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JAUNDICE DUE TO MATERNOFETAL INCOMPATIBILITY: CASE REPORT

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Abstract: Jaundice is the clinical manifestation of hyperbilirubinemia, with yellowing of the skin, sclera and mucous membranes. Through careful anamnesis and physical examination, it is possible to identify risk factors for evolution with hyperbilirubinemia and its gold standard diagnosis is made through the measurement of total bilirubin and fractions in the blood. That said, the hemolytic disease of the newborn is the main etiology of pathological jaundice, being associated with the presence of maternal autoantibodies that react against red blood cells of the newborn, with phototherapy being the most indicated intervention and, in some more specific cases, the exchange transfusion.
Goal: To report the necessary conducts in the face of a serious case of maternal-fetal incompatibility. **Discussion:** Since jaundice is a disease that can evolve seriously, essential measures at birth are discussed to better manage the case, with an assessment of the need for rigorous bilirubin collection, and even the possibility of indicating exchange transfusion.
Conclusion: It is evident that the investigation of the maternal history of previous pregnancies is extremely important to assist in directing the approach to newborns at high risk for the development of severe hyperbilirubinemia.
Keywords: Jaundice. Erythroblastosis fetalis. Hemolysis.

INTRODUCTION

Jaundice is one of the most frequent signs of the neonatal period, indicating hyperbilirubinemia by the manifestation of yellowish coloration of the skin, sclera and mucous membranes due to the accumulation of bilirubin in the tissues. This accumulation results from changes in the metabolism of this component, whether in formation, transport, uptake, conjugation or excretion in the pigment. At the end of 120 days, senescent

red blood cells are phagocytosed and, through the degradation of the heme group, indirect or unconjugated bilirubin originates, which is liposoluble and easily crosses lipoprotein membranes. Upon binding to plasma albumin, this pigment is transported to hepatocytes, where it will be converted into direct bilirubin by the conjugation process. Once conjugated, bilirubin becomes water soluble, allowing its renal and intestinal excretion. Together with the bile, bilirubin reaches the intestine (mainly at the level of the terminal ileum and colon), where it is degraded by the action of the local bacterial flora and is transformed into urobilinogen, which is mostly reabsorbed by the intestinal mucosa (returning to the liver), while a small fraction is eliminated together with the faeces.[4,5]

Current concepts of indirect hyperbilirubinemia follow the following nomenclature: "significant", when total bilirubin (BT) is at phototherapy level; "severe or severe", when BT is close to the level of exchange transfusion (EST) or any level of BT associated with the presence of signs of acute bilirubin encephalopathy; "extreme", when BT is already at the EST level, when BT ≥ 25 mg/dL or when BT is associated with signs of early or intermediate acute bilirubin encephalopathy. In addition to this categorization, jaundice can be classified as "physiological", due to limitations in the metabolism of bilirubin, occurring after 24 hours of the newborn's life, with a peak on the 3rd - 4th day of life, and "pathological", associated with pathologies that interfere with bilirubin metabolism, occurring before 24 – 36 hours of life or with BT ≥ 12 mg/dL, regardless of post-neonatal age.[5]

Through the neonatal history, physical examination and clinical evolution of the patient, it is possible to identify the presence of clinical and epidemiological risk factors associated with the development of significant hyperbilirubinemia in the first week of life, with the main examples of this group being those cited in Table below (Table 1).[5]

• gestational age ≤ 37 weeks, regardless of birth weight
• maternal-fetal incompatibility Rh, ABO, or irregular antigens
• umbilical cord clamping > 60 seconds after birth
• difficult breastfeeding or weight loss > 7% of birth weight
• brother with neonatal jaundice treated with phototherapy
• diabetic mother
• gender: male

Table 1 - Main risk factors with evolution of significant hyperbilirubinemia in the first week of life.[5]

