ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 13, Issue, 02, pp. 61696-61702, February, 2023
https://doi.org/10.37118/ijdr.26366.02.2023

REVIEW ARTICLE

OPEN ACCESS

HYPERBILIRUBINAEMIA IN NEWBORNS: A SYSTEMATIC REVIEW

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ARTICLE INFO

Article History:
Received 11th January, 2023
Received in revised form
21st January, 2023
Accepted 03rd February, 2023
Published online 25th February, 2023

KeyWords:
Hyperbilirubinaemia; Jaudice;
Systematic review.

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ABSTRACT

Jaundice in newborns is characterized by the appearance of a yellowish tint to the skin and sclera of full-term as well as pre and post-term newborns and is often presente in the neonatal period affecting half to two thirds of newborns. It is characterized by elevated levels of indirect bilirubin or unconjugated bilirubin in serum concentration greater than 1.5 mg/dl. This study constitutes a bibliographic review on this condition, clinic, pathophysiology, risk factors, diagnosis and therapeutic approach. It was adopted as methodological procedure the bibliographic research, carried out through sources of books, articles and electronic documents indexed in the Virtual Health Library portal, in the databases MEDLINE and LILACS, and on the Scielo Brasil portal. The data collection showed that the neonatal jaundice is a pathology that requires a careful therapeutic approach due to its potential to reach the central nervous system.

Citation: ***Rafaela Dilela Arruk, Leonardo Sampaio S. Ponzo, Alana Vasconcelos S. Santos, Larissa Meibe M. Carvalho et al. 2023.*** "Hyperbilirubinaemia in newborns: A systematic review*", International Journal of Development Research*, 13, (02), 61696-61702.

INTRODUCTION

Jaundice, also known as hyperbilirubinemia, is characterized by the triad of yellowish coloration of the skin, mucosa and sclera of the neonate, associated with fecal choluria and acholia, due to accumulation of bilirubin blood. It is one of the most frequent alterations both in newborns full-term (NTB) and premature (PTNB). Second research, 60 to 70% RNT and 80 to 90% RNPT develop the jaundice.[1] This clinical picture can occur in physiological processes, related to factors linked to the mother, the newborn (NB), the environment and even laboratory variations, and in pathological processes, arising from conditions such as ABO blood incompatibility or Rh, liver, biliary or metabolic abnormalities or infection.[2] At most cases in which it occurs, it is characterized as physiological, if starting after the first 24 hours of the NB's life and lasting, in average one week. When pathological, it appears before the first 24 hours of life.

Clinically, jaundice is evident when the serum bilirubin reaches values above 5 mg/dL and has a benign evolution. However, there may be a need to interventions such as: phototherapy, a non-invasive method that converts bilirubin into products that are less toxic or capable of be excreted or reabsorbed in the body; and the exchange transfusion (EXT), which quickly removes bilirubin serum, corrects anemia and reduces the intensity of the antigen-antibody reaction. Hyperbilirubinemia at excessively high levels, during the first 24 hours of life, can lead to the appearance of bilirubin encephalopathy (Kernicterus), a devastating condition, characterized by permanent neurological damage, residing in this aspect, the importance of early diagnosis and treatment of neonatal jaundice for prevention of this complication. A jaundice, many times, ends up not being detected and/or correctly and efficiently assisted by health professionals, the which makes the development of this research relevant, which seeks to present a bibliographic review about this clinical condition, its pathophysiology, risk factors, diagnosis and therapeutic approach.[3] A

understanding these aspects will help not only in the elaboration of the differential diagnosis and the establishment of adequate treatment, to better prevent the progression of neonatal jaundice to encephalopathy bilirubin (kernicterus). Based on these considerations, this article has the general objective of presenting a review of literature on the clinical aspects of neonatal jaundice and its diagnostic and therapeutic approach.[3,4] The specific objectives consist of in: deepening knowlege about neonatal jaundice; understand the etiopathogenesis of jaundice in the neonatal period; identify risk factors for neonatal jaundice; investigate the treatment of neonatal jaundice and its follow-up. This study it consists of a bibliographical research, like a literature review. Scientific articles, books and electronic publications in the area of health indexed in the portal of Virtual Health Library (http://www.bireme.br), in the databases MEDLINE and LILACS, and on the Scielo Brazil portal (http://www.scielo.br).

LITERATURE REVIEW

***Definition of neonatal jaundice**:* The term jaundice refers to the Yellow discoloration of the skin and mucous membranes resulting from deposition of bilirubin (bile pigment) in the blood. The bilirubin can stain all tissues, but jaundice is usually more intense in face, trunk and sclera. In the neonatal period it becomes a problem when it corresponds to the clinical expression of hyperbilirubinemia, which is defined as the serum concentration of indirect bilirubin (BI) higher than 1.3 to 1.5 mg/dL or direct bilirubin (BD) greater than 1.5 mg/dL, as long as it represents more than 10% of the value of total bilirubin (BT).[1] The fetus produces bilirubin from the 12th week of intrauterine life, excreting it in three ways: placenta, being completely excreted by the maternal liver, by the liquid amniotic fluid and by excretion from the fetal liver into the intestine.[2] From From birth, the newborn's liver takes over the processing function. However, its ability to excrete bilirubin is 1 to 2% smaller compared to that of the adult, and meanwhile, bilirubin increases in tissues, resulting in neonatal hyperbilirubinemia.[3] The process in term and preterm newborns is similar. The necessity of change from fetal to adult hemoglobin causes a increased destruction of fetal red blood cells, increasing the amount of bilirubin reaching the hepatocyte. Concomitantly, immaturity limits metabolism and excretion. of bilirubin.[4,5]

In the vast majority of cases, jaundice manifests itself during the first week of life, in about 60% of newborns term and 80% of preterm infants, reaching a maximum peak between three and the five days of the newborn's life. It usually starts to resolve itself around seven to 10 days of life, having a benign evolution. Although about 10% of NBs continue to have an icteric tone at the age of one month.[6,7] In most cases, neonatal jaundice represents a transient physiological phenomenon, not requiring therapeutic intervention.[8,9] Severe hyperbilirubinemia, defined as total serum bilirubin (BTS) above the 95th percentile for age, occurs in about 9% of newborns during the first week of life. Without adequate intervention, a progressive increase in hyperbilirubinemia for values greater than 25 or 30 mg/dl puts newborns at risk of suffering brain damage induced by bilirubin, a risk that increases significantly in preterm infants.[10] A Brazilian Society of Pediatrics considers that it takes place annually in Brazil approximately 1.5 million NBs with jaundice in their first days of life, around 250,000 in a serious condition, at risk of neurotoxicity, kernicterus or death.[11]

