal jaundice occurs as a result of the increase in bilirubin levels in the blood which accumulates in tissues including those of the skin and mucous membrane (2). This leads to the yellow discoloration seen in the skin (of pale babies) and the sclera. The increased serum bilirubin is usually present before it manifests as Neonatal jaundice (1). In most cases, it is harmless and is caused by the breakdown of red blood cells, although it is very important to monitor, as the severe case raises the risk of neurological toxicity, which can lead to seizures, hearing loss, cerebral palsy, and bilirubin encephalopathy and other serious neurological issues (1,2,6).

Over 20 million babies are at risk of complications from hyperbilirubinemia, which affects about 1.1 million babies globally each year (7). In particular, severe hyperbilirubinemia increases the risk of kernicterus development in 75,400 newborns and death in 114,000 newborns. Early detection and treatment are essential because this condition can result in kernicterus and bilirubin-induced neurological dysfunction (BIND) (8). Neonatal Jaundice is a major contributor to neonatal morbidity and mortality especially in sub-Saharan Africa, Asia, and Latin America (1), with Ethiopia having one of the highest rates of infant deaths from jaundice (6). In developing countries, common causes of severe jaundice include blood group incompatibilities, prematurity, G6PD deficiency, and infections, along with socio-cultural factors that may hinder access to medical care (1).

Severe jaundice is characterized by high serum bilirubin levels and the higher the serum bilirubin level, the higher the risk of developing neurological complications. The neurotoxic effect of hyperbilirubinemia can cause selective damage to the grey matter in the CNS which leads to neurological sequelae including acute, chronic bilirubin encephalopathy, and bilirubin-induced neurological dysfunction (7,8). Wagemann et al., (9) described that more than 50% of infants with serum bilirubin greater than 30mg/dl experience neurological sequelae which could present as visual and hearing disorders, signs of extrapyramidal cerebral palsy (6). Another study estimated that about 130,000 new born worldwide are exposed to significant risk of bilirubin-induced brain damage or death due to high bilirubin levels (10). A study by Wutschoff et al, showed that there is an association between hyperbilirubinemia (HB) and a higher risk of developmental delay, but only in a subset of the population (8). The greatest concern regarding significant neonatal jaundice is bilirubin-induced neurological dysfunction (BIND), a broad term encompassing the spectrum of neurotoxic effects caused by excessive bilirubin levels. This is caused by the unconjugated bilirubin crossing the still developing Blood Brain Barrier (11). This neurological dysfunction has not been extensively studied or explored and evidence shows that the impact of jaundice on the neurological system cannot be overlooked (11). It should be taken with much more importance as proper education and detection is necessary to improve prognosis (1).

Understanding the impact of neonatal jaundice on pediatric neurological health is crucial for early detection and intervention. Timely diagnosis and treatment, particularly in resource-limited settings, are essential to prevent long-term disabilities and ensure better health outcomes for affected children. This study aims to explore and identify the outcomes of neonatal jaundice on the developing brain, examining its underlying causes, and evaluate its long-term impact on pediatric neurological outcomes. Additionally, it discusses current diagnostic approaches, treatment strategies, and preventive measures to mitigate the neurological risks associated with severe hyperbilirubinemia.

Pathophysiology of Neonatal Jaundice

Neonatal jaundice primarily results from an imbalance between bilirubin production and elimination. At birth, newborns produce more bilirubin than adults due to a higher hematocrit and the shorter lifespan of fetal erythrocytes, which leads to increased hemolysis and bilirubin generation (4). However, the neonatal liver is functionally immature, exhibiting low activity of the enzyme uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1), which is responsible for conjugating bilirubin in the liver (12). As a result, unconjugated bilirubin accumulates in the bloodstream. In addition, elevated β-glucuronidase activity in the neonatal intestine promotes deconjugation of bilirubin, enhancing enterohepatic circulation and increasing bilirubin reabsorption into the bloodstream (13). This further contributes to elevated levels of unconjugated bilirubin.

Exacerbating factors such as hemolytic diseases (e.g., Rh or ABO incompatibility), infections, and birth trauma increase the breakdown of red blood cells, leading to higher bilirubin production (14). Meanwhile, hepatic and metabolic disorders such as neonatal cholestasis and biliary atresia impair the excretion of conjugated bilirubin, resulting in direct hyperbilirubinemia (15).

Because unconjugated bilirubin is lipophilic, it can cross the immature blood-brain barrier in neonates. Excessive levels can deposit in brain tissues, particularly the basal ganglia, leading to neurotoxicity, this condition is known as kernicterus. The pathophysiological consequences include disruption of neuronal cell membranes, impaired synaptic transmission, reduction in action potentials, mitochondrial dysfunction, and altered neurotransmitter synthesis (16–19).

