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Review Article

Treatment of neonatal jaundice - more than phototherapy and exchange transfusions

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Abstract. Jaundice is the most common reason for doing blood tests and starting therapy in newborn infants. In some neonates serum bilirubin levels may become excessively high, and in rare instances this may lead to brain damage (*kernicterus*). In such cases it is important to start treatment quickly. Herein we will discuss various approaches through which serum bilirubin levels may be reduced, thus potentially preventing brain damage. This paper is based on relevant publications found through a Medline search, from which a selection was made based on the authors' prior knowledge of and experience in the field. Case histories are used to illustrate the important points. Neonatal jaundice always has a foundation in normal physiology. However, the degree of jaundice may be accentuated by a number of pathological processes. These include hematomas and other occult hemorrhage, AB0- and Rhesus incompatibility, and increased enterohepatic circulation of bilirubin. In addition, genetic conditions such as galactosemia, hemolytic anemias, and Gilbert and Crigler-Najjar syndromes can significantly increase jaundice in newborn infants. Neonatal jaundice can be treated in several ways, including phototherapy, exchange transfusion, breast milk substitutes, and drugs (e.g. intravenous immune globulin and phenobarbital). By employing such therapies individually or in combination, it is possible to achieve rapid reductions of dangerously high bilirubin levels, and thus reduce the risk of sequelae. It is important to keep in mind that factors which may be unknown at the time of discharge from hospital or birthing unit can contribute to significant increases in total serum bilirubin levels after discharge. It is therefore important to evaluate an infant's risk status prior to discharge. Written therapeutic guidelines for professionals are useful adjuncts in management, and oral and/or written orientation in terms and language which the parents can understand will help them as far as the post-discharge management. A written orientation in the form of a brief handout may also be a useful tool for educating parents prior to discharge.

Key words: Newborn, jaundice, neonatal, therapy, phototherapy, pharmacology, intravenous immune globulin

1. Background

Jaundice is the most common reason for testing and treating newborn infants. The yellow color, seen in the skin and sclera, results from the accumulation of unconjugated bilirubin. In most infants this represents a normal transitional phenomenon which passes in a few days. But in some infants the bilirubin levels may become extremely high, and in these infants it is very important to start treatment without delay. Unconjugated bilirubin in its most common isomeric form IX∀ (*Z*,*Z*) has the ability to penetrate the blood-brain barrier and gain access to the brain, where it may cause permanent neurologic sequelae (*kernicterus*).

Neonatal jaundice is said to have been described in Chinese literature a thousand years ago (1). In Europe one of the earliest descriptions appears to be that of Bartholomaeus Metlinger in his book *Ein regiment der jungen Kinder* published towards the end of the 1400s (2). Johannes Orth described yellow discoloration of the basal ganglia of the brain in a neonate in 1875 (3), and in 1903/4 Georg Schmorl proposed the name *kernicterus* ('jaundice of the basal ganglia') for this patho-anatomical observation (4). In the first decades of the 20th century it became understood that this yellow discoloration of the basal ganglia had a clinical correlate in infants who survived extreme neonatal jaundice (5,6). These infants exhibited a clinical picture of choreoathetosis, paresis of upward gaze, and hearing loss. In some infants intellectual deficits were also believed to exist, though modern

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testing methods appear to show that many of these apparently developmentally challenged children do in fact have normal intellects.

Van Praagh described four clinical phases of kernicterus (7). In the first phase muscular hypotonia, lethargy, and poor sucking were observed, while in the second phase infants exhibited fever and muscular hypertonicity which might manifest as opisthotonos. In the presence of the latter signs all infants who survived developed chronic neurological sequelae. The third phase of kernicterus occurred towards the end of the first week of life, at which time spasticity gradually disappeared. Appearance of extrapyramidal abnormality, which constituted the fourth phase, took place in the second month of life or later. This neurological abnormality has usually also been referred to as *kernicterus*.

Recently a different terminology has been used, particularly as it applies to the acute signs of bilirubin effects on the brain (8). This terminology distinguishes between an early, an intermediate, and an advanced phase of acute bilirubin encephalopathy. The early phase consists of lethargy, reduced muscle tone, and poor suck, while the intermediate phase is characterized by moderate stupor, irritability, and increased muscle tone. Fever and high-pitched cry may alternate with drowsiness and hypotonicity. Hypertonicity takes the form of backward arching of the neck (retrocollis) and trunk (opisthotonos). In the advanced phase there is pronounced retrocollis/opisthotonos, shrill cry, anorexia, apnea, fever, deep stupor/coma, and occasionally seizures. Death may ensue in inadequately treated cases. While the early phase is reversible with appropriate treatment, the advanced phase is believed to be irreversible. The intermediate phase is also largely thought to be irreversible, but recent case reports appear to show a potential for complete or near-complete recovery in some such infants (9, 10). The purpose of the present paper is to suggest approaches which may hopefully aid more such infants to complete recovery.