***Pathophysiology**:* Bilirubin is a pigment of yellowish color, which results from the degradation of heme proteins and their most significant source is hemoglobin. The reticuloendothelial system, in particular the spleen, plays a key role in the destruction of red blood cells, a process which results in much of the newborn's bilirubin. In the smooth endoplasmic reticulum bilirubin is released into the circulation, where it reversibly binds albumin, but with a strong binding. Under physiological conditions only a small amount of bilirubin circulates freely.[12] Bilirubin is taken up by the hepatocyte and actively transported to the reticuloendothelial, where it is conjugated with glucuronic acid, becoming water soluble. Conjugated bilirubin, non-toxic to cells, is polar enough to be excreted by the bile or filtered by the kidney. Conjugated bilirubin, once in the intestine, is not absorbed and is eliminated as stercobilin and urobilinogen. The scarce intestinal flora of the NB leaves the bilirubin conjugate available for β-glucuronidase, enzyme of the cell wall intestine, which deconjugates it, allowing the return to the hepatocyte, the which is called increased enterohepatic circulation.[13] The unconjugated, non-ionized bilirubin is fat soluble and has the ability to cross cell membranes potentially neurotoxic. However, bilirubin toxicity free is generally avoided because it is conjugated to albumin.[10] The immature brain of newborns is even more susceptible to neurotoxicity of unconjugated bilirubin, which may cause difficulties neurological and intellectual, later evolving into the form chronic condition, kernicterus.[5,6] Hyperbilirubinemia reflects the relatively low conjugation of free bilirubin, by the immature liver of the NB, in the postpartum transitional period. Without this conjugation, bilirubin cannot be excreted in the biliary or renal level, accumulating in the tissues.[12] Elevated values of bilirubin or hyperbilirubinemia arise when the rhythm of bilirubin production, through the catabolism of red blood cells, exceeds the rate of elimination.[10] Usually, neonatal jaundice appears in the combination of the two factors, an increase in the replacement of red blood cells and a deficient conjugation of bilirubin in the liver. For this contributes to the fact that, in newborns, the lifespan of red blood cells is shorter than in adults, leading to accumulation of bilirubin and eventual jaundice.[12]

Several factors can contribute to affect the balance between bilirubin production and excretion processes as diferences genetic, environmental or even racial. For example, the capacity conjugation with albumin and compromised by acidosis, immaturity and competition with other substances such as salicylates, sulphamides and free fatty acids.10 The cause of hyperbilirubinemia is usually unconjugated bilirubin, and this situation is usually benign. However, a high fraction of direct bilirubin, signals the need to make the diagnosis differential for pathological jaundice. Hyperbilirubinemia is diagnosed when levels exceed what is defined as acceptable according to the age of the newborn. Thus, it is considered a physiological process, when bilirubin values remain below the 95th percentile for the respective gestational age. In the same sense, hyperbilirubinemia is defined as values of BTS greater than the 95th percentile on the Bhutani nomogram, methodology accepted by the American Academy of Pediatrics (AAP) and by the National Institute for Health and Clinical Excellence (NICE) (Figure 1).[14]

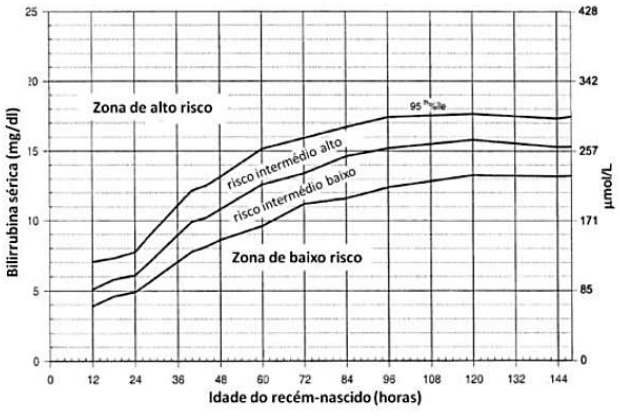

Figure 1. Nomogram for risk assessment of development of hyperbilirubinemia in newborns aged gestational age equal to or greater than 35 week

Persistent jaundice after 14 days of life of the NB can be a sign of a concomitant pathology and requires an evaluation urgent.15 From a clinical point of view, it is important to categorize the severe hyperbilirubinemia according to temporal onset, if early or late, regardless of its etiology. At In general, early hyperbilirubinemia is associated with a increased production of bilirubin, while the late

onset of hyperbilirubinemia is usually associated with a decrease in elimination, regardless of the increase or not in the production of bilirubin. Severe hyperbilirubinemia is a high-risk condition because it usually presents itself with a fast rise from BTS. In these cases, BTS can reach values greater than the 95th percentile in the first 12 hours of life. The identification of cases of hyperbilirubinemia and is usually performed by recognizing visual examination and subsequent assessment of transcutaneous bilirubin (TcB) or BTS.10 Rarely is an underlying pathology found other than physiologic jaundice as the cause of high bilirubin levels, high enough to meet the criteria indications for phototherapy treatment. However, in some cases, jaundice has a pathological cause.4,5 The conditions pathologies that can increase bilirubin production include isoimmunization, hereditary hemolytic diseases and extravasated blood such as, for example, in cephalohematomas. The etiology of jaundice early stage is usually hemolysis caused by incompatibility ABO. However, this situation is not always confirmed.10,12 The late onset of hyperbilirubinemia, with bilirubin values above the 95th percentile, after 72 hours of life, can be predicted with a correct triage before hospital discharge. This late jaundice, it usually results from a decrease in the elimination of bilirubin. Inadequate breastfeeding with consequent dehydration and increased enterohepatic circulation of bilirubin is one of the factors important. Other risk factors include risk factors familial and ethnic backgrounds, such as older siblings with jaundice, Asian or Mediterranean descent, Gilbert's syndrome, and even genetic alterations. 10