The differential diagnosis of the causes of indirect hyperbilirubinemia includes causes resulting both from overload of bilirubin to the hepatocyte and from impaired hepatic conjugation (Table 2). Perinatal hemolytic disease is a major cause of neonatal jaundice, characterized as a condition of hemolytic anemia caused by maternal-fetal blood incompatibility, resulting from aggression caused by maternal antibodies against antigens of fetal red blood cells. Maternal-fetal incompatibility can occur mainly through two systems: ABO and Rh system, with some differences in relation to immune response and prevalence (Table 3). After initial exposure to an erythrocyte antigen, the maternal immune system will trigger the production of IgM-type antibodies, unable to cross the placental barrier. When a second exposure occurs, a massive production of IgG will follow, low molecular weight antibodies, which cross the placental barrier and bind to fetal erythrocytes, causing hemolysis. If this process is prolonged, severe anemia can be generated in the fetus, increasing fetal

erythropoietin production and medullary and extramedullary erythropoiesis. In more severe cases, increased erythropoiesis can lead to hepatosplenomegaly, hypoalbuminemia, and hydrops fetalis. After birth, hemolysis leads to a high release of bilirubin in the blood and, due to hepatic immaturity, overload of hepatocytes and accumulation of unconjugated bilirubin occurs, resulting in jaundice. [3,4,5]

Bilirubin levels can be estimated by classifying jaundice in Kramer's Zones (picture 1), however, for its effective measurement, the gold standard method is serum bilirubin dosage. Thus, it is important to know the indications for requesting BT from the newborn, described in the Table below (Table 4).

• jaundice in the first 24 - 36 hours of life
• maternal-fetal ABO and Rh incompatibility
• jaundice in a newborn at 35 - 36 weeks (regardless of birth weight)
• jaundice in a newborn with difficulty breastfeeding and/or weight loss > 7% of birth weight
• jaundice in a full-term newborn below the level of the nipple line

Table 4 - Indications for total bilirubin collection in newborns.[5]

The therapy of choice for indirect hyperbilirubinemia is phototherapy and, in some more complicated cases, exchange transfusion must be considered. For both techniques, it is necessary to know how to stratify this newborn according to its risk of developing bilirubin encephalopathy (picture 2). Of great importance, this stratification allows the physician to indicate or suspend phototherapy and/or exchange transfusion through graphs generated based on the patient's hours of life and total bilirubin levels.[5]

GOALS

Report the necessary conducts in the face of a serious case of maternal-fetal incompatibility.

REPORT OF CASE

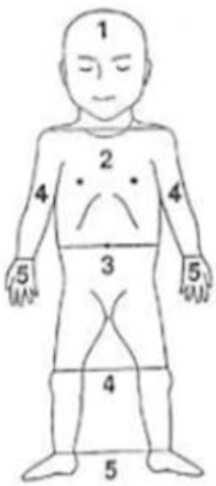
A male patient was followed up in the Pediatrics sector of the Hospital Escola Alcides Carneiro, with a gestational history of a mother aged 44 years, G10P10A0, with O negative blood typing, incomplete prenatal care (3 consultations), previous history of two newborns -borns who required phototherapy in the first days of life and 3 doses of Ampicillin given intrapartum due to prolonged ruptured membranes. The newborn was born by vaginal delivery, late preterm (GA: 36 + 5d, by Capurro), AGA, Apgar 8/9 and delayed clamping of the umbilical cord. With 29h of life, he evolved with physical examination showing Kramer zone II jaundice, 2 + / 4 +. On that same day, a first screening was requested, which came back normal with Rodwell 0 and low CRP, also requesting total bilirubin and fractions, with a total bilirubin of 13.9, with a predominance of indirect, and albumin of 4.3. At that moment, it was also discovered that the newborn's blood type is A positive, with a positive direct coombs and a positive eluate test. As the patient in question had less than 38 weeks of birth and the presence of a risk factor for developing encephalopathy, he was classified as high risk, with the level of phototherapy and exchange transfusion: 9 and 15.5, respectively. Therefore, BT is above the phototherapy indication level and below the exchange transfusion level, and double phototherapy is initiated. With 61 hours of life, after a new collection, there is an increase in total bilirubin to 21.4, a value that is above the phototherapy level (NF: 12.5) and above the exchange transfusion level (LE: 18), making with him being referred to the neonatal ICU with triple phototherapy. During this period,