Although European medical texts from the 1700-1800s contained many suggestions for treatment of jaundiced infants, it is likely that few if any of them where helpful (11). The first published case of successful treatment of erythroblastosis foetalis, in all likelihood a case of Rhesus immunization, came from Canada in 1925 (12). An “exsanguination transfusion” was performed by Dr. McDonald, who simultaneously removed 300 ml of blood from the anterior fontanelle and infused 335 ml of blood into the internal saphenous vein at the ankle in a 3.6 kg male infant, who recovered and did well. Performed at a time when the Rhesus blood group system was not discovered, this heroic procedure either was not repeated, or perhaps more likely, it may have been repeated, but unsuccessfully.

Following the discovery of the Rhesus blood group system by Landsteiner and Wiener in 1939, the road was paved for a scientific understanding of the mechanisms behind erythroblastosis foetalis, and for a more rational approach to treatment. The exchange transfusion pioneered by Wallerstein and Diamond (13-15) in the 1940s was first used to treat the anemia of erythroblastosis foetalis, and only a decade later did it become more widely used as a treatment for jaundice per se (16). The great breakthrough came in the 1950s with the discovery that light had a beneficial effect on jaundiced neonates (17). In the 1990s intravenous immune globulin (IVIG) started to be used as treatment for Rhesus and subsequently AB0 immunization, and has now largely replaced exchange transfusions as the first line of therapy for these conditions (18). Increased knowledge about the metabolism of bilirubin and the ways in which this may be enhanced, have resulted in the use of breast milk substitutes and phenobarbital to accelerate bilirubin excretion through bile and stool. Also, intravenous albumin to increase the binding capacity for bilirubin in serum in extreme jaundice is used by some as a bridge to exchange transfusion (19).

In the present paper we describe various ways in which neonatal jaundice may be treated, with a particular focus on rapid reduction of total serum bilirubin (TSB) levels in extreme jaundice. We use three patient cases to illustrate our points. All patients were admitted and treated for extreme jaundice, and all had complicating factors in addition to physiological jaundice.

2. Materials and methods

The basis for this paper is a Medline search from which papers were selected based on our prior knowledge as well as experience in this field. Some old references were found in the historical archive of one of us (TWRH). The paper illustrates therapeutic principles in neonatal jaundice with reference to experience from patients treated in our neonatal intensive care unit (NICU). The parents of the infants whose case histories are used have given their permission to publication of the data which are presented herein.

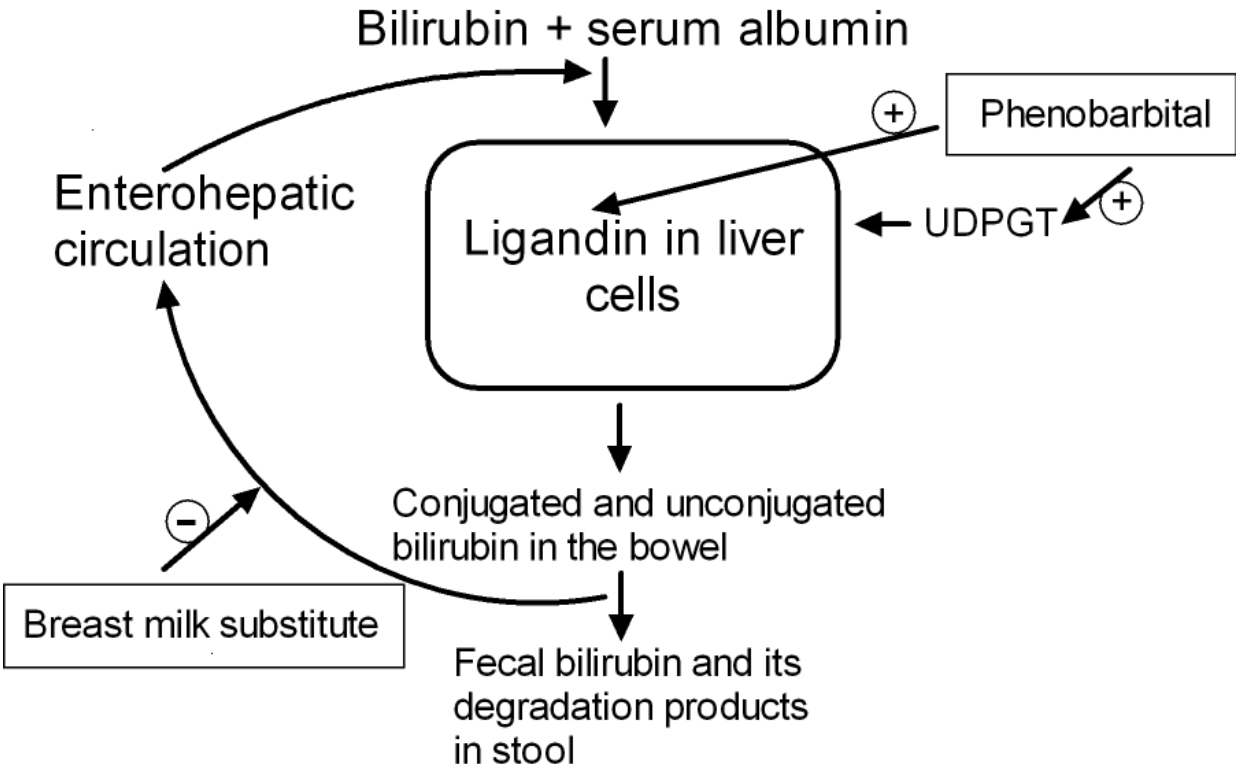

Fig. 1. Hepatic and intestinal metabolism of bilirubin.