Types of Neonatal Jaundice

Physiological Jaundice:

Physiological jaundice is the most common type of neonatal hyperbilirubinemia and is generally harmless, resolving without serious complications (20). It results from the normal transition of bilirubin metabolism after birth and is characterized by a transient increase in serum bilirubin levels. Physiological jaundice occurs due to the newborn's immature liver function and typically appears between 24 to 72 hours after birth. In term neonates, bilirubin levels peak around the 4th to 5th day, while in preterm infants, the peak occurs around the 7th day. The condition gradually resolves on its own, usually disappearing by 10 to 14 days of life, though it may persist longer in preterm babies (21). As previously discussed, the primary cause is the immature activity of hepatic enzymes, particularly uridine diphosphate-glucuronosyltransferase, which delays bilirubin conjugation and clearance. Newborns also experience a greater bilirubin burden as a result of accelerated red blood cell breakdown and intensified enterohepatic recycling. Physiologic jaundice is self-limiting and usually does not require medical intervention. However, monitoring is essential to differentiate it from pathological jaundice, which may require treatment.

Pathological jaundice:

Pathological jaundice as the name implies typically signals an underlying health issue. In contrast to physiologic jaundice which is mild and self-limiting, pathological jaundice is marked by unusually high and persistent bilirubin levels, necessitating immediate assessment and treatment. Key features include:

Early onset: Appears within the first 24 hours of life, often suggesting hemolysis, infection, or other underlying disorders (20).

Rapid bilirubin rise: A significant increase in serum bilirubin levels (>0.2mg/dL/hr) raises concerns about excessive bilirubin production or impaired clearance (20).

Prolonged duration: Jaundice persisting beyond two weeks in term infants (or three weeks in preterm infants) may indicate liver dysfunction, metabolic disorders, or biliary obstruction (10).

High bilirubin levels: Total serum bilirubin exceeding the 95th percentile for age increases the risk of bilirubin-induced neurotoxicity (10).

Causes of Pathological Jaundice

Hemolytic Disorders: The most frequent causes of hemolytic jaundice are Rh incompatibility, ABO blood group incompatibility, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, and other minor blood group incompatibilities.

- Rh incompatibility- Rhesus Hemolytic Disease of the Newborn occurs when a Rh-negative mother produces antibodies against the Rh-positive red blood cells of her Rh-positive baby (22). These maternal antibodies, typically immunoglobulin G (IgG), can cross the placenta and cause a range of symptoms in the fetus, including mild to severe hemolytic anemia and, in severe cases, fetal hydrops. This condition arises from maternal red-cell alloimmunization when the baby inherits Rh-positive blood from the father (23,24)

- ABO Incompatibility- ABO incompatibility occurs when an O blood group mother carries a fetus with blood group A or B. While this mismatch is present in up to 20% of pregnancies, only a small proportion result in hemolytic disease significant enough to cause jaundice (14). Hemolysis results from maternal IgG antibodies crossing the placenta and attacking fetal red blood cells. Jaundice typically develops within the first 24 hours after birth.

- A positive Direct Antiglobulin Test (DAT) can support the diagnosis, though a negative result does not exclude it (25). Routine cord blood screening in all at-risk newborns is no longer recommended. Instead, infants with early-onset jaundice or risk factors should be closely monitored, with bilirubin levels assessed as needed. Discharge timing should be individualized based on clinical findings, bilirubin trends, and access to follow-up care (5)

2. Jaundice associated with Glucose-6-phosphate dehydrogenase (G6PD) deficiency- G6PD deficiency (which is the most common enzymopathy) affects red blood cells and is a key disorder in the hexose monophosphate pathway (26). Testing for G6PD deficiency should be considered in infants with severe jaundice, especially if there is a family history of significant jaundice or if the infant is from a region where G6PD deficiency is prevalent. Variations in the UGT1A1 and OATP2 genes, which affect bilirubin conjugation, contribute to the progression of hyperbilirubinemia in G6PD-deficient newborns (27).

3. Breastfeeding and Breast Milk Jaundice: Jaundice due to breast feeding occurs within the first week of life, usually peaking around days 3–5 and results from insufficient milk intake, leading to dehydration and decreased stool output. Reduced stooling slows bilirubin excretion, increasing enterohepatic circulation and leading to higher bilirubin levels (28). This form of jaundice is more common in babies who are not feeding well. Reduced breastfeeding frequency can exacerbate physiological jaundice (29). Breast milk jaundice persists beyond the second week of life, often peaking between 10–15 days and resolving by the third week, though it sometimes lasts several weeks to months (30). It is believed to be due to certain factors in breast milk, such as β-glucuronidase, which deconjugates bilirubin in the intestine, increasing enterohepatic circulation (31). Severe bilirubin accumulation leading to cerebral damage is rare.