BILIRUBIN OVERLOAD TO HEPATOCYTE	DEFICIENCY OR INHIBITION OF BILIRUBIN CONJUGATION
• Hemolytic diseases: • Immune: Rh incompatibility, ABO or irregular antigens • Enzymatic: G-6-PD deficiency, pyruvate kinase • Red cell membrane: spherocytosis, hexokinase • Hemoglobinopathies: alpha-thalassemia • Bacterial or viral infections	Congenital hypothyroidism
Extravascular blood collections (cephalohematoma, hematoma, ecchymosis, hemorrhages)	Breast milk jaundice syndrome
Polycythemia	Gilbert's Syndrome
Increased enterohepatic circulation of bilirubin (hypertrophic pyloric stenosis, bowel obstruction, low breast milk supply)	Crigler-Najjar syndrome type 1 and 2

Table 2 - Etiology of indirect hyperbilirubinemia in the neonatal period.[5]

ABO SYSTEM	HR SYSTEM
Most frequently; milder cases	Less frequent; more serious cases
Mother: O / Fetus: A or B or AB	Mother: Rh negative / Fetus: Rh positive
Antibodies: anti-A and/or anti-B	Antibodies: anti-D
Diagnostic test: Eluate Test	Diagnostic test: Indirect Coombs test (done on the mother) and direct Coombs test (done on the newborn))

Table 3 - Differences between ABO and Rh maternal-fetal incompatibility.[7]



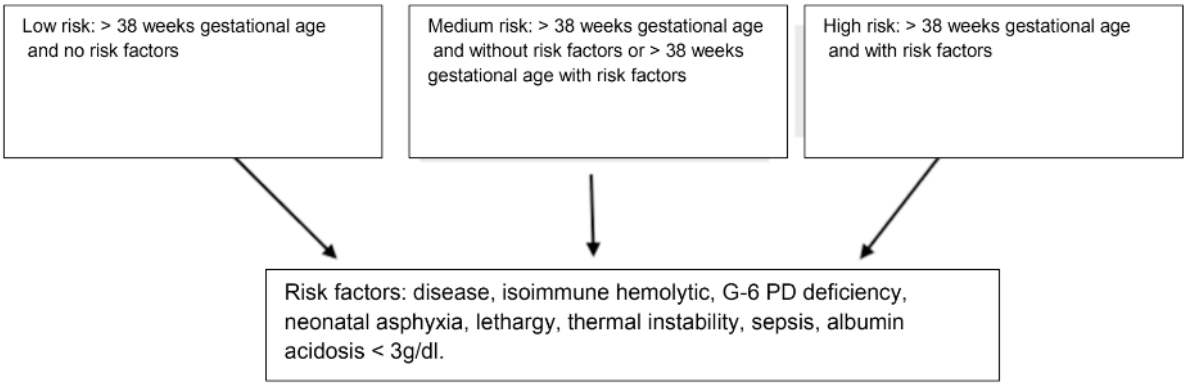
Zone 1: Head and neck jaundice (BT= 6mg/dl)
Zone 2: Jaundice down to the navel (BT = 9 mg/dl)
Zone 3: Jaundice down to the knees (BT =12 mg/dl)
Zone 4: Jaundice to the ankles and/or forearm (BT= 15mg/dl)
Zone 5: Jaundice up to the plantar and palmar region (BT =18mg/dl or more)

BT = total bilirubin (approximately)

Picture 1 - Krammer's Jaundice Zones

Krammer's classification into jaundice zones is important for the clinical classification of jaundice and estimation of total bilirubin values, even before laboratory tests. The stratification is carried out by means of the place on the body of the newborn in which the yellowish coloration is evidenced.