3. Physiology and Pathophysiology

Bilirubin is produced in the reticuloendothelial system and is the end product of heme catabolism. Bilirubin binds to albumin in serum and is then transported to the hepatocytes and subsequently into these, where it is bound to ligandin. In the hepatocytes it is bound to one or two molecules of glucuronic acid (conjugated) and excreted in bile. Hyperbilirubinemia is a very common phenomenon in newborn infants and is due to the simultaneous occurrence of two distinct phenomena (20). Fetal erythrocytes have a relatively short life span (45-90 days), and this results in increased production of bilirubin (20). In addition, reduced capacity for conjugation and excretion of bilirubin through the liver during the first days of life leads to accumulation of bilirubin in the organism.

Hereditary conditions exist in which the hepatic conjugation of bilirubin is reduced due to mutations in the gene that codes for UDPGT. One of these, Gilbert syndrome, is quite common, and is associated with moderately increased concentrations of unconjugated bilirubin in serum. Individuals with Gilbert syndrome are not visibly jaundiced under normal circumstances, but may become so when bilirubin production is increased (as might occur in trauma with extravasation of blood) or when enterohepatic circulation of bilirubin is increased (as might occur during fasting or starvation). However, the Gilbert gene has been shown to contribute to more pronounced jaundice in the neonatal period (21). In Crigler-Najjar syndrome type 1 and 2 (Arias syndrome) the conjugation deficit is much more serious, and these individuals have life-long severe jaundice with high risk of bilirubin-induced brain damage.

Following excretion in the bile bilirubin is for the most part transported out with the bowel contents. However, in situations where intestinal passage is delayed or completely blocked, bilirubin may be deconjugated and reabsorbed from the bowel. This cyclical course of conjugation, excretion, deconjugation, and reabsorption is known as enterohepatic circulation (Fig. 1) (20). Increased enterohepatic circulation is believed to contribute to the phenomenon known as “breast milk jaundice” (22,23). Increased enterohepatic circulation also occurs when the newborn infant does not receive sufficient amounts of milk, and is then occasionally referred to as “breast feeding jaundice”. Bowel atresia or bowel surgery in which enteral nutrition cannot be given, has the same effect.

Increased hemolysis may occur in neonates in hemolytic anemias (e.g. G-6-PD deficiency) and from immunologic causes (Rhesus, AB0, and other blood group incompatibilities). Under such circumstances bilirubin production increases and thus also the risk that the infant will develop severe jaundice. In industrialized countries Rh-immunization has almost disappeared following the routine administration of Rhesus prophylaxis to Rh-negative women. However, it is still seen in areas where limited resources are allocated to health care. AB0 incompatibility is now the most common immunological cause for severe jaundice in the industrialized world.

Factors which may increase serum bilirubin levels in neonates:

Genetic and ethnic factors

East Asian ethnicity, Gilbert syndrome, Crigler-Najjar syndrome, G-6-PD deficiency

Maternal causes

Diabetes

Metabolic diseases

Galactosemia, hypothyroidism

Immunology

Rh, AB0, Kell incompatibility

Birth trauma

Hematomas, intracranial and other occult hemorrhage

Other circumstances

Prematurity, excessive postnatal weight loss / inadequate postnatal weight gain, breast milk-assosiated jaundice, bowel disease / atresia, bile duct and liver disease, infections

In the bilirubin literature a distinction is sometimes made between 'physiological' and 'pathological' jaundice. Such a distinction is important as a didactic aid to understanding neonatal jaundice, but cannot always be applied to jaundice in specific infants. Thus, what we measure as total serum bilirubin (TSB) is the sum of the bilirubin produced by normal underlying physiology *plus* any added production from pathological processes. It may be helpful to think of the normal physiological underpinning as a mountain, and the pathological conditions as a glacier which caps the mountain. Mountains may vary in height and glaciers in thickness, resulting in wide variations in the total altitude at the peak of the glacier. The person who looks at the mountain with his bare eye cannot tell how much of the altitude is created by rock and how much by ice. A similar situation exists for jaundice in the newborn infant. With this caveat in mind, the text box below lists some conditions which may occasionally contribute to increased jaundice in newborn infants, and which it may be necessary to examine for in infants with high or persistently elevated TSB levels.

4. Therapy

Jaundice is an everyday occurrence in maternity wards and NICUs, and is usually not regarded as an emergency. Therefore it may be easy to forget that *extreme* jaundice is an emergency which untreated may lead to devastating sequelae. In such circumstances it is of the utmost importance that treatment be started aggressively and without delay.