Complications Of Bilirubin-induced Neurotoxicity

Bilirubin neurotoxicity disrupts crucial regulatory mechanisms, significantly altering gene expression (32). This alteration can affect how cells behave and develop, leading to various harmful outcomes like excitotoxicity, oxidative stress, inflammation, and programmed cell death (apoptosis) (33).

When bilirubin is processed in the liver, it is conjugated and excreted into bile. However, the presence of beta-glucuronidase in breast milk can lead to the reversion of conjugated bilirubin back to its unconjugated state within the intestines (31). The interplay between immature liver function and certain components of breast milk contributes to rising levels of unconjugated bilirubin in the bloodstream. Once in circulation, unconjugated bilirubin can cross the blood-brain barrier and enter brain cells, where it generates reactive oxygen species, and induce neuroinflammation by activating the glial cells (34). If left untreated, it can progress to chronic bilirubin encephalopathy, occurring in approximately one in every 100,000 cases (35).

Bilirubin-induced neurotoxicity (BIN) encompasses a spectrum of neurologic injuries caused by the deposition of unconjugated bilirubin in brain tissue. This deposition occurs when bilirubin crosses the immature blood-brain barrier (BBB), a process exacerbated by conditions such as acidosis, hypoxia, or sepsis, which increase BBB permeability (36). The resulting toxicity leads to oxidative stress, excitotoxicity, apoptosis, and neuroinflammation.

Acute Bilirubin Encephalopathy (ABE)

Acute bilirubin encephalopathy (ABE) is the earliest clinical presentation of bilirubin-induced neurotoxicity and typically appears within the first days of life. Clinical features include lethargy, hypotonia, poor feeding, high-pitched cry, and progressing signs like hypertonia, opisthotonus, and seizures in severe cases (37). If promptly treated, primarily via phototherapy or exchange transfusion, acute bilirubin encephalopathy can be reversible (38). However, prolonged exposure may lead to irreversible neuronal injury.

Chronic Bilirubin Encephalopathy (Kernicterus)

If not managed in the acute phase, acute bilirubin encephalopathy can progress to chronic bilirubin encephalopathy, commonly referred to as kernicterus. This condition is marked by permanent damage to specific brain regions, including the basal ganglia, cerebellum, hippocampus, and auditory pathways (36). Kernicterus often results from sustained serum unconjugated bilirubin levels are extremely elevated, although toxicity can occur at lower levels in preterm or clinically unstable neonates (5).

Kernicterus is classically characterized by a triad of sensorineural hearing loss, choreoathetoid cerebral palsy, and upward gaze palsy. Additional features include dysarthria, dental enamel hypoplasia, and cognitive or behavioral impairments, although intelligence may be relatively preserved in some individuals (39,40). The condition can be categorized based on symptom dominance. The auditory-predominant type manifests primarily as hearing loss and delayed speech, while the motor-predominant form presents with dystonia, spasticity, and abnormal postures. A proposed severity scale ranges from mild where individuals experience minor learning or motor difficulties to profound cases marked by non-verbal, wheelchair-bound individuals with severe sensorimotor deficits (5).

Sensorineural Hearing Loss

One of the earliest signs of bilirubin-induced neurotoxicity is **auditory neuropathy**, which may occur in isolation. Bilirubin has a specific affinity for the auditory system, particularly the cochlear nuclei and inferior colliculus (41). Auditory brainstem response (ABR) testing is crucial for early identification of bilirubin-induced hearing impairment, even when motor symptoms are absent.

Choreoathetoid Cerebral Palsy

When bilirubin-induced neurotoxicity affects the globus pallidus and subthalamic nucleus, it often results in choreoathetoid cerebral palsy, characterized by involuntary, writhing movements and dystonia. This form differs from the spastic variant of CP and often coexists with normal intellectual function (16). Bilirubin is known to induce mitochondrial dysfunction and apoptosis in these regions.

Cognitive and Behavioural Sequelae

Though many individuals with kernicterus retain cognitive capacity, subtle executive dysfunction, learning disabilities, and behavioral issues can arise, especially when exposure occurs during sensitive neurodevelopmental periods (5). These impairments may go unrecognized without comprehensive neurodevelopmental assessments.

Seizures and Neurological Dysfunction

In severe cases, bilirubin-induced neurotoxicity is associated with seizures, often due to heightened neuronal excitability from oxidative stress and glutamate toxicity (5). Seizures and other neurologic deficits including gaze abnormalities and ataxia reflect broader cerebral and cerebellar involvement.

The Long-Term Impacts of Neonatal Jaundice on Pediatric Neurological Outcomes

While neonatal jaundice Neonatal Jaundice clears within the first few weeks of life, it may persist beyond this timeframe. Neonatal Jaundice that lasts longer than 14 days in term infants or 21 days in preterm infants could signify an underlying medical condition (42). Similar to other neonatal conditions, jaundice can persist and lead to long-term complications such as developmental delays, respiratory difficulties, and neurological impairments (43,44), some of which may not become apparent until later childhood. Early identification and proper care are therefore important, as highlighted by Wei et al (45).