Risk factors*:* Some situations favor the appearance of jaundice in the neonatal period by generating an increase in circulation enterohepatic, such as prolonged fasting, delayed elimination of meconium, intestinal obstructive processes and certain substances present in the breast milk of some mothers. Others factors are also considered risk factors for the development of hyperbilirubinemia, such as birth weight, gestational age (IG) and the sex of the NB.[8,16] The AAP points out as major risk factors: jaundice observed in the first 24 hours of life; incompatibility blood group with presence of hemolytic disease; GI from 35 to 36 weeks; previous child who needed phototherapy; lactation exclusive maternal and Asian race. As minor risk factors we have: GA between 37 to 38 weeks; jaundice identified after discharge; previous child with jaundice; Microsomic NB of a diabetic mother; maternal age greater than or equal to 25 years and male gender. They are considered as reduced risk factors: NB with higher GI, or equal to 41 weeks; fed exclusively with milk adapted; black and discharged after 72 hours of life.[17] NICE, in its recommendations, identifies as risk factors for the development of severe hyperbilirubinemia: GI less than 38 weeks; previous child in need of phototherapy; exclusive breastfeeding and the jaundice developed in first 24 hours of life.[7] GA is identified in the literature as the most important risk factor. The hepatic maturity of newborns is proportional to the IG which leads to a deficient conjugation of the bilirubin. The risk of potential injuries is greater in a NB of smaller IG, since the latter's defenses against bilirubin toxicity they are also smaller.[12] In the study by Alpay et al.[18], however, in that 525 NBs were evaluated for the risk of developing severe hyperbilirubinemia, no difference was found statistically significant among the factors exposed above, as well as as between the GI factors, birth weight and maternal smoking. In the study at the University Hospital of Pennsylvania, in which 823 newborns were evaluated, it was noticed that GA less than 38 weeks and breastfeeding were strongly associated with the risk of newborns developing hyperbilirubinemia significant.[19] Breastfeeding associated with weight loss significant is an almost unanimous risk factor. Especially when the weight loss and greater than 7%, putting the NB at risk of dehydration and causing an increase in enterohepatic circulation of bilirubin.[12,20]

Although the relationship between neonatal jaundice and breastfeeding, there is no clarity about the mechanisms involved, especially in those of late onset. breast milk may contain a bilirubin conjugation inhibitor or promote the enterohepatic circulation of bilirubin as a result of its glucuronidase.[8,9] Dehydration, urinary tract infections and systemic disorders, as well as hypothyroidism, are also significantly associated with severe hyperbilirubinemia.[15] Hemolytic diseases, blood group incompatibilities and others, are a determining factor in hyperbilirubinemia, since cause an important increase in the production of bilirubin, being Rh incompatibility prophylaxis is recommended for pregnant women with negative Rh factor, through the administration of anti-D immunoglobulin during pregnancy and after delivery. NBs susceptible to this incompatibility are the children of group O mothers, in which the mother, during pregnancy or earlier, developed antibodies to the NB blood, that is, anti-A and anti-B antibodies. These antibodies cross the placenta and bind to the appropriate antigen from the erythrocytes. This results in erythrocyte catabolism, which leads to a increased production of bilirubin, leading to hyperbilirubinemia significant.[14] This process occurs in a smaller number of NBs in the group A and B blood, children of mothers with the opposite blood group, a since the predominant immunoglobulin is M, and this has difficulty to cross the placenta and cause harm to newborns. The presence of antibodies in erythrocytes can be detected by determining the direct antibody titers, also known as the Coombs test direct. A positive direct Coombs test is considered a factor. significant risk for the development of hyperbilirubinemia. However, not all NBs with a positive Coombs test develop hyperbilirubinemia. The group's determinations blood test and Coombs test can be performed on the patient's blood. umbilical cord.[14] Traumatic or oxytocin-induced delivery can cause hyperbilirubinemia by development of cephalohematoma and increased hemolysis, respectively. a delay in umbilical cord ligation and a low Apgar score also increase the risk of hyperbilirubinemia.[21]

Classification: Types of neonatal jaundice are classified according to the cause of appearance, namely, hyperbilirubinemia or physiological jaundice, pathological jaundice, jaundice associated with breastfeeding (IAA) and breast milk jaundice (MLI), and at the time in which it appears, and may manifest early, late or prolonged.[1] Early jaundice can be considered as that which becomes visible in the first 24 hours of life, and the diagnosis of isoimmunization hemolytic disease should be considered until proven otherwise.[16,21,22] Late jaundice can be considered as the one that becomes visible after the first 24 hours of life and can depend on a large number of etiologies. However, in most cases in which there are no other associated symptoms, the diagnosis is that of jaundice characteristic of the NB. In these cases, if the jaundice is discreet, in general, there is no need to measure bilirubin, from the point of view of assistive view. If jaundice seems relevant, the first step for the differential diagnosis is the dosage of total bilirubinemia and fractions. Prolonged jaundice is the one that evolves more dragged than the so-called proper or physiological one of the NB (> 8 days in NBs and over 14 days in PTNBs).[16,21,23]

Physiological jaundice*:* Physiological jaundice is characterized by its onset after 24 hours after birth, usually in NBs without associated comorbidities. Reaches a peak around the 3rd to 5th day of life regressing in up to 10 days if RNT, or up to 20 days, if PTRN.[23] It stems from an individual predisposition and results from a production Accelerated build-up of bilirubin with limited ability to excrete pigment liver. Achieves serum levels of indirect bilirubin between 13 to 15 mg% and maximum peak on the third and fifth days of life or between the fifth and seventh days of life (depending on GA). You PTNBs may have more intense physiological jaundice than than the RNT because they still present erythrocyte, hepatic immaturity and gastrointestinal. It is a clinical condition in general benign and reversible.[8,24] Physiological jaundice is a diagnosis of exclusion and is usually due to five situations: increased synthesis of bilirubin by increasing the number of erythrocytes and decreasing half life of these; decrease in the ability of albumin to bind to bilirubin and less effective transport, since newborns have low plasma albumin levels; conjugation and excretion less effective, due to delayed maturation of the liver and the systems enzymatic; increase in enterohepatic circulation since the the newborn's intestine is sterile and does not have the capacity to hydrolyze bilirubin to stercobilin and also due to the presence beta-glucuronidase, which transforms conjugated bilirubin into non-conjugated conjugated, easily absorbed by the intestinal mucosa; and for impaired hepatic uptake of bilirubin, resulting from decreased ligandin.[9,21]