4. 1. Exchange transfusion

A "double volume" exchange transfusion will remove >90% of erythrocytes which are antibody labeled through Rhesus or AB0 immunization, as well as antibody which is currently found in the circulation. However, antibody which is outside the circulation during the exchange will subsequently equilibrate to the blood and there bind to new red cells which are released from the infant's hematopoietic organs. Therefore, it is not uncommon to have to repeat an exchange transfusion due to such "rebound". Exchange transfusions were the first really effective mode of therapy for infants with jaundice, and were frequently performed in NICUs all over the world. However, the need for exchange transfusions was much reduced following the introduction of phototherapy, and almost disappeared following the introduction of immunotherapy, first for the pregnant woman and subsequently for the antibody-affected infant (18).

Exchange transfusions are still called for in cases of extreme jaundice not controlled by phototherapy, when immune globulin is without adequate effect, and in infants who are critically sick (severe anemia, hydrops, neurological symptoms). Our own experience, although admittedly anecdotal, suggests that intravenous immune globulin (see below) is less likely to be effective in Rhesus immunized infants when the hemoglobin value at birth is less than 10 g/dL. Some would argue strongly for performing an exchange transfusion in infants with very high TSB levels, even if phototherapy and intravenous immune globulin are successful in significantly

reducing the TSB, and point to the medico-legal vulnerability if such an infant should develop chronic kernicterus. To the best of our knowledge there are no evidence-based answers to this predicament, and individual judgment must be used.

For a technical description of exchange transfusion we refer the reader to handbooks. Suffice it here to say that in cases where an exchange transfusion is thought to be necessary, obtaining the necessary tests and ordering the blood must be counted as an emergency procedure. Order a volume of blood corresponding to 160-170 mL/kg body weight, and add at least 100 mL for the dead space in the tubing and blood warmer. In our experience it is hardly ever possible to get the blood and be ready for the procedure in less than 2 hours, and it often takes longer. This is a long time to wait in an infant with extreme jaundice, and particularly if that infant exhibits signs of intermediate to advanced stage acute bilirubin encephalopathy (8). In such circumstances effective and aggressive interim measures are called for.

4. 2. Phototherapy

It is fair to say that phototherapy was discovered by nurse Jean Ward at Rocheford Hospital, Essex, England in 1956, although the findings were published by the doctors who worked with her (17). She liked to expose the newborn infants in her ward to the sun, and observed that jaundiced skin exposed to sunlight appeared less yellow than skin which had been covered by clothing or diapers. Further studies then showed that light had a therapeutic effect in neonatal jaundice, although the mechanisms were not fully understood initially. We now know that light converts the fat -soluble bilirubin IX∀ (*Z*, *Z*) to more polar isomers (*E*, *Z*; *Z*, *E*; *E*, *E;* and lumirubin), which are more soluble in water. It is the increased solubility in water which allows bilirubin photoisomers to be excreted in bile and urine without needing to be conjugated in the liver (24).

Phototherapy is without doubt the most commonly applied treatment in newborn medicine. Data vary depending on the underlying epidemiology of neonatal jaundice, inclusion or exclusion of premature infants in the data base, practice parameters and therapeutic guidelines, but may be close to 10% of all newborns receive phototherapy in some settings (25).

Bilirubin circulates in the blood and thus also in the capillaries of the skin. The higher the TSB, the more bilirubin is affected by light. Consequently, the effect of phototherapy is greater (26). Another important determinant of phototherapy effect is the *irradiance*. This is typically measured in W/cm^2 or $\mu W/cm^2/nm$. Irradiance should be measured on the skin surface which faces the light source. Fluorescent tubes can be brought as close to the infant as 10 cm, provided proper surveillance of body temperature is carried out. The effect of phototherapy increases with irradiance (27). Although the irradiance does not need to be measured for every baby given phototherapy, it should be measured at intervals. This will serve as an additional control that the energy output is maintained, or a reminder to change light bulbs when their useful life is nearing its end. It can also serve a didactic purpose in showing the staff how the irradiance delivered to the baby can be optimized. Thus, every unit which offers phototherapy should ideally possess a light meter appropriate for the wave length area of the phototherapy unit.

Perhaps the most important concept in practical phototherapy is *spectral power* (irradiance multiplied by the size of the irradiated area). This concept serves to remind us that the larger the skin area irradiated by the phototherapy lamps, the more bilirubin molecules will be impacted by the light and thus exposed to possible change. On the other hand, skin which is covered up (hats, diapers, walls of "nests") will not be part of the phototherapy process. In our nursery experience, this is one of the most common failures in the application of phototherapy.

The primary goal of phototherapy is to lower TSB levels, or failing that, to keep them from increasing unacceptably. However, as the polar isomers formed through the action of light on the bilirubin molecule are, based on their physicochemical characteristics, believed to be less likely to cross the blood-brain barrier, useful effects of phototherapy may be achieved even before TSB levels start to go down (25,28). Bilirubin elimination is the combined result of rates of formation and rates of clearance of the polar isomers. The wavelength of the light employed in phototherapy is an important determinant of the efficacy. Although bilirubin absorbs light more strongly around 460 nm wavelength (blue light), penetration into the skin increases with increasing wavelength (25). Thus, light in the 460-490 nm wavelength range is believed to be most effective.

