

Jaundice in the newborn infant

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About half of all newborn infants born at term develop jaundice during their first days of life, and the lower the gestational age the more frequent the jaundice is. Newborns develop hyperbilirubinemia because of a large bilirubin production, low hepatic excretion and enterohepatic recirculation. At birth the newborn is not icteric. After birth, the plasma bilirubin concentration increases.

Jaundice appears first in the face and spreads from there down across the body and extremities to the palms of the hands and the soles of the feet. In newborns almost all bilirubin in plasma is unconjugated. The severity of the jaundice depends on gestational age, gender, family factors, race, nutrition, time of the first meal and frequency of meals.

Only unconjugated bilirubin is toxic. When plasma bilirubin concentration is very high, the infants can have signs and symptoms of central nervous system involvement. In severe acute bilirubin encephalopathy

(classic kernicterus), magnetic resonance imaging (MRI) shows abnormalities in the globus pallidus and subthalamic nuclei.

In recent years, the industrialized world has seen an increasing number of term or near-term infants with classic kernicterus.

At present the initial screening for jaundice is done visually. On the basis of this a possible measurement of transcutaneous bilirubin concentration is considered. If this is above a certain limit, plasma bilirubin concentration is determined. On a routine basis plasma total bilirubin concentration is determined. A screening of term and near-term infants by measurement of the transcutaneous bilirubin concentration has been proposed.

However, jaundice in the first 24 hours of life always requires the determination of plasma bilirubin. The 2004 guidelines from AAP (American Academy of Pediatrics) advise a systematic assessment before

discharge for the risk of hyperbilirubinemia. This may be done by measuring the bilirubin level using TSB (total serum bilirubin) or TcB (transcutaneous bilirubin) and/or assessing clinical risk factors.

Phototherapy is the treatment of choice. At very high plasma bilirubin concentrations, exchange transfusion is performed. Tin-mesoporphyrin is a very promising treatment, which has not, however, come into clinical use yet.

Introduction

About half of all newborn infants born at term (gestational age > 37 weeks) develop jaundice during their first days of life, and the lower the gestational age the more frequent the jaundice in the infants.

Approximately 75 % of the bilirubin production comes from heme released from hemoglobin in aged circulating erythrocytes in the reticuloendothelial system (RES) in the spleen, liver and bone marrow. The remaining approx. 25 % is created by “inefficient” erythropoiesis and from heme-containing proteins (myoglobin, catalase, cytochromes, etc.). Heme is converted by heme oxygenase into biliverdin, which is reduced to bilirubin by biliverdin reductase.

From RES bilirubin is released in plasma where it binds very tightly to albumin and is transported to the liver, where the liver cells take it up. Here and with the aid of ligandin, bilirubin is transported to the endoplasmatic reticulum, where it is conjugated to bilirubin diglucuronide by binding to glucuronic acid with the aid of uridine diphosphoglucuronyl transferase. This makes bilirubin more water-soluble and it can be excreted with the bile.

In the intestinal lumen during the first week of life, β -glucuronidase may split off glucuronic acid after which bilirubin may be reabsorbed from the intestine. Thus, there is an enterohepatic recirculation of unconjugated bilirubin.

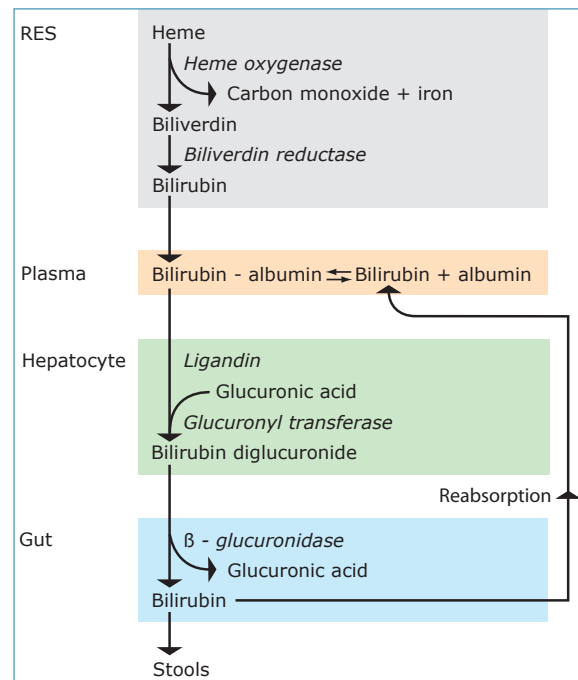


FIG. 1. Bilirubin metabolism. RES: Reticuloendothelial system

Hyperbilirubinemia in the newborn

Newborns develop hyperbilirubinemia because of:

1. a large bilirubin production, twice as large per kg bodyweight as in adults, caused by a high hematocrit and a short erythrocyte lifetime (90 days in term infants)
2. a low excretion of bilirubin, as the hepatic processes are immature
3. the enterohepatic recirculation

At birth, the newborn is not icteric, as bilirubin can pass the placenta and be excreted by the mother. At birth, the newborn's plasma bilirubin concentration is slightly higher than that of the mother, 15-40 $\mu\text{mol/L}$. After birth, the infant's plasma bilirubin concentration increases. If it exceeds 60-80 $\mu\text{mol/L}$, a yellow coloring of the skin will appear [1].

It starts in the face and spreads from there down across the body and extremities to the palms of the hands and the soles of the feet [2]. In term newborns the hyperbilirubinemia most often culminates on day 3-5 of life, in preterm newborns most often on day 5-7 of life. The reason for this is that the liver function matures and the enterohepatic recirculation decreases.

The latter because the gut is colonized by bacteria that can transform bilirubin into stercobilin, which is then excreted with the stools. The average maximum plasma bilirubin concentration in term newborns is approx. 90-100 $\mu\text{mol/L}$. In uncomplicated hyperbilirubinemia almost all bilirubin in plasma is unconjugated and the conjugated fraction is negligible [3].

The severity of the jaundice depends on:

1. Gestational age. The lower the gestational age, the more immature the liver and thus the higher the plasma bilirubin concentration.
2. Gender. Boys have a higher bilirubin concentration than girls [4].
3. Family factors. If an infant has had severe jaundice, there is an increased risk that its siblings will also get it [5].
4. Race. In average, the Mongoloid race has a higher plasma bilirubin concentration than the Caucasian race, which again has a higher concentration than the Negroid race [4].
5. Nutrition. Infants feeding on breast milk have a higher bilirubin concentration than infants feeding on formula, so-called breast milk jaundice [6].
6. Time of the first meal and frequency of meals. The earlier the infant has its first meal and the more meals it has, the lower the plasma bilirubin concentration, as the enterohepatic recirculation is thereby reduced due to a reduced gut transit time [7].

A contributing factor to an increased plasma bilirubin concentration can be polycythemia, cephalhematoma and suggillations. Additional factors can be hemolysis by isoimmunization (Rhesus and ABO blood type immunization) or spherocytosis, erythrocyte glucose-6-phosphate dehydrogenase deficiency, galactosemia, sepsis, intestinal obstruction, hepatitis, etc.

Only unconjugated bilirubin is toxic. Its toxic effect on cells is still not quite clear. In high plasma concentrations, bilirubin as acid can precipitate in phospholipid membranes. The toxicity of bilirubin is therefore considered to be pH-dependent [8].

When plasma bilirubin concentration becomes very high, infants can have signs and symptoms of central nervous system involvement, acute bilirubin encephalopathy. In phase 1, the infants may display the following clinical symptoms: Lethargy, poor sucking, hypotonia, stupor and a weak Moro reflex. A few cohort studies [9,10] have found an association between hyperbilirubinemia and subtle long-term effects in term infants, but in most studies such a relationship has not been observed.

In phase 2 (classic kernicterus) the infants may have the following symptoms: Hypertonicity, opisthotonus, pronation spasms of the arms, seizures, apnea, fever and a high-pitched cry (**Fig. 2.**). These infants almost always suffer permanent brain damage such as reduced hearing, dystonic or athetoid cerebral palsy, retarded psychomotor development and paralysis of upward gaze.



FIG. 2. The infant was born near term and had extreme hyperbilirubinemia due to Rhesus blood type immunization. He developed classic kernicterus with opisthotonus, hypertonicity, pronation spasms of the upper extremities, seizures and fever.

By kernicterus there is a preferential disposition of bilirubin in the globus pallidus, subthalamic nuclei, hippocampus, putamen, thalamus and cranial nerve nuclei, especially 3, 4 and 6 [11]. By magnetic resonance imaging (MRI), abnormalities are seen in the globus pallidus and subthalamic nuclei [12].

In recent years, the industrialized world has seen an increasing number of term or near-term infants with classic kernicterus [13, 14].