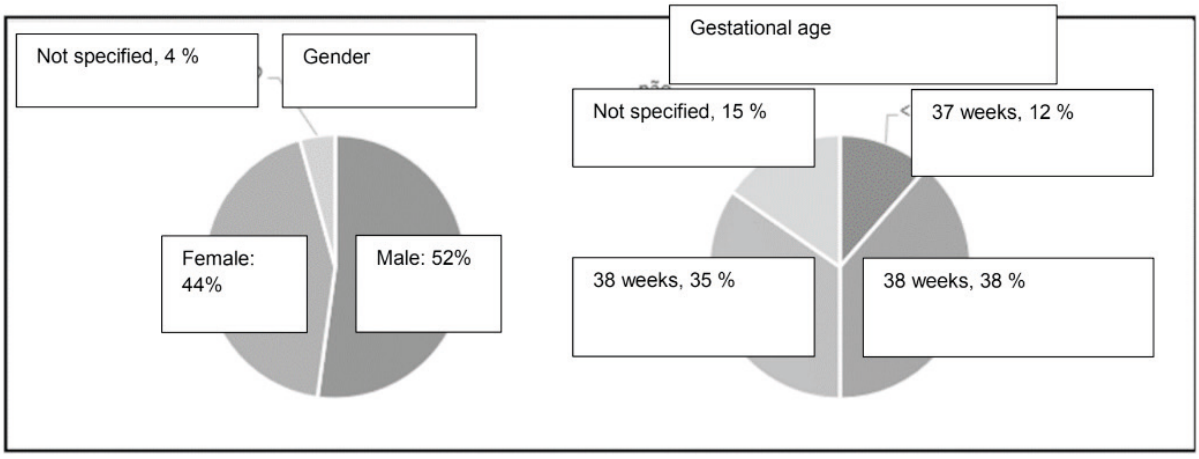
Source: Ministry of Health, Secretariat of Health Care, Department of Programmatic and Strategic Actions, Pan American Health Organization. Neonatal IMCI manual: framework of procedures. 3rd edition. Brasilia: Ministry of Health, 2012. Page 22.



Picture 2 - Risk classification for progression to bilirubin encephalopathy.[3,5]

Classification used to indicate or suspend treatment with phototherapy and/or exchange transfusion, based on the gestational age of the newborn and the risk factors associated with poor evolution. Note that the risk factors do not add up and the presence of just one of them already causes the newborn to score as "positive" for the risk factor criterion, being only dependent on the gestational age to complete the classification.

Source: Compiled from the authors, 2023



Graph 1 - Prevalence of severe jaundice at Hospital Alcides Carneiro, in the neonatal ICU setting, stratified by gender and gestational age

Source: Compiled from the authors, 2023

he obtained a maximum total bilirubin of 23.9, with a level of phototherapy and exchange transfusion of: 13 and 18.5, respectively. He remains in the ICU until the 7th day of life, undergoing quadruple phototherapy during this time, with limited breastfeeding time, intravenous hydration, supplementation with formula and performing daily collections of bilirubin. With 7 days of life, the total bilirubin has reduced to 14.5, now with a phototherapy level of 15, which allows discharge to the shelter, but maintaining only phototherapy. At 8 days old he maintains a total bilirubin level still close to the 7-day old level. With 9 days of life, he finally presents a drop in total bilirubin to 11.5, allowing the suspension of phototherapy and collection of rebound bilirubin. At 10 days of age, the patient had a total rebound bilirubin of 10.9, 4 points below the phototherapy level (NF:15), which led to the newborn's hospital discharge.

DISCUSSION

Jaundice is a frequent condition in newborns and it is known that approximately 60% of full-term newborns and 80% of preterm newborns tend to develop jaundice in the first days of life. In addition, between 2004 - 2019, in Brazil, there were 902 infant deaths with the underlying cause of death recorded as hemolytic disease of the fetus and newborn.[5,6]

This work involved carrying out an epidemiological investigation at Hospital Alcides Carneiro, where, between January 2021 and January 2022, approximately 8 out of every 1000 live births developed severely jaundice, requiring them to remain in the neonatal ICU. Of 23 children, males (52% of cases) were more prevalent than females (44% of cases), with 4% of children not identifying their gender. Regarding gestational age, there was a close relationship between cases born < 38 weeks (38%) and those born ≥ 38 weeks (35%), with 15% of children without specification of gestational age.

As observed, although common in newborns, jaundice can be severe, and it is imperative that the neonatologist knows how to properly manage these cases. Analyzing the evolution of the patient in question, through the review of current literature, one can understand the need for a better approach to the neonate.

