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NEONATAL HYPERBILIRUBINEMIA: ETIOPATHOGENESIS AND MANAGEMENT

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ABSTRACT

Objective: To investigate the etiopathogenesis of hyperbilirubinemia in neonates, analyzing the complications resulting from the high level of bilirubin in the patients' bodies and the

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appropriate treatment. Literature Review: Neonatal hyperbilirubinemia can be benign - which occurs due to the immaturity of the liver; or pathological - related to maternal and perinatal factors, such as the time of pregnancy, presence of gestational Diabetes Mellitus, preeclampsia, genetic aspects, changes in breastfeeding, congenital infections, tyrosinemia and significant weight loss of the newborn is. It affects 60 to 80% of children in the first days of life, usually due to physiological factors, but when pathological, it occurs more often in the first 24 hours. The existence of an imbalance, or ineffectiveness, in the breakdown of red blood cells and the metabolization of their waste products encompasses the pathogenesis of the condition. The severity of complications includes bilirubin-induced neurologic dysfunction, which, when free, has the potential to cross the blood-brain barrier and can lead to a spectrum of neurotoxic lesions collectively referred to as Bilirubin-Induced Neurologic Dysfunction (DNIB), which are capable of interfering with the neurologic and motor development of the neonate and leading to bilirubin encephalopathy (EB). From the most severe condition, there is the possibility of developing hearing alterations, abnormalities in motor control, oculomotor deficiencies, and tooth enamel dysplasia. Thus, the objectives of treatment are to prevent severe conditions and neurological disorders induced by bilirubin, using mainly phototherapy, which is an effective treatment that converts excess bilirubin into more water-soluble photoisomers, facilitating its excretion by the liver and kidneys of the newborn. Final Considerations: The prevention and early diagnosis of cases of neonatal jaundice are extremely relevant to avoid serious complications and unnecessary clinical interventions. Thus, there must be close monitoring of pregnant women, as well as newborns, in search of optimizing the patient's prognosis through the multidisciplinary action of trained professionals.

Keywords: Jaundice. Encephalopathy. Bilirubin.

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INTRODUCTION

Neonatal jaundice, also known as neonatal hyperbilirubinemia (HN), is a frequent phenomenon during the first days of the baby's life and occurs as a result of the increase in serum total bilirubin (BT), which causes the appearance of clinical manifestations such as yellowish pigmentation of the skin, mucosa, and sclera (BOMFIM, et al., 2021).

In neonates, it is observed that approximately 60% of full-term births and 80% of premature infants have jaundice in the first days of life (GEEST, et al., 2022). However, the causes of this problem are diverse: physiological, pathological, hereditary, and related to maternal blood, such as RH factor incompatibility between mother and newborn (NB), characteristics of breast milk, and quality or frequency of breastfeeding (due to failure to breastfeed in the first weeks of life) (FREITAS, et al., 2022).

Most cases of jaundice are of physiological origin, called Benign Neonatal Hyperbilirubinemia (HNB) - which happens due to hepatic immaturity to eliminate bilirubin - and, therefore, have a favorable prognosis and often do not require intervention. However, about 10% of live births tend to develop pathological jaundice, which, in addition to hepatic immaturity, is associated with some other factor, such as hereditary, and, consequently, requires monitoring and treatment (GODOY, et al., 2021; RODRIGUES, et al., 2019).

According to the National Academy of Pediatrics, due to the serious consequences that neonatal jaundice can cause, serum BT levels in newborns should be investigated between 24 and 72 hours after birth, so that it is possible to intervene early, given that cases in which total bilirubin is equal to or above 20 mg/dL have a higher risk of Bilirubin Encephalopathy (EB) and, also, neonatal morbidity and mortality (FREITAS, et al., 2022; RODRIGUES, et al., 2019). In this sense, there is a need for agile intervention in scenarios of pathological jaundice, since EB was responsible for approximately 20% of hospital admissions of newborns in the first month of life, being an important problem in this age group (FREITAS, et al., 2022).