Neurodevelopmental disorder (Autism Spectrum Disorder) (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD))

The long-term consequences of neonatal jaundice are under active investigation, with studies finding high bilirubin levels associated with neurological problems, including ASD, ADHD, and cerebral palsy (10,40,46,47). Chen et al.(47) enrolled 1,080 participants (2,016 newborns with neonatal jaundice and 8,064 age- and gender-matched controls without neonatal jaundice between 1999 and 2011. They found that participants with neonatal jaundice Had a higher incidence of autism spectrum disorder (ASD) (1.3% vs. 0.7%), developmental delay (6.7% vs. 4.7%), and developmental speech or language disorder (5.5% vs. 3.7%) than controls, with a statistically significant difference. Although the study did not show any statistical difference in the incidence of ADHD, a study from 2000 to 2004 of 24,950 neonatal jaundice causes and 69,964 matched non-jaundice controls in Taiwan showed that neonatal jaundice was associated with an increased risk of ADHD (45).

The neurotoxic effect of bilirubin may vary from oxidative stress, impaired metabolism, and neuroinflammation, which may impair neuronal function and development (2,4,47). Magai et al. (48) assessed cognitive abilities, language skills, perceptual-motor abilities, and academic performance and found that survivors of neonatal jaundice had significantly lower scores in all areas compared to controls. Although the study did not highlight any sexual differences in the results, Seidman et al. (49) found a significant association between low IQ scores (less than 85) in full-term male participants and high bilirubin levels above 20 mg/dL; however, they found no such association for female participants.

Motor and sensory impairment

Bilirubin toxicity may affect brain regions like the cerebellum and basal ganglia (subthalamic nucleus and globus pallidus), which are responsible for coordinated and voluntary movement (22). The globus pallidus, a brain region responsible for coordinated movement, is highly sensitive to bilirubin toxicity. This can lead to neuron loss, demyelination, and gliosis, which are associated with athetoid or dyskinetic cerebral palsy (50). Kahraman et al. found lower motor scores in infants with high bilirubin levels than in controls. The study also emphasized using the General Movement Assessment to identify motor risks in infants with NJ (50,51).

Other long-term impacts have been associated with hearing loss, speech and language impairment, and vision loss. Severe hyperbilirubinemia affecting the auditory pathway may lead to auditory neuropathy spectrum disorder (52). Research has shown that NJ can increase the risk of hearing impairment, including conductive, sensorineural, and mixed hearing losses (53–55). Even moderate bilirubin levels can lead to long-term hearing loss (56). Boskabadi et al. (57) evaluated 200 term infants with severe NJ and found an incidence of 4.8% sensorineural hearing loss. The study also observed that a notable proportion of participants across the study groups exhibited neurological complications like eye movement disorders, opisthotonus, and microcephaly (57).

Researchers have identified language impairments as a potential long-term consequence of NJ, but existing research on this association is inconclusive (58). Amin et al.'s study showed no significant association between hyperbilirubinemia and language impairment. This study was also consistent with the Ogun et al. (59). However, because of the close link between hearing loss and language delay, we cannot dismiss the possibility of an association (60).

Some infants exposed to bilirubin toxicity experience long-term issues like transient abnormalities in visual evoked potentials, strabismus, and oculomotor dysfunction (61,62). These may lead to long-term visual impairments even with bilirubin levels below the neurotoxic threshold (63). Good *et al*.(61) reported that infants exposed to bilirubin had lower sweep visual evoked potential (sVEP) signal amplitudes compared to the control group. This reduction was observed across all the specific cortical functions (grating acuity, contrast sensitivity, and vernier acuity), suggesting the widespread vulnerability of the visual system.

Screening, diagnostic techniques and the management approaches to neonatal jaundice

The procedure for the treatment of neonatal jaundice depends on the Total Serum Bilirubin (TSB) level in relation to the gestational age and presence of risk factors that can make the newborn susceptible to neurotoxicity (64). It is therefore necessary to have a clear understanding of the available screening methods and their modalities, which will guide in choosing the most appropriate treatment, preventing under or overtreatment. Pathologic neonatal Jaundice is treatable and its neurotoxic complications can be averted if diagnosed and treated promptly (64). The main purpose of screening is to exclude pathological causes or carry out further investigation to find out the cause while commencing treatment to prevent neurotoxicity. Intervention is dependent on where the TSB level falls on the risk zone using the Hour-specific serum bilirubin nomogram (65)