Faced with chances of maternal-fetal incompatibility (pregnant woman with blood type O or Rh negative), it is important to carry out a good maternal investigation, in relation to previous pregnancies, in search of other children with evolution to jaundice and history of positive antibodies in tests of coombs or eluate. This way, it is possible to predict the risk of a bad evolution through hyperbilirubinemia.

Exchange transfusion is the treatment of choice for more severe cases of hyperbilirubinemia, with severe hemolytic disease due to Rh incompatibility being its main indication. In order to be able to indicate this procedure at birth, it is necessary to collect a red series and total bilirubin (BT) and fractions in the umbilical cord, with BT levels > 4 mg/dL and / or hemoglobin < 12 mg/dL, or also by calculating hemolysis in the first 36 hours of life, coursing with BT elevation levels ≥ 0.5 – 1.0 mg/dL/hour.

This technique operates by removing red blood cells with antibodies attached to them and circulating antibodies, leading to a reduction in bilirubin and improvement in anemia. Because it is associated with high morbidity (metabolic, hemodynamic, infectious, vascular, hematological complications), it is important to be cautious in its indication.[5,6]

When the newborn does not fit these conditions or does not have a risk of serious evolution, treatment for jaundice must be

indicated based on the previously mentioned phototherapy and exchange transfusion charts, contained below (pictures 3 and 4). Phototherapy is the most used treatment, with the aim of degrading bilirubin through light energy absorbed by the newborn's skin. Its effectiveness is evaluated by the decline in BT after a time of exposure to light, and the body surface area exposed to light is directly related to the rate of bilirubin decline and, therefore, it is important to maximize both the area and the time of exposure.[5]

In addition, another measure that is relevant in cases like this is the use of the Risk Normogram chart. It works based on the percentiles of the first collections of total bilirubin obtained between 18 and 72 hours, in which the newborn will be classified according to the risk of developing a high level of bilirubin. With that, we have one more tool to predict bad evolution and anticipate collections of total bilirubin and fractions.[5]

CONCLUSION

The reported case demonstrates the relevance of previous gestational histories compared to the current pregnancy, in addition to the determination of risk factors for the development of severe pathological jaundice for the establishment of a targeted, early and effective conduct. Therefore, it is important to carry out complete prenatal care in a reference location and a good anamnesis in the delivery room, with the investigation of pregnancies that presented jaundice or positive indirect coombs. Therefore, we can conclude that the essential measures in cases where the history suggests a bad evolution are primarily: the collection of umbilical cord blood, the calculation of the hemolysis speed and the use of the risk normogram.