In this sense, it is observed that jaundice and its complications are the seventh leading cause of infant death worldwide (SOUSA, et al., 2020). Therefore, it is noted how crucial early identification and intervention are for a good prognosis. It is also worth noting that the severity of the clinical situation of this condition is directly influenced by the period in which it develops, since when it appears early (before the first 24 hours of the baby's life) it is considered pathological and can trigger tissue lesions, especially in the central nervous system (CNS) (BOMFIM, et al., 2021). This fact is due to bilirubin's ability to cross the

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blood-brain barrier (BBB) and cause damage to the neonate's CNS, mainly causing EB - which can cause developmental delays, postural deformity, hearing loss, and death (RODRIGUES, et al., 2019).

Given this body of evidence, it is essential to understand the factors that are intrinsically related to neonatal hyperbilirubinemia, such as etiopathogenesis, pathophysiology, early diagnosis, as well as intervention methods, and appropriate treatments. Thus, this narrative review article deals with these issues, to gather information that serves as a basis for health professionals, to minimize severe cases that irreversibly compromise the health of the newborn.

METHODOLOGY

This study is a narrative review, whose objective is to gather and critically analyze the relevant literature on the proposed topic, providing a comprehensive theoretical synthesis. The collection of materials was carried out from March to September 2024, in a non-systematic way, seeking to ensure breadth and diversity in the sources consulted. To this end, recognized scientific databases were used, such as Scielo, PubMed, Medline, and Update, as well as complementary references suggested by specialists in the field. The inclusion criteria included articles published in Portuguese and English, published from 2015 onwards and that were relevant to the topic under analysis. All the selected material was read in full, categorized into thematic axes, and submitted to a critical interpretation, seeking to identify patterns, gaps, and significant contributions to the field of study.

RESULTS AND DISCUSSION

DEFINITIONS, ETIOLOGICAL FRAMEWORK, AND RISK FACTORS FOR THE DEVELOPMENT OF NEONATAL JAUNDICE

The most affected population, according to Ramos et al. (2022), comprises NB with few hours of life, who need full attention and observation after birth, as it is a critical period for the elevation of serum bilirubin levels, which can progress to central nervous system (CNS) toxicity.

In this context, some etiological factors have the potential to cause neonatal jaundice in the first month of life, whether physiological or pathological. This happens because, during the intrauterine period, bilirubin can pass through the placental barrier and be excreted from then on by the mother, a situation that changes after birth, as this function

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is attributed to the newborn's body, which does not always respond immediately, which can cause a serum accumulation (RAMOS, et al., 2022).

HNB, formerly known as physiological jaundice, encompasses the transient and normal increase in serum or total plasma bilirubin (TSB) levels that occurs in almost all newborns. It is due to the immaturity of the NB's liver to adequately excrete bilirubin, defined by elevated total levels (above 2 mg/dl), elevated serum levels (above 12mg/dl), and expressed after the first day of life. This is the most common form, with a predominance of indirect bilirubin and an increase in total bilirubin levels, which can be investigated and treated according to gestational age (GA) (REGO, et al., 2019).

From this perspective, benign neonatal hyperbilirubinemia is explained by the fact that the newborn's liver is not yet fully developed, which can cause a delay in the elimination of bilirubin (FERRAZ, 2022). In addition, the probability of its involvement can be evaluated based on history, associated risk factors, and total bilirubin (BT) levels with fractions (REGO, et al., 2019).

On the other hand, pathological jaundice has an etiology correlated with maternal and perinatal factors, such as the time of pregnancy, the sex of the newborn, and also possible multiple associated factors, including gestational diabetes mellitus (GDM), preeclampsia, changes in breastfeeding, congenital infections, tyrosinemia, and significant weight loss in the first days of life. These factors make the newborn vulnerable to jaundice, capable of promoting complications such as severe neurological damage (GODOY, et al., 2021).