Prenatal antibody screening of the mother should be done prior to delivery, in cases where this is positive or not done, the direct antiglobulin test (DAT) should be done in the newborn (66). Using the cord or peripheral blood, the infant’s blood group should be done as soon as possible. This is to identify newborns with maternal anti-erythocyte antibodies (66). A positive DAT suggests that the mother’s antibodies are attacking the newborns' red blood cells leading to hemolysis (5). In such cases, there is a neurotoxicuty risk factor due to hyperbilirubinemia. The TcB or TSB should be measured immediately, then at hours 4 and 8, then every 12 hours afterwards, this is to be done three times. For mothers who received Rho(D) immune globulin (RhIG), the newborn can have a positive DAT, with no hemolysis and are treated as DAT negative (14). DAT positive neonates with range >5-40 should have a full blood count, retics, and blood film, which is to be repeated at week 3 and 6 (66).

Screening and diagnosis of neonatal jaundice

VISUAL ESTIMATION: All infants should be visually monitored every 12 hours until discharge for signs of jaundice(4, 64). In newborns noticed to be jaundiced within 24 hours of delivery, the TSB should be done immediately (within 2 hours). It should be repeated every 6 hours till these two things happen, the levels fall below the treatment threshold and the measure is either stable or falling (5). Visual assessment is supplementary to obtaining a TSB or Transcutaneous bilirubin (TcB) test and does not replace the importance of having this test done. TSB should be measured within 24-48 hours after delivery, in cases where discharge is early, it should be done before discharge (5).

TRANSCUTANEOUS BILIRUBIN (TcB): This is a point-of-care testing method using a transcutaneous bilirubinometer. The bilirubin level of the blood is measured non-invasively by shining light onto the skin and analyzing the reflected light (67) . Being non-invasive, it reduces trauma and likelihood of infection following blood withdrawal for TSB (68). According to the American Academy of Pediatrics (AAP), if the TcB is greater or within 3mg/dL of the phototherapy treatment threshold, or if it is ≥15mg/dL, the TSB should be measured (5). TcB measurement is to be used when the newborn's gestational age is above 35 weeks and the newborn is older than 24 hours. TSB should be used otherwise.

TOTAL SERUM BILIRUBIN: A blood sample is collected preferably from the heel of the baby and then analysed in the laboratory quantifying the total serum bilirubin. This gives a more accurate measurement of the bilirubin level in the body. Neonates with persistent jaundice at 3 - 4 weeks of life should be screened for conjugated bilirubin. The high fraction of conjugated bilirubin is a signal to pathologic causes like biliary atresia, congenital hypothyroidism and the likes hence a need for more investigation (64,69).

The rate of increment in the bilirubin level can be calculated when more than one TcB or TSB is done. A rate of ≥0.3 mg/dL per hour in the first 24 hours or ≥0.2 mg/dL per hour after can be a sign of hemolytic diseases (70), Direct antiglobulin test (DAT) should be done in this case if not previously done (64). This is a pointer to further laboratory examination to better understand the cause of the increased bilirubin and best way to manage.

Hour-specific serum bilirubin nomogram

The Bhutani nomogram is a graphical tool which plots the neonate’s total serum bilirubin (TSB) against the age in hours. It is one of the most widely used hour-specific nomograms. It is used to predict the level of risk for developing Hyperbilirubinemia (*Physiologic (Nonpathologic) Hyperbilirubinemia*, n.d.). Another reference tool used in screening is Bilitool from Bilitool.org (*Physiologic (Nonpathologic) Hyperbilirubinemia*, n.d.). Other bilirubin assessment tools and guideline are TcB nomogram (10), another tool similar to the Bilitool is the Stanford Bilirec and premie Bilirec used for infants ≥ 35 weeks of gestation and <35weeks of gestation respectively (71). The Hyperbilirubinemia Consensus from Emory school of medicines states that in cases with hemolysis, the serum bilirubin must be checked every 4-8 hours.

Bilitool is a web-based and mobile application used for recommendation of care for newborns with jaundice, based on the American Academy of Pediatrics (AAP) 2022 Clinical Practice Guideline Revision: Management of Hyperbilirubinemia. It is used for Newborns 35 weeks and above gestational age. It uses the age in hours together with the risk factor for developing severe Hyperbilirubinemia to predict the level of risk for developing hyperbilirubinemia.

There have been some modifications to the 1999 Bhutani nomogram to address some of the weaknesses such as small sample size which cannot be stratified to differentiate between age, race, gestational age between 35 to 40 weeks (19). The risk of hyperbilirubinemia is assessed based on percentile ranges. A TSB below the 40th percentile is considered low risk. Levels between the 40th–75th, 75th–95th, and above 95th percentile fall into intermediate, high-intermediate, and high-risk zones respectively (46). In 2021, Bahr et al modified version, the TSB hour specific serum bilirubin levels of the 0-12 hours which was absent in the Bhutani model of 1999 is included (19).