Pathologic jaundice: Jaundice is considered pathologic when evident in the first 24 hours and is characterized by: bilirubin above 5 mg/dL on the first day of life, 10 mg/dL on second day, or more than 13 mg/dL on subsequent days; if the levels of bilirubin increases by more than 5 mg/dL/day; if the newborn show signs and symptoms suggestive of serious illness. It presentes duration of jaundice for more than 10 days in RNT and more than 21 days in PTNB.[23,24,25] Numerous clinical conditions that can cause pathological jaundice in the NB and these conditions should be ruled out if jaundice persists, or if other related symptoms manifest. These disorders include: biliary atresia - obstruction of the bile ducts resulting from insufficient development of these before birth (in utero); galactosemia; cephalhematoma; glucose-6-phosphate dehydrogenase deficiency - hereditary defect. of enzymes, linked to sex and which results in the breakdown of blood cells red when the person is stressed by an infection or by cause of certain medications; neonatal sepsis; infection by congenital cytomegalovirus (CMV); congenital toxoplasmosis; syphilis congenital; congenital herpes; congenital rubella; administration of sulfa-based drugs in the mother with an advanced stage of pregnancy; Crigler-Najjar syndrome - hereditary disorder of blood metabolism bilirubin, in which it cannot be changed to its soluble form in water, glucuronide bilirubin. This disorder is caused by a enzyme imbalance in the liver (deficiency of glucuronosyl transferase type I); spherocytosis (hemolytic anemia congenital); cystic fibrosis; pyruvate kinase deficiency; thalassemia; Gilbert syndrome – An inherited, multifactorial disorder that affects the way bilirubin is processed by the liver and causes jaundice; congenital hypothyroidism; Lucey-Driscol syndrome; Gaucher disease; Niemann-Pick disease.[26] Pathological jaundice observed mainly in high-risk neonates results from the blood type or group incompatibility; infection or biliary, hepatic, or metabolic abnormalities.[23] Jaundice pathological, as it consists of higher rates of BI (12 to 13 mg/dl) into the bloodstream, can lead to Kernicterus, characterized by the deposit of BI in the cephalic region with risk of development of permanent damage such as mental retardation, deafness and motor impairment. It is believed that the largest group risk for the development of kernicterus either in neonates carriers of hemolytic disease of the NB, when the mother has the Rh fator negative and the fetus presents the positive Rh factor, then the incompatibility and the sensitized mother produces anti-Rh antibodies. This sensitization of the immune system leads to hemolysis of the erythrocytes that have, as a final product, the release of bilirubin in excess.[26]

Breastfeeding-associated jaundice*:* IAA is related to breastfeeding pattern of the neonate. The underlying cause of IAA is a deficient caloric intake, which results in hepatic transport and reduced body bilirubin removal. Generally, the newborn that develops the AAI has not been able to stimulate a early and adequate supply of breast milk. The IAA in general manifests itself between 48 and 72 hours after birth. The level of serum bilirubin peaks at 15 to 19 mg/dl at 72 hours, increasing by an average of 5mg/dl/day. Its treatment involves measures which ensures an adequate supply of breast milk, recommended to breastfeed the newborn every two hours to Stimulate breast milk production and intestinal motility neonate. IAA is one of the main complications observed in early discharges.[26]

Breast milk jaundice*:* ILM usually appears after the first week of life in healthy breastfed newborns exclusive maternal care, high levels of bilirubinemia by the end of the first month, which may last until the second or third month of life.[16,21] Several causes have been suggestions regarding ILM. Initially, it was attributed to the presence of steroid hormones in human milk that would act as conjugation inhibitors; then, the presence of acids was attributed unsaturated fatty acids with powers that also inhibit conjugation and that would be present due to lipase activity lipoprotein in human milk; current theory relates it to the level B-glucuronidase enzyme levels in breast milk. it is believed that this enzyme causes a greater absorption of intestinal bilirubin in the neonate, blocking its excretion. The participation of reabsorption of bilirubin via the enterohepatic circulation in the pathophysiology of this type of jaundice is proven, but still the fator etiology is not known. There is no knowledge, until the days of bilirubin encephalopathy (Kernicterus) caused by this type of jaundice.[16,22,26,27] When excessively high levels occur after being other causes of differential diagnosis have been ruled out, one can consider a diagnostic test for prolonged breast milk jaundice. This test is carried out by suspending breast milk, temporarily, for up to 48 hours, in those cases where other causes have been duly ruled out. The level of bilirubinemia decreases rapidly, in a few hours, and there may be a slight increase to the reintroduction of breastfeeding, however, not reaching the previously found values. The differential diagnosis should mainly be performed with some forms of hypothyroidism congenital, which may be unapparent in the neonatal period, and the familial Crigler-Najjar type II jaundice whose hepatic conjugation is usually less than 5%.[16] There is controversy regarding the need or not, of treatment for ILM. Conservative treatment involves temporarily suspend breastfeeding until the level of bilirubin decreases; this usually takes between 24 and 48 hours.[27]