Phototherapy can be delivered by different types of lamps, all of which have some advantages and some drawbacks. It is important that those who employ phototherapy in practice be aware of the strengths and weaknesses of their

particular setup. Commonly used today are fluorescent lamps, quarts lamps, and fiberoptic units, while units employing photodiodes are the most recent arrival on the scene. Most phototherapy units require the infant to be treated away from the mother's bed, as the strong light will deprive the mother of her much-needed rest. From this perspective, the advantage of fiberoptic units is that the baby can be treated next to the mother's bed, though some report that they find the noise from the cooling fan in the lamp-house disturbing (personal experience).

Flurorescent lamps are widely used, and can be either white ("daylight"), blue or "special blue". Green, turquoise, and other hues have also been tested (29-31), but have not found wide popularity. Special blue lamps are more effective than blue or white lamps, but they are more expensive, a fact which may pose a challenge in countries where limited resources are available for health care. Phototherapy with daylight fluorescent lamps can typically be expected to deliver 8-10 $\mu W/cm^2/nm$ (32), but a well-configured phototherapy unit with daylight lamps can deliver more than 20 $\mu W/cm^2/nm$ (33). Special blue lamps can be expected to deliver >30 $\mu W/cm^2/nm$ (32), and with use of reflecting surfaces and short distance from lights source to the skin these irradiance values can be doubled (34,35).

Inadequate maintenance of the phototherapy units (failure to clean filters, failure to replace worn-out bulbs, purchase of cheaper and improper bulbs) can result in significantly lower values (36). Thus, in many units there is likely to be room for significant improvement. Indeed, the simple expedient of changing bulbs at specified intervals, cleaning optical filters, moving the lamps close to the infant, and providing reflecting surfaces in and around the beds can significantly improve the yield of phototherapy.

Fiberoptic pads or vests provide light with high irradiance and no risk of overheating. They are also easy to deploy for home use. The concept of spectral power explains why fiberoptic pads have certain limitations. Thus, although the irradiance supplied by a fiberoptic pad may be more than adequate, the irradiated area can only be as large as the size of the pad. In moderate jaundice the effect may be adequate, but in extreme jaundice where there is a need to "attack" as many bilirubin molecules as possible with photons, a fiberoptic pad is inadequate by itself. It may, however, be a very useful adjunct to therapy if the infant is positioned on the pad and the other body surfaces are exposed to fluorescent or diode lights.

Regarding spotlights, these provide a circular pool of light where the energy is highest in the center and drops off significantly towards the edges of the light circle (37). Thus, while a small premature infant may be adequately covered by one spotlight, and is not likely to move away from the high-energy center of light, a bigger baby will not have high energy delivery to large parts of its body, and may move away from the light. Also, spotlights cannot be moved closer to the infant because of the risk of overheating and burns. Phototherapy units with photodiodes as light sources are seeing increasing use. They provide blue light at a suitable wavelength and with high irradiance when set at maximal output. They can be brought close to the infant without risk of overheating.

The use of additional fluids during phototherapy was based on older literature suggesting that there was increased fluid loss from the baby during phototherapy. Newer data suggest that water loss is not increased in thermally stable infants during phototherapy (38). In our unit we discontinued routine fluid supplements during phototherapy a decade ago, and follow the state of hydration by conventional clinical and laboratory means. We have not seen any untoward effects of this policy. Home phototherapy is used by some. The advantage is that the baby does not need to be in an expensive (and perhaps scarce) hospital bed. The family may also appreciate having the baby at home, assuming the concept of a medical treatment applied at home does not frighten them. A different perspective on phototherapy in the home is that this treatment is used to reduce the risk of neurotoxicity, and it might be argued that an infant at risk of such toxicity should be under medical supervision. Whether there are actual savings involved in using home phototherapy will depend on health care costs and how health care is financed in the particular setting.

Many studies have shown that phototherapy is both effective and safe. Although phototherapy in the individual patient is not very resource intensive, jaundice is the most common reason why newborn infants need medical treatment. On a societal level significant resources are therefore invested in treatment of neonatal jaundice. Thus, it makes sense to have written guidelines for such treatment, and to make every effort to keep the treatment period as short as possible.

4. 3. Intravenous immune globulin (Octagam®)

In antibody-mediated neonatal jaundice (AB0, Rh, Kell) maternal antibodies bind to the infant's

red cells. When these arrive at the reticuloendothelial system, they will be destroyed. This, in the next instance, leads to increased bilirubin production. Historically this type of neonatal jaundice was often treated with an exchange transfusion. A new treatment principle consists of giving these infants IVIG (39). The mechanism of action is believed to be analogous to that of immune thrombocytopenia - the immune globulin covers the antibodies bound to the cell surfaces. In a recent study from our own NICU we have shown that this treatment very significantly reduces the need for exchange transfusion (18).