Factors influencing severity and prognosis of neonatal jaundice

PREMATURITY AND LOW BIRTH WEIGHT: A major key factor of NJ neurological outcome is the gestational age with preterm infants being at a higher risk of bilirubin neurotoxicity because of their immature brain development and other perinatal risk factors like sepsis, and gene variants. Prematurity and lower gestation periods cause infants to have slower breakdown and processing and have immature livers unlike full-term babies (8,71). This immaturity can lead to elevated bilirubin levels which may persist longer and affect the developing brain and sensory system. Normal bilirubin levels may vary, but the range of accepted level for healthy full-term infants is usually 12.4 mg/dL for bottle-fed infants and 14.8 mg/dL for breastfed infants (72). Levels higher than these call for closer attention.

Low birth weight infants are at risk of higher incidence of NJ and can aid neurodevelopmental and death outcomes. Infections also put the neonates at risk of neurodevelopmental and death outcomes: Han et al (73) showed the major causes of extreme bilirubinemia, with sepsis the highest rank, and hypoxic hepatitis being the second.

MATERNAL FACTORS: First pregnancies have a higher risk of NJ (73,74). Studies have also shown the influence of the mother's age and the baby's sex, with male infants being more susceptible to bilirubin toxicity (74); which may indicate that NJ may be associated with X-linked genes. The maternal age being a huge risk factor may be attributed to their susceptibility to gestational diabetes. Yu et al (75) identified maternal conditions that influence high risk of NJ, including diseases of the digestive system (with a higher incidence), leiomyoma of the uterus and infectious-related diseases like salpingitis and oophoritis. Other maternal risk factors include the mode of birth, with vaginal birth increasing the risk of NJ. Ayalew et al (74) in their study demonstrated that cesarean birth had a 76% protection against NJ compared to vaginal delivery. Additionally, ABO incompatibility can lead to hemolysis of the neonate's blood due to an attack from the mother's antibodies, which is one of the causes of NJ (61).

Management approaches of neonatal jaundice

PHOTOTHERAPY: It is a non-invasive treatment of hyperbilirubinemia in the newborn (76) achieved by the use of visible light from sources like fluorescent bulbs, halogen quartz lamps, light-emitting diodes fiber optic blanket, and fiberoptic mattresses (77). The light causes photochemical reactions which convert bilirubin to a more water soluble and excretable state. The effectiveness depends on the dose which is bent on the wavelength and intensity of the light, the surface area of the body exposed to the light as well as how close the light source is to the neonate (77). In severe hyperbilirubinemia, intensive phototherapy is preferable as it increases the rate of conversion and excretion of bilirubin, achieving treatment faster (78). A narrow-spectrum LED blue light with an intensity of at least 30 $\mu W/cm^2$ per nm at a wavelength range of 460 to 490 nm range is used, as this range does not pose any danger or unnecessary heat (70,78). Adequate breastfeeding and proper coverage of delicate organs like the eyes and testes prevent damage from the excessive light. The haemoglobin concentration, hematocrit or complete blood count should be done before initiating phototherapy. This is to check for anemia or to establish a baseline, should anemia develop later. Initiation of phototherapy is dependent on a specific range, if TSB threshold value is reached, which is dependent on the gestational age of the infant, the age in hours and if any risk factors for bilirubin-related brain problems are present using the hour-specific nomogram (5).

The TSB should be monitored every 12 hours after phototherapy has started in hospitalized infants. The age of the child, the presence or absence of neurotoxicity risk factors, the TSB concentration and trajectory determines the frequency of measurement (5).

Risk factors that can be predisposed to bilirubin encephalopathy should be recognised as they contribute to the determination of the phototherapy threshold. The thresholds are lower in newborns with risk factors and preterm neonates.

Table 1. Risk factors predisposing to bilirubin encephalopathy.

Risk Factors
• Gestational age <38 wk and this risk increases with the degree of prematurity
• Albumin <3.0 g/dL
• Isoimmune hemolytic disease (ie, positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
• Sepsis
• Significant clinical instability in the previous 24 h

These risk factors, the gestational age, age and albumin measurement play a significant role in determining the phototherapy threshold. The figure below shows the phototherapy threshold for neonate at age 0 -336 hours with gestational age of 35 to > 38 weeks with one or more risk factor for kernicterus. The below figure is adopted from the American Academy Pediatrician (64).