Diagnosis*:* The diagnosis of neonatal jaundice is clinical and laboratory. In clinical investigation, it is important to analyze the history maternal obstetrics and childbirth to identify factors that may may be contributing to hyperbilirubinemia, such as drugs maternal (diazepam, oxytocics), type of delivery (forceps, pelvic, cesarean section), delay in umbilical cord clamping, group blood, Rh factor and maternal Coombs.[28] The history of jaundice neonatal in a parent or sibling is in favor of hemolytic anemia caused, for example, by spherocytosis. The presence of a brother who already had neonatal jaundice can guide us towards the diagnosis of isoimmunization. The existence of an acute maternal pathology during pregnancy may suggest a congenital infection of the newborn. The development of diabetes during pregnancy increases the incidence of neonatal jaundice. In NB with infrequent defecations or persistent vomiting it is necessary to suspect increased circulation enterohepatic due to, for example, pyloric stenosis, atresia bowel disease or Hirschsprung's disease. A decrease in the contribution caloric also causes hyperbilirubinemia by increased circulation enterohepatic disease.[21] On clinical examination, the diagnosis of hyperbilirubinemia is done by assessing skin color and of the mucous membranes of the NB. Icteric skin tone is not noticeable until that serum bilirubin levels are greater than 5 mg/dL. The examination should preferably be carried out under natural lighting, locating the regions with the greatest evidence of accumulated bilirubin, following the parameters of Kramer's dermal zones, considering its caudal cranium evolution, appearing initially on the face and progressing towards the trunk and finally the extremities (head and neck, about 6 mg/dL; chest, abdomen, and thighs, 12 mg/dL; hands and feet, 16 mg/dL), although it is not a reliable method.[20,29] According to these parameters, jaundice starts on the face (zone I), when the serum bilirubin levels are low, progresses to the chest to the navel (zone II), to the abdomen (zone III), then for the limbs, except the feet and hands (zone IV) and, finally, to the palms of the hands and soles of the feet (zone V), when levels bilirubin serum levels are already quite high. In this way, the intensity of jaundice can be subdivided into mild, moderate and accentuated. The mildest jaundice is the one that is found only on the face in a light way, while the most intense is found in zone V, accentuated.[30]

In addition to the clinical assessment of jaundice using Kramer's zones, the Ingram's Icterometer (developed by Gosset in 1960) is also a device that helps in assessing the intensity of the color yellow of the skin. By pressing this device at the base of the nose, one can compare the skin tone of the neonate with five ranges of different yellow tones, which are correlated with average levels of indirect bilirubin.[31] In the 1980s, the transcutaneous bilirubinometers, a device that operates through the principle of skin reflectance, making a measurement of the BTc, which is an assessment of the yellow coloration of the skin and especially the tissue subcutaneous.[20] Measurements from transcutaneous bilirubinometers do not are invasive and, as such, do not cause pain, being only necessary Place the device on the newborn's skin and press lightly to take the reading (Figure 6). The reading is instantaneous, not representing any cost other than the cost of acquiring the equipment. A evaluation by transcutaneous bilirubinometers can still be carried out several times, with certain

intervals of time, to estimate the evolution of values during hospitalization.[32,33,34] A BTS measurement makes it possible to identify cases of hyperbilirubinemia which, managing to evade visual assessment, would otherwise pass unnoticed and would put newborns at risk.[20] In the study by Barbosa et al.[35], a total of 210 measurements were performed with TcB in the frontal region of 210 healthy, white, full-term NBs who were not submitted to phototherapy or exchange transfusion. BTc correlated well with serum bilirubin (SB) (r = 0894; p < 0.001). The sensitivity of the test was 92% and the specificity of 90%, identifying all children with BS > 13mg/dl, with false-negative determinations of 0.95% and false-positive determinations of 8.58%. The negative predictive value of 98% correctly predicts the absence of hyperbilirubinemia in all cases. On physical examination, it is also important to check the presence of signs that justify jaundice neonatal, such as the presence of cephalohematoma or omphalitis.[21]The laboratory tests basically consist of: 1) concentration serum bilirubin - total and fractions; 2) blood group, Rh factor and direct Coombs; 3) hematocrit or hemoglobin.[28]

substance (limirubin), which is colorless, non-toxic, water soluble and easily excreted via the biliary tract and urine without the need for hepatic conjugation. Only the bilirubin that is close to the skin surface will be directly altered by light.[24,38] The level serum level that indicates the use of phototherapy depends on the contexto clinic in which the NB is located and must be individualized. levels Higher serum bilirubin levels tend to show better response to phototherapy. If phototherapy is installed at the time When bilirubin is on the rise, its effectiveness may not be translated into a drop in the level of bilirubin, but in a stop of progression of jaundice. On the other hand, if phototherapy is installed by the time bilirubin is naturally falling, the effectiveness can be translated by the increase in the speed of the fall of bilirubin levels.[39] Other factors to be considered are the type of jaundice, length of postnatal life, weight, gestational age, presence of comorbidities, among others. Bhutani's nomogram an easy-to-use tool for indicating phototherapy is shown, based on GA and presence or absence of risk factors (Figure 3).

Chart 1. BT level (mg/dL) for phototherapy indication and exchange transfusion (EXT) in newborns > 35 weeks of age gestation at birth. Adapted from AAP

		Total Bilirubin	(mg/Dl)	
AGE	Phototherapy	Phototherapy	Exchange Transfusion	Exchange Transfusion
	$35^{0/7}$-$37^{6/7}$ weeks	> $38^{0/7}$ weeks	$35^{0/7}$-$37^{6/7}$ weeks	> $38^{0/7}$ weeks
24 HOURS	8	10	15	18
36 HOURS	9,5	11,5	16	20
48 HOURS	11	13	17	21
72 HOURS	13	15	18	22
96 HOURS	14	16	20	23
5-7 DAYS	15	17	21	24

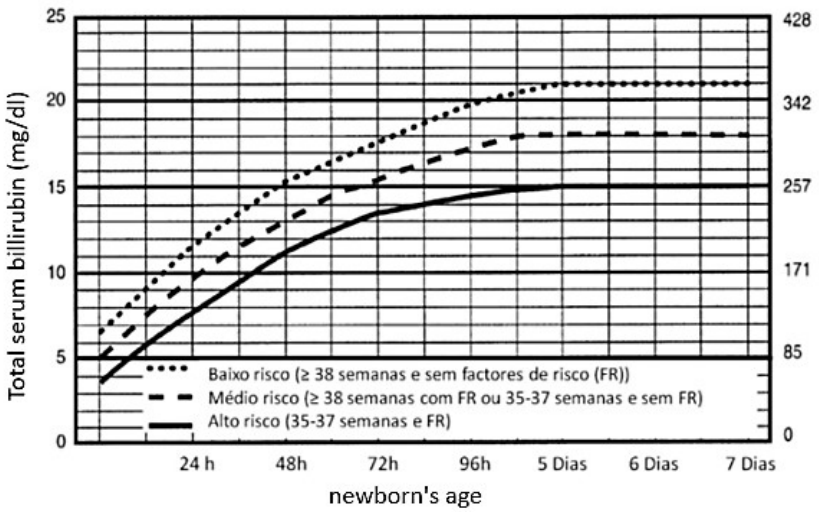

Figure 3. Phototherapy recommendation nomogram intensive care in newborns with gestational age greater than or equal to 35 weeks.