Almost all premature infants with gestational age less than 35 weeks have elevated levels of total serum bilirubin, due to the increase in the production of this substance caused mainly by the high degradation of red blood cells, the reduction in the elimination and conjugation of bilirubin caused by the immaturity of the liver and the increase in the enterohepatic circulation of bilirubin. Another factor that also contributes to hyperbilirubinemia in this population is the delay in the introduction of enteral feeding, which can limit intestinal flow and bacterial colonization, resulting in an additional increase in the enterohepatic circulation of bilirubin (WONG and BHUTANI, 2020), thus observing that prematurity is an important factor in the development of jaundice.

Regarding gender, there is a convergence in the literature by Carvalho and Lavor (2020) and Adugna (2023) on the prevalence of males in the studies followed, which corroborates the information that gender is a risk factor for neonatal jaundice.

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Regarding GDM, some frequent outcomes are noted in this context, such as increased risk of prematurity, metabolic and growth imbalances, fetal macrosomia (birth weight greater than 4 kilograms), hyperbilirubinemia, and increased risk of intrauterine fetal death and neonatal death. How these effects related to the metabolic disorder occur is not yet well defined, but it is observed that hyperglycemia inside the uterus can cause fetal dependence, lead to hypoglycemia in the postpartum period and, consequently, brain injury (THEVARAJAH and SLIMMONS, 2019).

Preeclampsia, a complication of pregnancy characterized by hypertension and organ dysfunction, can affect the liver, resulting in damage. In severe cases, it is possible to cause HELLP syndrome, which involves the destruction of red blood cells, elevated liver enzymes, and a low platelet count. This condition compromises liver function and can lead to the development of jaundice, which increases the risk of triggering coagulopathies, with high consumption of fibrinogen and platelets. Consequently, the risk of hemorrhage increases and is capable of triggering a sequence of adverse events, with the risk of fulminant hepatic necrosis, given the rapid progression of these events, which corroborates the development of bilirubin accumulation, thus, preeclampsia emerges as one of the main maternal causes for the unfolding of jaundice. (CARVALHO and LAVOR, 2020; PERAÇOLI, et al., 2005).

About breastfeeding, it is essential to distinguish between Breast Milk Jaundice (ILM) and breastfeeding-associated jaundice (IAA). ILM is defined as the persistence of benign neonatal hyperbilirubinemia beyond the first two to three weeks of age, usually presents after the first three to five days of life, and peaks within two weeks of birth, progressively decreasing to normal levels over three to twelve weeks. It is therefore considered a physiological jaundice that occurs due to the high concentrations of beta-glucuronidase present in milk, which generate an increase in enterohepatic circulation that causes the deconjugation of already conjugated bilirubin (CARVALHO and ALMEIDA, 2020; ITOH, et al., 2023).

IAA, also known as jaundice due to failure in breastfeeding/lactation, is due to suboptimal intake of fluids and calories during the first seven days of life, being considered pathological, it is directly related, therefore, to inadequate nutrition of the neonate, which may be due to low milk supply or ineffective suction and latching that result in a decrease in intestinal motility and an accumulation of bilirubin that cannot be eliminated by the newborn (ADUGNA and ADO, 2023; CARVALHO and ALMEIDA, 2020).

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Given this, it is observed that the effectiveness of breastfeeding can be evaluated through the weight of the newborn, monitored during the first days of life, given the importance of its variation. Thus, a failure in the breastfeeding process is evidenced through weight loss, so the accumulation of bilirubin is facilitated, becoming one of the risk indicators for jaundice associated with breastfeeding (WONG and BHUTANI, 2022).

About infections that lead to pathological jaundice, there are two aspects: 1) infections that affect the accumulation of bilirubin directly, linked to excretion problems, and 2) indirectly, with failures in metabolism. Therefore, about 35% of neonatal sepsis cases were associated with indirect hyperbilirubinemia, caused by infections, whether urinary tract, such as Escherichia coli, or viral infections such as cytomegalovirus and herpes simplex virus (GOTTESMAN, 2015; WONG and BHUTANI, 2020). The mechanism, however, is not yet understood, but it is suggested that it occurs due to greater damage to red blood cells, due to the increase in oxidative stress in the NB, which overloads the hepatocytes (KAPLAN, 2024; WONG and BHUTANI, 2022).