The reasons for this may be:

1. The infants are discharged earlier from the maternity ward, so that the jaundice culminates after discharge from the ward.
2. The risk of kernicterus in term or near-term infants has been underestimated.
3. Only very few doctors have seen infants suffering from classic kernicterus.
4. The number of immigrants has increased. It can be clinically difficult to assess the intensity of jaundice with dark skin.
5. More mothers wish to breastfeed their newborn babies, leading to an increased frequency of hyperbilirubinemia, so-called breastfeeding-associated jaundice [6]. This is partly because feeding on breast milk, as mentioned, leads to high plasma bilirubin concentration, partly because breastfed infants often receive less nutrition than formula-fed infants.

Monitoring

The initial screening for jaundice is done visually, assessing partly its intensity and partly how far it has progressed. On the basis of this it is decided if it is necessary to measure the transcutaneous bilirubin concentration with a bilirubinometer. This measurement is made either on the forehead or on the chest. From the instrument a bundle of light is transmitted to the skin and the reflected light is analyzed [15].

If the transcutaneous bilirubin concentration exceeds a certain limit, plasma bilirubin concentration is determined [16]. Measurement of transcutaneous bilirubin concentration is mainly employed on maternity wards in healthy term or near-term infants (gestational age 35-36 weeks), but it can with advantage also be employed on the neonatal intensive care units in infants of a gestational age > 32 weeks [16].

Due to the increased number of infants with classic kernicterus and the difficulty of assessing the intensity of jaundice in infants with dark skin, a screening of term and near-term infants has been proposed by measurement of the transcutaneous bilirubin

concentration [15], the end-expiratory carbon monoxide or a combination of both [17]. The 2004 guidelines from AAP (American Academy of Pediatrics) advise a systematic assessment before discharge for the risk of hyperbilirubinemia. This may be done by measuring the bilirubin level using concentration of plasma total bilirubin or transcutaneous bilirubin and/or assessing clinical risk factors [18].

On a routine basis plasma total bilirubin concentration is determined, and it is regarded as identical to the concentration of unconjugated bilirubin as the concentration of conjugated bilirubin in newborns without liver disease is, as mentioned, negligible [3]. Upon suspected liver disease, fractional bilirubin is determined, i.e. the concentration of unconjugated as well as conjugated bilirubin.

Determination of free bilirubin in plasma is primarily used for research purposes. Development of jaundice within the first 24 hours of life always requires determination of plasma bilirubin.

Treatment

Phototherapy

Phototherapy is the primary treatment of choice. Irradiation of the skin with blue or blue-green light transforms bilirubin into photobilirubins, which are isomer compounds of bilirubin. Whereas bilirubin is lipid-soluble and very hard to dissolve in water, photobilirubins are more polar and dissolve easily in water.

They can be excreted through the liver to the bile without conjugation. Light affects the skin to a depth of 1-2 mm [19] and the yellow coloring of the skin disappears in the irradiated areas. The infants' eyes must be covered during the treatment to avoid the risk of injuring the retina. Phototherapy has no side effects of significance, but:

1. the infants often suffer from secretory diarrhea [20]
2. there is an increased insensible water loss from the skin. Therefore preterm infants need extra fluid, which is especially important in extreme preterm infants
3. an exanthem may be observed

4. when exposing infants with liver disease to light, a gray-brown discoloring of skin, plasma and urine can be observed, a condition known as the bronze- baby syndrome. The pigments are created when exposing bilirubin and copper porphyrins to light [21]. The condition is presumably of no importance [22].

Exchange transfusion

By exchange transfusion the infant's blood is exchanged, often through the umbilical vein, with a volume twice the infant's blood volume, so that a major part of bilirubin is removed. This procedure entails a significant morbidity in the form of necrotizing enterocolitis, circulatory collapse and sepsis, even mortality.

Tin-mesoporphyrin injection [23]

This is a very promising treatment, which has not come into clinical use yet. Tin-mesoporphyrin is a heme analog that competes with heme for the binding sites of heme oxygenase. This reduces the breaking down of heme and thus the production of bilirubin, reducing the need for phototherapy considerably. It can be used prophylactically and in advanced hyperbilirubinemia. The treatment seems to have no side effects of significance.

Prevention of acute bilirubin encephalopathy

The following could presumably assist in reducing the incidence of severe hyperbilirubinemia:

1. A reconsidered view of the risk of acute bilirubin encephalopathy with very high plasma bilirubin concentrations, as it seems to be greater than generally thought.
2. Ensuring that all mothers after birth receive both verbal and written information on jaundice in the newborn infant.
3. Be more liberal in giving infant formula supplements in situations where breastfeeding is difficult to establish.
4. Screening of infants of non-Caucasian origin for the risk of developing a high plasma bilirubin concentration might be reasonable.
5. When authorized guidelines for phototherapy and exchange transfusions exist, they should be followed.

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