Treatment: The main objective of the treatment of neonatal jaundice is the prevention of bilirubin-induced neurological dysfunction, which includes kernicterus, in its acute and chronic forms.[36] The forms of therapies that control hyperbilirubinemia in the neonatal period used include phototherapy, exchange transfusion (EXT) and pharmacological agents.[37] Serum levels of BT for indication of phototherapy and EXT in term and preterm NBs are not consistently considered in the literature. Based on limited evidence, the periodic assessment of BT, the GA and postnatal age, in addition to the aggravating factors of the injury neuronal bilirubin. Table 1 below shows the values for newborns at 35 or more weeks of gestation. Decrease by 2 mg/dL the level of indication for phototherapy or EST if disease hemolytic (Rh, ABO, other antigens), G-6-PD deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis or albuminemia <3 g/dL. EST should be performed immediately if there are signs of bilirubin encephalopathy or if BT is 5 mg/dL above reported levels.

Phototherapy: Phototherapy is the first option in most cases. It consists of exposing the NB to a light source that converts the bilirubin impregnated in the skin and mucous membranes, in another

In full-term newborns without risk factors for severe hyperbilirubinemia, Phototherapy should be started when bilirubin levels at 24-48 hours are greater than 15 mg/dL, greater than 18 mg/dL at 49-72 hours and greater than 20 mg/dL after 72 hours. In RN with risk factors such as hemolysis, polycythemia, hypoxemia, sepsis and acidosis, phototherapy is started when serum bilirubin at 24-48 hours is greater than 7 mg/dL, greater than 12 mg/dL at 49-72 hours and greater than 15 mg/dL after 72 hours. [40,41] The wavelength for effective treatment lies at 400-500nm range. Blue-green light spectrum is usually used (450nm) because it has greater penetration into the skin, making it faster the decrease in bilirubin levels.[24] In conventional phototherapy 7 to 8 fluorescent lamps of 20 watts are used. The main Disadvantages are low irradiation when used type lamps. “daylight” and the fact that it cannot be used on babies in cribs radiant heat. It is recommended to maintain conventional phototherapy at 30 cm from the patient, keep the incubator acrylic clean and check periodically that all lamps are on. An alternative to Conventional phototherapy is the use of an acrylic cradle with fluorescent lamps placed at a distance of 5 cm below the patient.[28,39] Dichroic halogen phototherapy (phototherapy Bilispot) uses tungsten-halogen lamp, where only 40% of heat accompanies the light beam.

When placed at 40-50 cm of the newborn, provides a luminous halo of 20 cm in diameter with high irradiance in the center. It is effective in small NB. for RN with more than 2500 g, it is recommended to use 2 or 3 Bilispots with tangential halos in order to increase the area exposed to light. A fiber optic phototherapy (Biliblanket or luminous mattress) uses a special halogen light through a fiber optic cable. He has reduced dimensions (13 cm × 10 cm), being very effective in premature. High intensity phototherapy uses 16 lamps special blue ones arranged in a cylinder shape around the RN.[28,39] Carvalho et al.[42] evaluated 34 newborns with a birth weight of 2500g, jaundiced (total bilirubin 12 mg%) requiring phototherapy. Patients with positive direct Coombs and those who had serious pathologies. The patients studied were randomly divided into two groups. Group I NBs (n=17) underwent Biliblanket phototherapy. Group RNs II (n=17) received conventional phototherapy equipped with 7 white fluorescent lamps. The BT concentration was dosed from 8/8 h through micromethod during the first 48 hours of treatment and the irradiance emitted by both phototherapies was measured daily using a photodosimeter. The two groups do not differed in terms of gestational age, birth weight and age at time of initiation of phototherapy. The average irradiance emitted by the Biliblanket was significantly superior to that of phototherapy conventional (42.6 vs 9.8 uw/cm2/nm, p > 0.001). Phototherapy should be suspended when the level is considered to be low enough not to cause toxicity, generally around 12 mg/dl in healthy newborns. The need for bilirubin collection in a "rebound test" after discontinuing phototherapy is debatable, having considering that the average increase in bilirubin is about 1 mg/dl. A clinical reassessment 24 hours after discontinuation of phototherapy.[24,39] Phototherapy may present as adverse effects insensible loss of water, especially in premature infants, due to increased and exposed body surface that added to the delay in regulation of breastfeeding can lead to dehydration; diarrhea; susceptibility to hyperthermia and hypothermia due to exposure direct from the heat source (light); rashes and erythema; darkening of the skin (tan baby syndrome); burns by increased exposure; thrombocytopenia; mild hemolysis; thrombocytopenia and retinal damage.[1,28,39]

Exchange transfusion: The main objective of EXT is to remove excess bilirubin, in order to prevent its effects toxic. About 85% of circulating red blood cells are replaced when the exchanged blood volume reaches twice the volume of the RN (80ml/kg). As bilirubin is removed from the plasma, the extravascular bilirubin rapidly equilibrates and binds to albumin in exchanged blood.[28] EXT in term NB without factors risk should begin when bilirubin levels at 24-48 hours are greater than 20 mg/dL or greater than 25 mg/dL after 49 hours. If the newborn has risk factors, it begins when the serum bilirubin is greater than 20mg/dL at any time. Case an increase in total bilirubin greater than 1mg/dL/hour also occurs it is advisable to start this treatment.[40,41] EXT has a 1 to 5% risk of mortality and 12% of serious morbidities, including thrombocytopenia, portal vein thrombosis, enterocolitis necrotizing, electrolyte disturbances, cardiac overload and infection.[43]