From this perspective, there is also cholestasis, causing the form of direct hyperbilirubinemia, involving the impairment of bile excretion, unrelated to liver activity itself, and can be due to genetic, obstructive, idiopathic, infectious origin, among others (GOTTESMAN, 2015; WEHRMAN, 2023; WONG and BHUTANI, 2022). It is observed, therefore, that the infectious origin is related to jaundice in neonates, among them we can mention syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes (also known by the mnemonic STORCH), which affects the secretory activity of the gallbladder, with a higher number of cases associated with cytomegalovirus (GOTTESMAN, 2015).

Other pathologies corroborate the jaundiced condition. Tyrosinemia type 1, for example, is characterized as an autosomal recessive aminoacidopathy that has failures in the enzymes that are present in tyrosine metabolism, such as fumarylacetoacetate hydrolase (FAH), which results in the accumulation of metabolites that will cause liver and kidney toxicity, explaining the clinical findings of the disease, such as the symptomatological picture of jaundice (ŠKARIČIĆ, et al., 2019).

DEVELOPMENT OF JAUNDICE: BIOCHEMICAL, MOLECULAR AND GENETIC MECHANISMS

Bilirubin is a product of heme catabolism. In newborns, approximately 80 to 90% of bilirubin is produced during the breakdown of red cell hemoglobin or by ineffective

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erythropoiesis. The remaining percentage, between 10 and 20%, is derived from the breakdown of other protein components of the heme group, such as cytochromes and catalase (WONG and BHUTANI, 2022).

The pathogenesis of neonatal jaundice involves a complex imbalance between the production, conjugation, excretion, and metabolism of bilirubin, with hepatic immaturity and hemolysis standing out as preponderant factors (MITRA and RENNIE, 2017).

In the cells of the reticuloendothelial system, the enzyme heme oxygenase (HO) hydrolyzes the heme molecule, transforming it into a molecule of carbon monoxide and a molecule of biliverdin – a reaction that releases iron and consumes oxygen. In this way, the enzyme biliverdin reductase (BVR) reduces biliverdin to bilirubin, thus forming unconjugated or indirect bilirubin (BI). This is a hydrophobic molecule, therefore, it binds to albumin to be transported to the liver, where it will be conjugated to glucuronic acid and will continue glucuronidation, to make the bilirubin molecule conjugated or direct (BD), which is water-soluble and will be incorporated into bile (CONTI, 2021).

Neonates are relatively ligandin deficient, so the ability to retain bilirubin in hepatocytes decreases, which may result in bilirubin re-entry into the circulation (Hansen et al., 2020). In NB, bilirubin metabolism is in a transition between fetal and adult, and the hepatic enzyme uridylphosphate-glucuronyl-transferase A1 (UGT1A1), responsible for the low conjugation of BI in BD, has its low activity low; In full-term newborns, enzyme activity at seven days of age is approximately 1 percent of that of the adult liver and does not reach adult levels until 14 weeks.

In this regard, it is observed that differences in maximum TSB levels and in the time required for resolution may result, in part, from genetic variability in the hepatic conjugation capacity of bilirubin (DENNERY, et al., 2001). As an example, polymorphisms in the *UGT1A1 gene have been observed* (AKABA, et al., 1998; SKIERKA, et al., 2013), due to differences in the number of thymine-adenine (TA) repeats or "TATA box" in the promoter region of the gene so that these polymorphisms correlate with decreases in UGT1A1 enzyme activity. Other variations have been identified, such as *UGT1A1*6*, *UGT1A1*9*, *UGT1A1*16*, *UGT1A1*27,* and *UGT1A1*28*, however, all correlate with reductions in enzyme function and it is observed that further research is needed to fully elucidate the impact of these mutations on a child's risk of developing hyperbilirubinemia.

There is also hepatic bilirubin overload due to greater degradation of fetal hemoglobin since the newborn has more red blood cells than the adult and produces 6 to

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10 mg/kg/day of BI, while the adult produces 3 to 4 mg/kg/day. Thus, slower intestinal motility and a reduced number of intestinal bacteria are observed in the NB, resulting in stasis of the newly formed BD, which undergoes the action of the enzyme beta-glucuronidase, forming BI again, which will be reabsorbed (enterohepatic circulation), saturating the conjugation process (GREGORY, et al, 2010).