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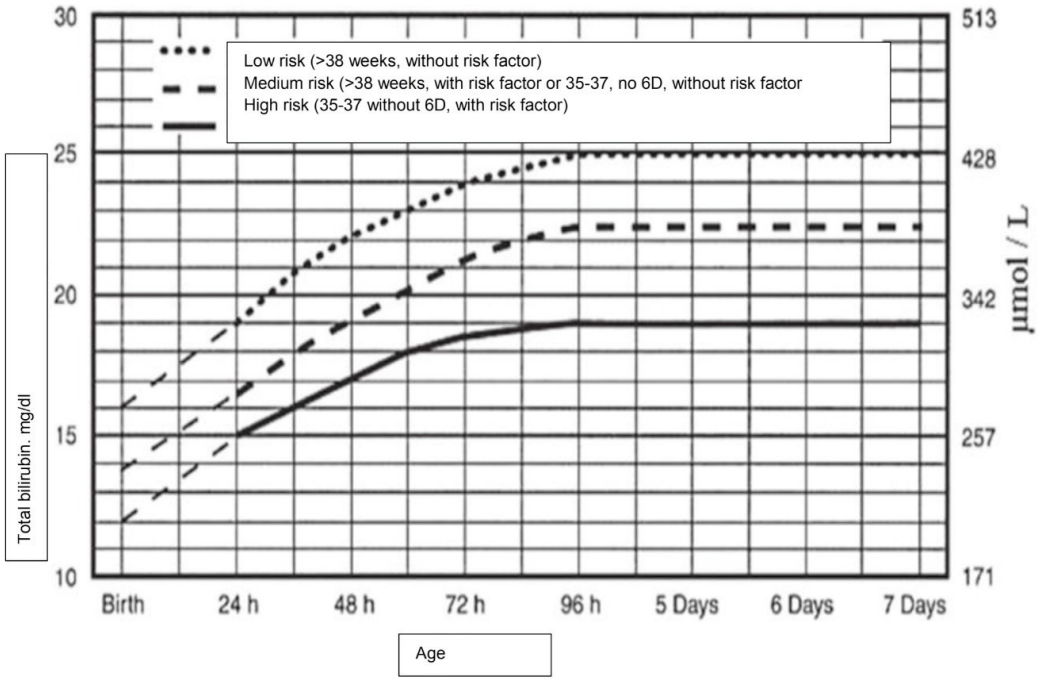
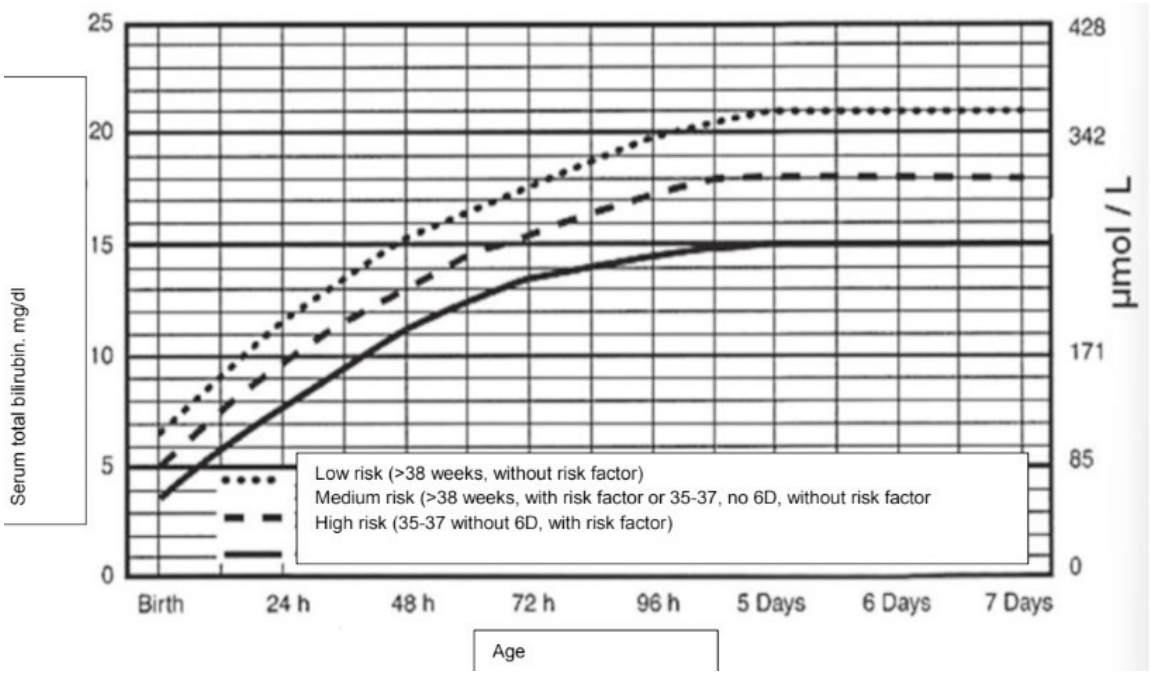