We give immune globulin (Octagam®) 500 mg/kg iv over 2h, repeating the dose if necessary. If there is reason to suspect particularly strong immunization, 1 g/kg may be used (8). IVIG seems to be very useful in cases of mild to moderate hemolysis/immunization. When immunization is very strong, as evidenced by high maternal antibodies or a birth hemoglobin of <9-10 g/dL, our anecdotal experience suggests that an exchange transfusion may still be required. Side effects of IVIG are rare, but transitory hypo- or hypertension has been described, along with transitory fever or flushing (40). Long term risks are likely to be comparable to those involved in the use of other blood products.

4. 4. Reduction of enterohepatic circulation

Breast milk contains a ß-glucuronidase which, by uncoupling bilirubin from its binding to glucuronic acid (de-conjugation), enhances reabsorption of bilirubin from the gut (23). Both L-aspartate and breast milk substitutes which contain casein hydrolysates inhibit the ß-glucuronidase activity and have been shown to increase the excretion of bile pigments in faeces (22). Infants who receive regular breast milk substitutes also appear to have less jaundice than those who are breast fed (41). It is possible that the protein hydrolysates contain more binding sites for bilirubin, but this is currently a speculation. If the production of breast milk is delayed and the infant receives too little milk, this may also result in increased reabsorption of bilirubin from the gut (breast feeding jaundice).

Although the mechanism for breast milk jaundice has yet to be fully elucidated, it has been well documented that breast milk substitutes given in lieu of, or as a supplement to breast feeding, may reduce the degree and duration of jaundice in infants believed to be suffering from this problem (41).

The available data suggest that reduction of enterohepatic circulation of bilirubin is an important mechanism for this therapeutic effect. As interruption of breast feeding may disturb mother-infant bonding and impede breast milk production, we try to avoid this. Instead, we have chosen to use 5 mL of Nutramigen® after each breast meal. It is likely that other breast milk substitutes may also be used with similar effect. By giving this after breast meals we may achieve the desired effects without interfering with the mother's breast feeding pattern.

4. 5.Enzyme induction

It is well known that many enzymes are inducible. This also applies to the enzymes involved in binding and conjugation of bilirubin in the liver. Thus, treatment with phenobarbital will increase both the concentration of ligandin and the activity of UDPGT in liver cells (20). This leads to increased uptake of bilirubin in liver cells and increased conjugation and excretion into the bile. In a variant of severe genetic insufficiency of UDPGT (Crigler-Najjar syndrome type 2 [Arias syndrome]), treatment with phenobarbital may stimulate UDPGT activity sufficiently that brain toxic levels of TSB are avoided (42).

Phenobarbital treatment may be considered as an adjunct when TSB values remain high over more than 1-2 weeks, or when bilirubin values rebound repeatedly after treatment with e.g. phototherapy (43). The drug should only be given for 3-5 days in a dose of 5 mg/kg/day orally. We prefer to administer this drug in the evening.

5. Case reports

Patient 1. A boy born to a primiparous, previously healthy, woman through uncomplicated vaginal delivery at 36 weeks gestation, BW 3590g, Apgar score $9^1/9^5$. At 3h of age the infant developed apneas and was transferred to our NICU where hemorrhages were diagnosed, both in the brain parenchyma and on the brain surface. He was discharged home at 9 days of age, but readmitted following an outpatient visit on day 12.

He had not shown any evidence of drowsiness or cerebral irritability, but was observed to be extremely jaundiced, and his TSB was 468 micromoles/l. He was immediately put in intensive phototherapy, and given IVIG plus Nutramigen® by mouth. IVIG was given because the mother-infant blood group constellation suggested the possibility of AB0 incompatibility (mother's blood group 0 Rh+, the infant's B Rh-).

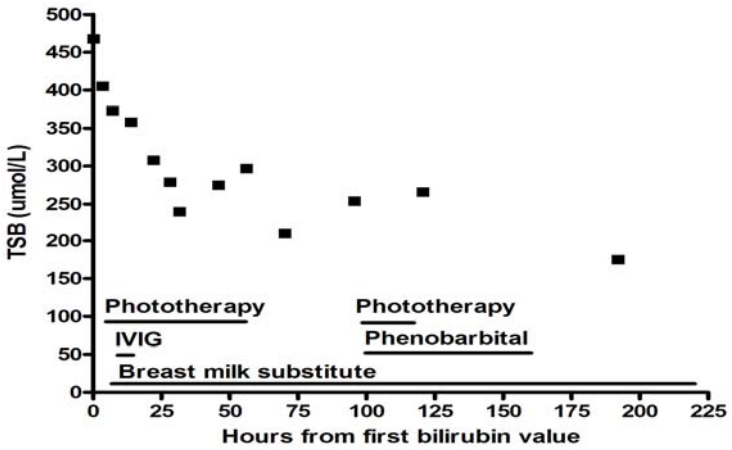

Fig. 2. Course of TSB in case 1 during treatment with phototherapy, IVIG, Nutramigen®, and phenobarbital. TSB fell by 40% during the first 24 h. On the 5th day after admission TSB rose again, and it was assumed that hematomas were contributing to this through increased bilirubin formation. Phenobarbital was given to augment bilirubin excretion, and with good effect.