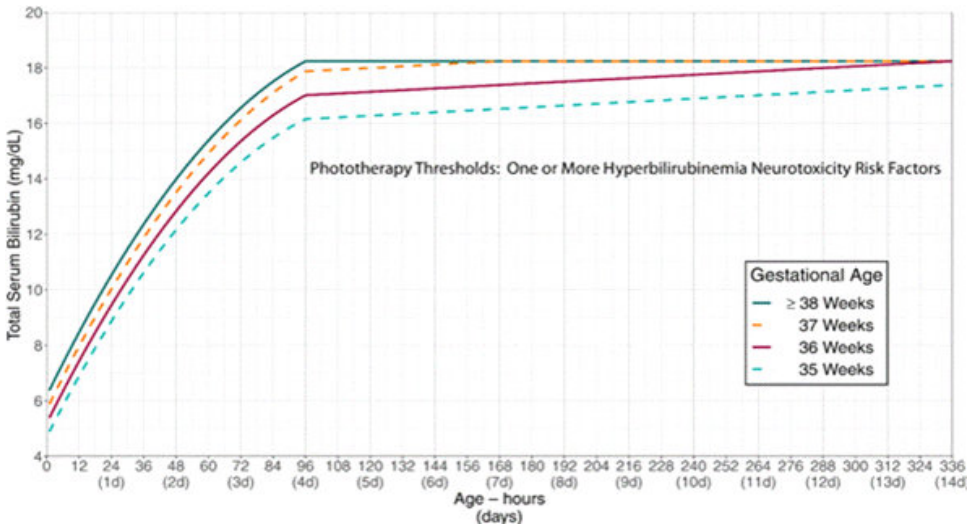

Figure 1. Phototherapy threshold for neonate at age 0 -336 hours with gestational age of 35 to > 38 weeks with one or more risk factor for kernicterus.

Under the AAP guidelines 2022, a new term “Escalation-of-care” was introduced. This is an intensive care which is given to newborns with excessive and rapidly elevated Serum bilirubin (79). This is done to avoid the need for exchange blood transfusion and the possibility of developing kernicterus. It is defined as TSB level below 2mg/dL of the exchange transfusion threshold (79). The threshold as indicated in the figure below is dependent on the gestational age. Once this level is reached or exceeded, the care should be escalated. Infants with TSB levels at or above the exchange transfusion must be transfused immediately. Also, those with signs of acute bilirubin encephalopathy must also receive exchange transfusion immediately (79). Prior to this, blood type, total and direct bilirubin, complete blood count, crossmatch screening must have been done (79).

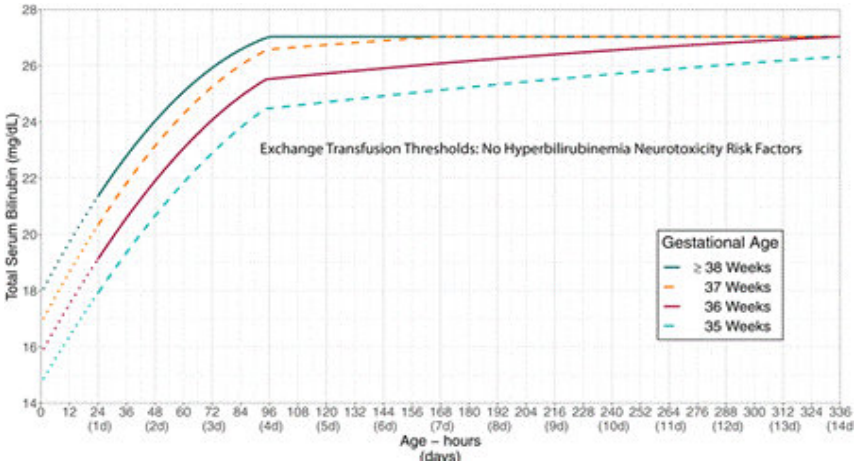

Figure 2. Showing the Exchange transfusion threshold per gestational age (64).

EXCHANGE BLOOD TRANSFUSION (EBT): This is a medical procedure carried out by slowly and carefully exchanging the blood of the neonate with the blood of a donor (37). This is done to affect a rapid reduction in the bilirubin level in the blood (37). It is indicated when intensive phototherapy is ineffective and in cases of excessive hemolysis (37)). In cases of newborn with signs of bilirubin encephalopathy, urgent exchange transfusion is required (64).

Using a more reliable screening method like TSB may become essential in early detection of pathological hyperbilirubinemia and immediate treatment is necessary to put a halt to the rapidly increasing bilirubin level to prevent neurotoxicity.

Intravenous Immune Globulin (IVIG) treatment

There has been variable response to the use of IVIG treatment in Neonatal jaundice due to the rate of IVIG treatment in isoimmune jaundice due to ABO and Rh blood group incompatibility (79) In a study conducted by (80), 3 groups were studied, the first group had multiple administration of IVIG, the second had one dose and the third had no dose. All three groups had phototherapy. There was no need for exchange transfusion in the 1st group, there was a 12% and a 33% rate in the 2nd and 3rd group respectively. The duration for phototherapy treatment was also shorter in the 1st group compared with the 2nd and 3rd. (80). It is therefore advisable that multiple doses of IVIG be administered in these cases, as it likely blocked the ongoing hemolysis better (80). In another study by Okulu et al , the single dose did not show effectiveness in reducing the need for exchange transfusion which could be due to the advanced technology of the phototherapy (37).