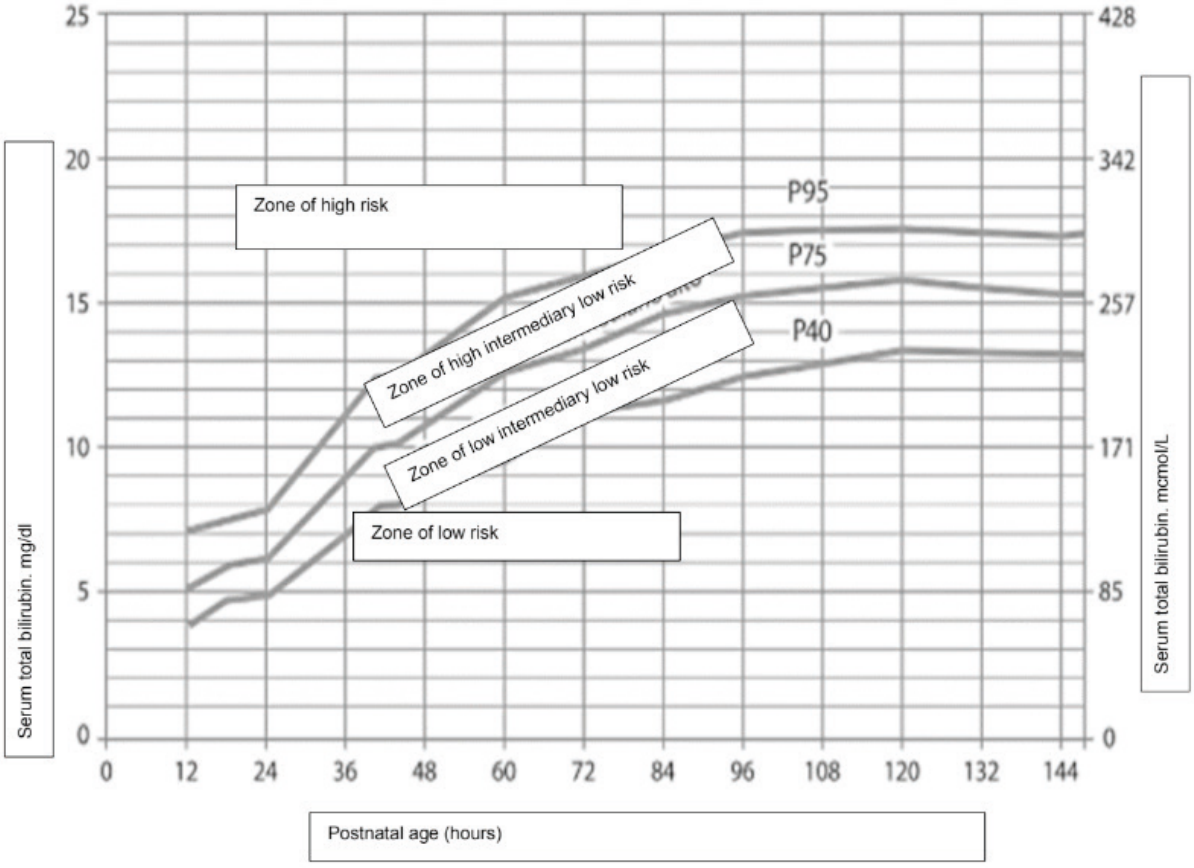
Picture 3 - Total bilirubin level (mg/dl) for indication of exchange transfusion in newborns ≥ 35 weeks of gestational age at birth. Immediate exchange transfusion must be performed if there are signs of Kernicterus (hypotonia, opisthotonos, fever or neurological cry) or total bilirubin ≥ 5mg/dl above the corresponding line.

Source: American Academy of Pediatrics. Pediatrics. 2004; 114; 297-316.23



Picture 4 - Bilirubin level (mg/dl) for indication of intensive phototherapy in newborns ≥ 35 weeks of gestational age at birth.

Source: American Academy of Pediatrics. Pediatrics. 2004; 114; 297-316.23



Picture 5 - Risk nomogram for evolution with high bilirubin levels

Through this graph, it is possible to assess the risk of evolution of newborns with total bilirubin levels > 17.5mg/dl, based on their postnatal age and their serum bilirubin level. Newborns > 95th percentile have a 40% risk of reaching this value; between 75th - 95th percentile, the risk is 13%. Between the 40th and 75th percentiles, the risk drops to 2%; and in those < 40th percentile, the risk is almost non-existent.

Source: Bhutani et al. Pediatrics. 1999; 103:6-14