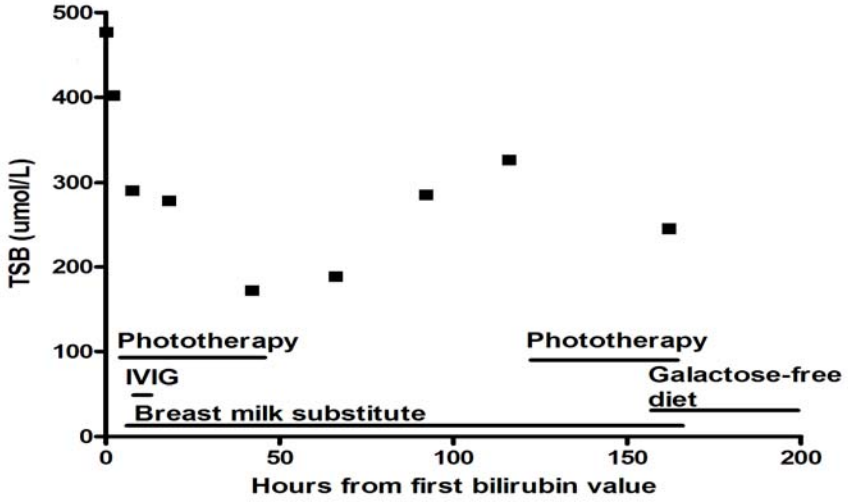

Fig. 3. Course of TSB in case 2. The mother-infant blood group constellation suggested AB0 incompatibility as a cause for the infant's extreme jaundice, though DAT was negative. In addition, there was a significant postnatal weight loss - 13% of birth weight. The infant was treated with phototherapy, IVIG, and Nutramigen®. TSB fell 40% during the first 8 h. The infant was subsequently diagnosed with galactosemia, and treatment was supplemented with a galactose-free diet.

The effect of the treatment is illustrated in Fig. 2 The child has been normal on subsequent follow-up.

Patient 2. The mother was a primipara and had been healthy throughout pregnancy. A girl was born by uncomplicated vaginal delivery at 38 weeks gestation, Apgar score was $9^1/10^5$, BW 3410g. The infant was breast fed and was discharged home at 3 days after an unremarkable stay in the maternity ward. After a day at home she began to vomit, and to the parents she gradually started to appear both cyanotic and jaundiced. She was hypotonic and on the day of admission was reported to have had an attack of backward arching both of neck and body (opisthotonos) lasting 15-20 seconds. She was brought to the maternity unit where a TSB of 489 micromoles/l was documented. She was emergently transferred to our NICU for further treatment; her admission weight was 2980g and TSB was 477 micromoles/l. Initially we suspected AB0 incompatibility, and she was treated with phototherapy, IVIG, and Nutramigen® per os with good effect (Fig. 3). On

the fifth day after admission she once again needed phototherapy, which was continued until satisfactory values of TSB had been obtained. An increasing fraction of conjugated bilirubin raised suspicion of metabolic disease and a diagnosis of galactosemia was entertained on day 12 of life, and subsequently confirmed by biochemical analyses. A galactose-free diet had been instituted on clinical suspicion even before the diagnosis had been confirmed, and has been followed up. At the age of 2 years she had delayed speech development, as frequently seen in children with galactosemia. Otherwise her neurological development has been within normal range, showing no evidence of bilirubin-associated brain damage.

Patient 3. The third child of a mother whose first child received phototherapy for neonatal jaundice. The second child was stillborn at 29 weeks of pregnancy. The case patient was a boy born vaginally at 37 weeks gestation, BW 3532 G, Apgar score $10^1/10^5$. He was admitted to the NICU at 3 days of age, weighing 3228 g, jaundiced and feeding poorly. His TSB was 449 micromol/L, DAT was positive, and AB0 incompatibility was confirmed. He had no neurological symptoms. He was treated with phototherapy, IVIG, and Nutramigen®. However, TSB began to rise again, and the infant was given phenobarbital po (Fig. 4). When asked specifically, the father confirmed that he had Gilbert syndrome, though this information had not been obtained neither in the obstetrical nor the neonatal chart. The parents declined genetic studies of the infant.

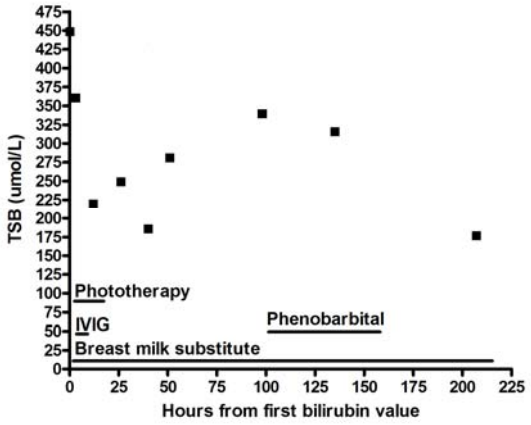

Fig. 4. Course of TSB in case 3 during treatment with phototherapy, IVIG, Nutramigen®, and phenobarbital. TSB fell approximately 50 % during the first 12 h. However, the TSB values rebounded, and a diagnosis of Gilbert syndrome was suspected based on the father's history. Phenobarbital was given for a few days with good effect.