Neonatal jaundice: prevention and future directions

Strategies for Early Detection and Prevention

1. Universal Bilirubin Screening and Risk Assessment

Timely identification of jaundice in newborns is one of the key strategies for preventing the risk of developing significant hyperbilirubinemia, a prominent cause of neonatal jaundice and its associated complications, including kernicterus and neurological impairment (81). Universal bilirubin screening using transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) measurements has been recommended by various health organizations to improve early detection (81). TcB screening is a non-invasive, cost-effective method that allows for rapid assessment, reducing the need for frequent blood sampling (82).

The Bhutani Nomogram, a widely used risk assessment tool, can help predict the likelihood of severe hyperbilirubinemia based on bilirubin levels in relation to postnatal age in hours. By plotting a newborn's total serum bilirubin (TSB) levels on the nomogram, healthcare providers can identify infants at low, intermediate, or high risk for developing severe jaundice. The nomogram is especially useful in guiding clinical decision-making for phototherapy or exchange transfusion. (83,84). While stratifying risks, additional factors, including prematurity, ABO incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and sepsis, should be considered (85,86).

2. Promoting Early and Frequent Feeding

Early initiation of breastfeeding within the first hour of birth and frequent feeding promote stooling, thereby enhancing bilirubin elimination (87). The World Health Organization (WHO) advocates for exclusive breastfeeding in the first six months of life, which has been associated with lower rates of severe jaundice (87). Inadequate breastfeeding may worsen jaundice in newborns primarily due to dehydration and inadequate calorie intake, which lead to reduced elimination of bilirubin.

3. Parental Education and Community-Based Interventions

Educating parents about neonatal jaundice symptoms, risk factors, and the importance of timely medical evaluation is crucial in preventing complications. Home-based monitoring using smartphone applications and remote bilirubin measurement devices has emerged as a promising approach to improving parental awareness and early detection (88,89). Community-based programs integrating trained healthcare workers to provide home visits have shown effectiveness in reducing severe hyperbilirubinemia cases in resource-limited settings (90).

Emerging Research and Innovations in Management

1. Phototherapy Advancements

Phototherapy remains the mainstay of neonatal jaundice treatment. Conventional blue-light phototherapy effectively reduces bilirubin levels by converting unconjugated bilirubin into water-soluble isomers excreted in urine and stool (91). However, emerging research focuses on optimizing phototherapy efficiency through new light-emitting diode (LED) systems, which offer higher irradiance, lower heat production, and increased energy efficiency compared to conventional fluorescent lamps (92).

To facilitate home-based treatment for mild-to-moderate jaundice, portable and wearable phototherapy devices have been developed reducing hospital admissions and healthcare costs. These innovations are particularly beneficial in low-resource settings where hospital access is limited.

2. Pharmacological Approaches

Emerging pharmacological interventions aim to enhance bilirubin metabolism and excretion. Tin mesoporphyrin (SnMP), a heme oxygenase inhibitor, has demonstrated efficacy in reducing bilirubin production and preventing severe hyperbilirubinemia (91). Clinical trials are ongoing to assess its safety and effectiveness as an adjunct to phototherapy (93) Probiotic supplementation has also been explored for its role in modulating gut microbiota to enhance bilirubin excretion, with promising preliminary findings (94).

3. Gene Therapy and Genetic Screening

With advancements in molecular medicine, genetic screening is now becoming more widely available. This makes it easier to identify conditions like G6PD (Glucose-6-Phosphate Dehydrogenase) deficiency and Gilbert syndrome, which can increase the risk of severe jaundice in newborns (85). With this improved access to genetic testing, healthcare providers can more effectively detect and manage these conditions early, helping to prevent complications associated with jaundice in infants. Early identification of at-risk infants allows for targeted interventions, including prophylactic phototherapy and dietary modifications. Future research into gene-editing technologies, such as CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9), holds potential for correcting genetic disorders contributing to neonatal jaundice.

Conclusion

Neonatal jaundice is a common condition affecting newborns worldwide, resulting from elevated serum bilirubin levels. While physiological jaundice is often harmless, severe hyperbilirubinemia can lead to significant neurological complications, including acute bilirubin encephalopathy and kernicterus. This review examines the impact of neonatal jaundice on pediatric neurological outcomes, highlighting the pathophysiology, risk factors, and long-term consequences.

Evidence suggests that untreated or poorly managed jaundice can result in motor dysfunction, auditory impairment, and cognitive delays, affecting quality of life. Advances in neonatal care, such as phototherapy and exchange transfusion, have reduced severe complications, yet challenges persist in low-resource settings where early detection and treatment may be limited.

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