The process begins with the degradation of hemoglobins, where heme groups, which have not been reused to form new heme groups, undergo the action of the enzyme heme oxygenase, converting them into biliverdin. Subsequently, the action of the enzyme biliverdin reductase occurs, which transforms biliverdin into indirect bilirubin, which binds to serum albumin and is transported to the liver, where the unconjugated bilirubin becomes conjugated through the action of the enzyme uridine diphosphate glucuronyl transferase (UDP-GT), being excreted by the liver through the gallbladder. When in the intestine, the microbiota itself hydrolyzes conjugated bilirubin and transforms it into two metabolites: stercobilinogen and urobilinogen. Stercobilinogen is excreted through the feces, while urobilinogen returns to the bloodstream, from where it goes to the kidneys and is eliminated in the glomerular filtration process, which contributes to the yellowish color of the urine (CONTI, 2021; SULLIVAN, 2017).

NEUROLOGICAL CONSEQUENCES OF SEVERE NEONATAL HYPERBILIRUBINEMIA

The main consequence of severe neonatal hyperbilirubinemia is a spectrum of neurotoxic lesions collectively referred to as Bilirubin-Induced Neurological Dysfunction (DNIB) (DAS and VAN LANDEGHEM, 2019). DNIB occurs when free (or unbound) bilirubin crosses the blood-brain barrier and binds to brain tissue. This causes molecular and cytological lesions in brain cells, which can result in cell death by apoptosis and/or necrosis. The most frequently affected brain regions include the basal ganglia and brainstem nuclei for oculomotor and auditory function and are responsible for the clinical features observed (HANKO, et al., 2005).

DNIB includes acute and chronic bilirubin encephalopathy (EBA and EBC, respectively), as well as more subtle neurological dysfunction. EBA can present typical symptoms of neurotoxicity, characterized by the presence of lethargy, hypotonia, and weak sucking, and may progress to death due to complications (BOMFIM, 2021).

The chronic manifestation of the disease, EBC (formerly called kernicterus), encompasses clinical features that are typically evident after one year of age in those who

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have been affected by the disease, such as abnormalities in motor control, movements, and muscle tone, hearing disorders with or without hearing loss, oculomotor deficiencies, especially impairment of the upward vertical gaze and dysplasia of the enamel of the deciduous teeth. Thus, some manifestations are choreoathetoid cerebral palsy, and sensorineural hearing loss due to auditory neuropathy (DAS and VAN LANDEGHEM, 2019; VAN, et al., 2016).

It is worth noting that, despite these severe sequelae, the fraction of bilirubin that can enter the central nervous tissue is small, because at physiological pH indirect bilirubin is predominantly solubilized by binding with albumin, minimizing its toxicity. Thus, the implications often occur when the binding capacity with albumin is exceeded; which may occur due to mechanisms of competition for binding sites or low serum albumin concentration, which will lead to an increase in the concentration of circulating free bilirubin (BL), which is fat-soluble and capable of penetrating the blood-brain barrier (DING, et al., 2021).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, an enzyme that decreases protection against free radicals, is currently recognized as one of the most important pathogens of hyperbilirubinemia that leads to severe conditions (KEMPER, et al., 2022). This fact is due to hemolysis generated by oxidative damage, which leads to the release of unconjugated bilirubin, causing accentuated levels of the substance to cross the blood-brain barrier and, thus, cause DNIB (LAMENDES, 2021).

An infant with G6PD deficiency may develop a sudden and extreme increase in TSB (total serum bilirubin) that may be difficult to predict or avoid (KEMPER, et al., 2022), leading to the accumulation of bilirubin in neural tissues, in which there is the adhesion of bilirubin to the cell membrane of the neuron producing changes in mitochondria, oxidative stress, energy failure, and cellular apoptosis (PRAZERES, et al., 2019), causing neuronal loss and dysfunction.