Pharmacological treatment: The pharmacological agents used in the management of hyperbilirubinemia can accelerate metabolic pathways normal clearance of bilirubin (fernobarbital), inhibit the enterohepatic circulation of bilirubin and interfere with the formation of bilirubin by blocking the breakdown of heme (metalloporphyrins) or by inhibiting hemolysis (intravenous immunoglobulin).[24] Phenobarbital increases the activity of glucoronyltransferase, improving the bilirubin conjugation. However, the administration of phenobarbital in pregnant women was not effective in reducing the degree of jaundice in newborns, in addition to the drug, it can cause dependence in the mother and excessive sedation in the NB. The combination of phenobarbital and phototherapy in NB does not reduce serum bilirubin levels more quickly than phototherapy alone.[28] Studies have shown that phototherapy metalloporphyrin, a potent heme oxygenase inhibitor, reduces the conversion of the heme radical into bilirubin and, in this way, would have a place in the treatment of jaundice in newborns, in addition to being effective in prevent or minimize neonatal jaundice resulting from deficiency of glucose-6-phosphate dehydrogenase (G6PD) and in cases of ABO blood incompatibility with positive Coombs.[44] A G6PD deficiency should be investigated in every NB who presentes non-physiological jaundice, even if another cause explains the hyperbilirubinemia. It is a genetic disease associated with X chromosome that affects individuals of both sexes equally. At the There are two forms of the disease during the neonatal period: acute hemolytic with rapid rise of indirect bilirubin triggered by agentes oxidants (antimalarials, infection, menthol powders, naphthalene, among others others) and mild hemolytic associated with genetic polymorphism with reduced expression of glucuronyl transferase and limited conjugation of bilirubin, without the presence of anemia. It is estimated that it can reach up to 7% of the Brazilian population, with the G-6-PD neonatal screening performed on filter paper and the quantitative dosage performed in blood withnormal reticulocytes.[45]Human immunoglobulin reduces the need for EXT in isoimmune hemolytic disease. is managed at a dose of 0.5 to 1 g/kg, two hours after birth and repeated after 12 hours if necessary.[28]

CONCLUSION

Neonatal jaundice is a frequent pathology in the neonatal period, etiology, in most cases, multifactorial. It is a pathology that requires a careful therapeutic approach due to its potential to reach the central nervous system and may cause irreparable damage to the newborn health. Therapy includes phototherapy, exchange transfusion and the administration of adjuvant drugs, such as metallo-porphyrins heme oxygenase inhibitors, phenobarbital and immunoglobulin intravenous. The treatment instituted depends on the type and intensity jaundice, and several factors should be considered, such as maternal obstetric history, delivery and neonatal history. Phototherapy has been the most used therapy, as it is a non invasive method and high impact for decreasing plasma bilirubin levels, regardless of the maturity of the neonate, the presence or absence of hemolysis or the degree of skin pigmentation.

REFERENCES

AALPAY, F.; SARICI, SU.; TOSUNCUK, HD. et al. The value of first-day bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy term newborns. Pediatrics, v. 106, no. 2, p. e16, 2000.

ALKALAY, L.A.; SIMMONS, F.C. Hyperbilirubinemia Guidelines in Newborn Infants. Pediatrics, v. 115, p. 824-825, 2005.

AMERICAN ACADEMY OF PEDIATRICS. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics, v. 114, no. 1, p. 297-316, 2004.

ARAUJO, BF. Management of jaundice in the newborn. In:FERREIRA, J. P. (Org). Pediatrics: diagnosis and treatment. Porto Alegre: Artmed, 2005.

ARAÚJO, M.C.K.; RAMOS, J.L.A.; VAZ, F.A.C. Jaundice Neonatal. Modern Pediatrics, v. 36, p. 84-90, 2000.

BAKKEHEIM, E.; BERGERUD, U.; SCHMIDT-MELBYE, A. et al. Maternal IgG anti-A and anti-B titers predict outcome in ABOincompatibility in the neonate. Acta Paediatrica, v, 98, p. 1896-1901, 2009.

BARBOSA, A.D.M.; NOVAIS, M.E.; PERNETTA, C. Transcutaneous bilirubinometry: an important screening method of newborns with hyperbilirubinemia. Arch. Bras. Med., v. 67, no. 2, p. 112-115, 1993.

BASTOS, F.; SEGRE, C.A.M.; BRITTO, J.A.A. preliminary study on the approach to the treatment of neonatal jaundice in maternity hospitals in the city of São Paulo, Brazil. Einstein, v. 5, n. 1, p. 56-62, 2007.

BESSER, I.; PERRY, Z. H.; MESNER, O. et al. Yield of recommended blood tests for neonates requiring phototherapy for hyperbilirubinemia. Isr Med Assoc J., v. 12, no. 4, p. 220-224, 2010.

BHUTANI, V.K.; JOHNSON, L.; SIVIERI, E.M. predictive ability of a predischarge hour-specific serum bilirubin for subsequent

significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics, v. 103, no. 1, p. 6-14, 1999.

CANADIAN PAEDIATRIC SOCIETY (CPS). Guideline for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants. Pediatric Child Health, v. 12, Sup., p. 1B-12B, 2007.

CARVALHO, M. Treatment of neonatal jaundice. J Pediatr (Rio J), v. 77, Suppl.1, p. S71-S80, 2001.

CARVALHO, M.; LINS, M.F.C.; GOLDANI, M.P.S. et al. Comparison between conventional and fiberoptic phototherapy: bright mattress. *J. Pediatr.* (Rio J.), v. 68, no. 7/8, p. 289-292, 1992.

COLVERO, AP; COLVERO M.O.; FIORI, R.M. Phototherapy. Scientia Med., vol. 15, no. 2, p. 90-95, 2005.

DAL MORO, A.N.; SILVESTRI, K.; SILVA, R. M. Clinical evaluation of jaundice: Correlation with serum bilirubin levels. Medical Archives of Santa Catarina, v. 33, no. 4, p. 15-22, 2004.

DAVIDSON, L.; THILO, E.H. How to make kernicterus a "never event". Neoreviews, v. 11, p. e308-314, 2003.

DICKEN, P.; GRANT, L.J.; JONES, S. An evaluation of the characteristics and performance of neonatal phototherapy equipment. Physiol. Meas., v. 21, p.493-503, 2000.

DRAQUE, C.M. Neonatal jaundice. Available in: http://www.unasus.unifesp.br/biblioteca_virtual/esf/1/casoscomplexos/Danrley/Complexo_01_Danrley_Ictericia.pdf. Access: 10 Jan. 2023.

ENK, I.; ABEGG, M.P.; ALVES, R.J.V. et al. jaundice as a cause of neonatal hospitalization: the experience in a tertiary care servisse Porto Alegre, RS. AMRIGS Magazine, v. 53, no. 4, p. 361-367,2009.