The neurotoxicity resulting from this accumulation may result in damage to the auditory system of neonates with a history of hyperbilirubinemia. In this context, Alvarenga et al. (2024) emphasize that it is essential to monitor the hearing and language development of these children, during the first year of life, every month in primary care, to, in cases of delay or deficit, direct them to specialized services for audiological evaluation.

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MANAGEMENT OF JAUNDICE IN NEONATES

Pathological neonatal jaundice can manifest with serious consequences, so early diagnosis and intervention are necessary to avoid complications. Diagnosis includes the identification of bilirubin overload to the hepatocyte or hepatic conjugation deficiency and, in most cases, the investigation includes routine tests (REGO, et al., 2019).

Thus, the goals of neonatal hyperbilirubinemia treatment are to prevent severe hyperbilirubinemia and bilirubin-induced neurological disorders by avoiding unnecessary interventions that can interfere with the successful initiation of breastfeeding and the bond between parents or caregivers and the newborn (KEMPER, et al., 2022).

Risks appear when the origin of this jaundice is not physiological, which requires adequate monitoring for rapid detection, which usually occurs between the third and fifth day of life, aiming at early treatment. Thus, the performance of an attentive and competent multidisciplinary team is essential for the follow-up of neonatal jaundice, through anamnesis, inspection, and routine physical examination. Upon confirmation of hyperbilirubinemia, treatment is initiated, which can be with phototherapy, blood transfusion, or the use of drugs that accelerate the metabolism and excretion of bilirubin (GODOY, et al., 2021).

Currently, phototherapy has been mainly used, an effective procedure that allows bilirubin, present in excess, to be converted into photoisomers with greater water solubility so that they can be excreted by the liver and kidneys of the newborn more easily. Thus, NB should receive adequate nutrition and hydration, as well as adequate urine production, since the main mechanism of phototherapy involves the excretion of lumyrubin (Figure 2) (the main photoproduct of bilirubin) also in the urine (KEMPER, et al., 2022).

Phototherapy consists of exposing the newborn, naked, but with eye and genital protection (FERRAZ, 2022), for as long as possible to an LED (Light-Diode Emitting) light, preferably blue, which, at specific values, uses a narrow spectrum with a transfer of up to 30 μW/cm2 per nanometer, as above this it can cause heating problems to the newborn, with a wavelength that is close to 460 nanometers, with a margin of error of 15 nanometers, plus or minus, because, after this margin, irradiation and wavelength are impaired and efficacy becomes insufficient (DHEISON, et al., 2021; KEMPER, et al., 2022).

In addition, the color of the light is also relevant, because, historically, white light was used as the main choice, however, with the arrival of blue light, this has become the current priority. The difference is because the wavelength that is effective in isomerizing bilirubin is

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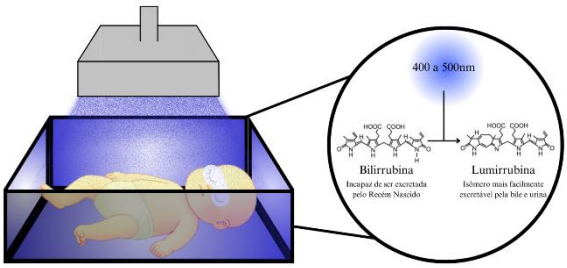
between 400 and 500 nanometers so there is little absorption when the values are outside this range. Thus, it is noteworthy that white light has its main wavelength peak in the range of 550-600 nanometers, while blue light, between 425-475 nanometers, demonstrates about 45% more energy found in the efficacy range for bilirubin isomerization, when compared to white fluorescent light (DHEISON, et al., 2021).

Figure 1: Process of conversion of bilirubin into lumyrubin that occurs in phototherapy.



Source: CONFESSOR, et al., 2024.

In cases where phototherapy cannot be fully efficient, blood transfusion can be used, however, this procedure is less used because it is more invasive and has a higher risk of causing neurotoxicity and mortality (BOMFIM, et al., 2021; GODOY, et al., 2021). It is the removal of the blood from the newborn in cycles with, at the end of each cycle, infusion of the same amount of blood from a compatible donor, from a catheter inserted through the umbilical vein and positioned in the inferior vena cava. In this way, the procedure guarantees a reduction in serum bilirubin by up to 50% (GODOY, et al., 2021).

To perform an acute transfusion, some criteria must be observed, including the following: 1) Signs of acute bilirubin encephalopathy, including lethargy, hyper- or hypotonia, poor sucking, high-pitched crying, recurrent apnea, opisthotonus, or seizures; 2) TSB at the threshold of need for extraordinary transfusion, which differ depending on gestational age and whether the newborn has risk factors for neurotoxicity; 3) Bilirubin/albumin (B/A) ratio at or above exchange transfusion threshold (BHUTANI, et al., 2016).

In addition, there is also the option of pharmacological treatment through the facilitation of bilirubin conjugation, this conversion occurs through the action of the UDP-glucuronyl transferase enzyme (UDP-GT), present in the liver. A priori, a direct approach can be carried out, through small doses of the barbiturate phenobarbital, which, pharmacologically, acts in the regulation of the expression of the enzyme glucuronyl

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transferase (CARNEIRO, et al., 2020; SULLIVAN, 2017.). However, this use of phenobarbital has presented harms that exceed the advantages of use, such as excessive sedation in newborns, and the lack of efficacy soon after delivery, not demonstrating a significant improvement in hyperbilirubinemia in most cases (CARNEIRO, et al., 2020).

Furthermore, the treatment of hyperbilirubinemia with phototherapy did not show significant improvements when associated with phenobarbital, which, similarly, presented more harm to that used in pregnant women and newborns, in comparison with the benefits. Thus, the use of Phenobarbital is recommended in a restricted way for the specific case of Crigler Najjar Syndrome type II - which is an autosomal recessive disease with reduced activity of the enzyme glucuronyl transferase, where this association is useful (CARNEIRO, et al., 2020).

There are also other adjuvant drugs: 1) intravenous immunoglobulin, which decreases the levels of unconjugated bilirubin in the blood through the isomerization of blood Rh; 2) metallo-protoporphyrins which, although not yet approved, act as competitive inhibitors of the enzyme heme oxidase, reducing the conversions of the heme radical into biliverdin (CARNEIRO, et al., 2020).

It is also possible to use the approach based on the combination of phototherapy or pharmacotherapy with the stimulation of intestinal activity for a more efficient fecal excretion, which can be through greater motricity of peristalsis, or also with the use of probiotics and prebiotics (CARNEIRO, et al., 2020).

Finally, the kangaroo method, which consists of inducing an increase in the frequency of breastfeeding through greater and more constant physical proximity of the newborn to the mother, seeks an increase in intestinal peristalsis and consequent facilitation of fecal excretion of bilirubin (CARNEIRO, et al., 2020; GOUDARZVAND, et al., 2017).

FINAL CONSIDERATIONS

Neonatal jaundice is a disease of physiological (benign) or pathological origin, which can lead to serious complications, such as bilirubin encephalopathy, which can lead to neurological dysfunction, impairment of the newborn's neuronal and motor development, and even death. Therefore, focus should be placed on screening and early diagnosis (usually between the third and fifth day of life), especially in premature infants, due to the

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potential for irreversibility of the sequelae of the disease, which can only be identified after one year of age of the affected individual.

In this context, it is essential to have a multidisciplinary team so that the diagnosis and appropriate therapeutic management of the NB can be carried out as soon as possible, to achieve a good prognosis. Therefore, it is understood that neonatal hyperbilirubinemia is an important topic of discussion among health professionals - who will perform routine anamnesis, inspection, and physical examination - and the NB's family members, as the treatment has different approaches, such as breastfeeding, use of medications and phototherapy.

Thus, it is important to emphasize the need to carry out more studies on neonatal jaundice to improve the knowledge of professionals, enabling them to provide effective and good quality treatment, improving the prognosis of cases, and reducing the appearance of complications.

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