FERREIRA, A.L.C.; NASCIMENTO, R.M.; VERÍSSIMO, R.C.S.S. Irradiance of phototherapy devices in maternity hospitals in Maceio. Rev Latino-am Enfermagem, v. 17, no. 5, p. 695-700, 2009.

FERREIRA, G.R.; VASCONCELOS, C.K.B.; SILVA, M.M. et al. Development of "intelligent" device for radiation monitoring in neonatal phototherapy. Rev Med. Minas Gerais, vol. 20, no. 2, p. 198-202, 2010.

FOUZAS, S.; MANTAGOU, L.; SKYLOGIANNI, E. et al. Transcutaneous bilirubin levels for the first 120 postnatal hours in healthy neonates. Pediatrics, v. 125, no. 1, p. e52-57, 2010.

GOMES, N.S.; TEIXEIRA, J.B.A.; BARICHELLO, E. Care of the newborn in phototherapy: the knowledge of the team of nursing. Rev. Electric Enf., v. 12, no. 2, p. 342-347, 2010.

GONÇALVES FILHO, J. Neonatology: practical guide. João Pessoa: Idea, 2008.

GUIMARÃES, H.; SANTOS, T.N. Neonatal jaundice. files of Medicine, v. 5, p. 1-8, 1991.

GUNDUR, N.M.; KUMAR, P.; SUNDARAM, V. et al. Natural history and predictive risk factors of prolonged unconjugated jaundice in the newborn. Pediatr Int., v. 52, no. 5, p. 769-772, 2010.

KAPLAN, M.; NA'AMAD, M.; KENAN, A. et al. failure to predict hemolysis and hyperbilirubinemia by IgG subclass in blood group A or B infants born to group O mothers. *Pediatrics,* v. 123, no. 1, p. e132-137, 2009.

KENNER, C. Neonatal Nursing. 2nd ed. Rio de Janeiro: Reichmann and Affonso, 2001.

KEREN, R.; LUAN, X.; FRIEDMAN, S. et al. The comparison of alternative risk-assessment strategies for predicting significant neonatal hyperbilirubinemia in term and near-term infants. Pediatrics, v. 121, p. 170-179, 2008.

KOPELMAN, B.I.; SANTOS, A.M.N.; GOULART, A.L. et al. Diagnosis and Treatment in Neonatology. In: ALMEIDA, MF; DRAQUE, C.M. (orgs). Phototherapy. Sao Paulo: Atheneu, 2004.

LEITE, M.G.C. validation of the "Bilicheck®" for dosage of bilirubin in neonates. Thesis (Doctorate). Campinas: UNICAMP, 2007.

LEITE, M.G.C.; GRANATO, V.A.; FACCHINI, F. P.; MARBA, S.T.M. Comparison between transcutaneous and plasma dosage of bilirubin. J. Pediatr. (Rio J.), v. 83, no. 3, p. 283-286, 2007.

MAISELS, M.J. Screening and early postnatal management strategies to prevent hazardous hyperbilirubinemia in newborns of 35 or more weeks of gestation. Semin Fetal Neonatal Med., v. 15, no. 3, P. 129-135, 2010.

MAISELS, M.J.; McDONAGH, A. F. phototherapy for neonates jaundice. N Engl J Med., v. 358, no. 9, p. 920-928, 2008.

MERRIT, K.A.; COULTER, DM. Application of the Gosset Icterometer to screen for clinically significant hyperbilirubinemia in premature infants. J Perinatol., v. 14, no. 1, P. 58-65, 1994.

MOREIRA, V.L.; SACRAMENTO, C.B.; ALECRIN, A.F. et al. Neonatal jaundice and phototherapy: the nurse's contribution to the effectiveness of the treatment. R. Research: Care Found. Online, v. two, n. 4, p. 1286-1296, 2010.

PAGANINI, C.B.L.; FERREIRA, A.B.; GALACCI, C.B. Jaundice neonatal: risk factors for readmission in a population of newborns in the city of São Paulo. Arq Med Hosp Fac Cienc Med Santa Casa São Paulo, v. 54, no. 2, p. 51-55, 2009.

PETROVA, A.; MEHTA, R.; BIRCHWOOD, G.; OSTFELD, B.; HEGYI, T. Management on Neonatal Hyperbilirubinemia: Pediatricians' Practices and Educational Needs. BMC Pediatrics, v. 6, p. 1-7, 2006.

PORTER, L.M.; DENNIS, L.B. Hyperbilirubinemia in the Term Newborn. Am Fam Physician., v. 65, p. 599-606, 2002.

QUINTAS, C.; SILVA, A. Neonatal jaundice. Available in: http://www.portalneonatal.com.br/ictericianeonatal/arquivos/Ictericia%20Neonatal%20revisao.pdf. Accessed on: 10 Jan. 2023.

RAMOS, J.L.A. Newborn jaundice: current aspects. Rev Fac Cienc Med Sorocaba, v. 4, no. 1-2, p.17-30, 2002.

RANDEV, S.; GROVER, N. Predicting neonatal hyperbilirubinemia using first day serum bilirubin levels. Indian J Pediatr., v. 77, no.2, p. 147-150, 2010.

RENNIE, J.; BURMAN-ROY, S.; MURPHY, M.S. neonatal jaundice: summary of NICE guidance. BMJ, v. 340, p. c2409, 2010.

SEGRE, C.A.M. Perinatology: fundamentals and practice. São Paulo: Savier, 2002.

SEGRE, C.A.M.; BASTOS, F.; RIELLI, ST. Assessment of neonatal hyperbilirubinemia using a non-invasive analyzer invasive. Modern Pediatrics, v. 39, no. 10, p.401-404, 2003.

SILVA, A.S. Handbook of Neonatology. Rio de Janeiro, 2002.

SMITHERMAN, H.; STARK, A.R.; BHUTANI, V.K. early recognition of neonatal hyperbilirubinemia and its emerging management. Semin Fetal Neonatal Med., v. 11, no. 3, p. 214-224, 2006.

VINHAL, R.M.; CARDOSO, T.R.C.; FORMIGA, C.K.M.R. Jaundice neonatal and kernicterus: know to prevent. Magazine move, v. 2, no. 3, p. 93-101, 2009.

WONG, J. Fundamentals of Pediatric Nursing. 7 ed. River of January: Elsevier, 2006.

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