6. Discussion

Treatment of jaundice in the newborn infant requires solid knowledge both about the pathophysiology and treatment options in this condition. In Norway the Norwegian Pediatric Association has formulated a national consensus on treatment which may be found on the web (http://www.legeforeningen.no/asset/32991/1/32991_1.pdf). All infants who qualify for therapy according to these guidelines can reasonably be regarded as deviating from normal variation, and in these we routinely determine blood groups on mother and infant as well as DAT as a screening for blood group incompatibilities.

The cases described above illustrate how, in the presence of very elevated TSB levels or an unusual course, the practitioner needs to think in terms of causes which may contribute to this. In case 1, both AB0 immunization and sequestration of blood were possible contributory causes. In addition to phototherapy and IVIG for possible isoimunization, Nutramigen® was used to increase enteral excretion of bilirubin. In case 2, where clinical suspicion of acute intermediate phase bilirubin encephalopathy (44) was entertained, we used the same treatment options. In addition, significant postnatal weight loss may have contributed to increased enterohepatic circulation in this infant (Fig. 1). An unusual course as far as serum bilirubin values also raised suspicion of metabolic disease, which was confirmed.

In case 3 the diagnosis of AB0 incompatibility seemed certain, and the infant received phototherapy and IVIG, as well as Nutramigen®. Rebound of TSB values raised the possibility of a variant in bilirubin excretion, and oral treatment with phenobarbital for enzyme induction proved efficacious. The fact that the father turned out to have known Gilbert syndrome, makes it quite likely that the infant may have the same disorder. Gilbert syndrome is not unusual (45), though many may not be aware that they have this condition. As confirmation of this diagnosis would not have had any therapeutic implications for this infant, the parents' reluctance as far as genetic testing was obviously respected.

Unconjugated bilirubin which is not bound to albumin is neurotoxic, and visible yellow coloring of the brain's basal ganglia gave rise to the term *kernicterus*. The clinical correlate consists of choreoathetosis, gaze paresis, neurogenic hearing loss, and developmental delay in a minority. Newborn infants with pronounced jaundice and significant neurological symptoms are, with modern terminology, said to have acute

intermediate to advanced bilirubin encephalopathy (44). Whether reversibility of brain toxicity is possible under these circumstances has been debated. However, there are some case reports which support the possibility of reversal (9,10). Thus, in case 2 there were neurological symptoms (opisthotonos) compatible with acute intermediate bilirubin encephalopathy (10). The child, who is now >2 years old, does not have neurological sequelae known to be associated with bilirubin toxicity, and this case supports the concept of reversibility of acute bilirubin neurotoxicity in some infants. Emergent and aggressive intervention is therefore called for in infants with such symptoms.

In infants with extreme jaundice and neurological symptoms phototherapy is an emergency procedure. Phototherapy is more effective the higher the TSB value, and rapid conversion to photoisomers can be expected (28). As bilirubin photoisomers are more polar than the normally predominant IXα (*z,z*) isomer, conversion to photoisomers per se should theoretically be neuroprotective, although this has not been tested experimentally.

If phototherapy is not effective in a case of extreme jaundice, it is necessary to check the technical equipment and set-up, including measurements of irradiance. Also, one should consider whether additional work-up or studies may be indicated. Most jaundiced infants are otherwise healthy, but if risk factors are present (see text box) they may worsen and/or prolong the hyperbilirubinemia. In our three case reports we have given examples of such conditions which, if they are present, may suggest a need for supplementary therapies.

7. Conclusions/ Recommendations

Extreme jaundice requires emergency intervention in order to prevent lasting neurological damage. The first step is always phototherapy, which can be expected to be more effective the higher the TSB, and will result in biliary and urinary excretion of polar bilirubin isomers. In addition, it is possible that water soluble bilirubin isomers may be less able to enter the brain.

A breast milk substitute should probably be given routinely in extreme jaundice, as long as there are no direct contraindications to enteral nutrition (22). This will reduce enterohepatic circulation. Also, in extreme jaundice there should be a low threshold for giving IVIG if there is reason to suspect blood group incompatibility, even if DAT is not positive. A brief course of phenobarbital or another enzyme inductor may be considered in cases where TSB remains high, or when TSB rebounds rapidly and significantly after a treatment period. The family and case histories need to be explored for hereditary or metabolic conditions which increase the risk of hyperbilirubinemia (hemolytic anemias, Gilbert syndrome, Crigler-Najjar syndrome, galactosemia).

The risk for significant neonatal jaundice should always be assessed prior to discharge from a maternity ward or neonatal unit (46). This is of particular importance if mother and infant are discharged within the first three days after birth. An information leaflet is a useful adjunct to predischarge orientation of the parents. In the neonatal subgroup of the Norwegian Pediatric Association we have prepared a leaflet which is available as a download from the internet, and which can be used and reproduced freely by all NICUs and maternity wards in the country. An English version of this brochure is also available (http://www.legeforeningen.no/asset/43831/1/43831_1.pdf), and readers who find this useful are welcome to download and use, adapt, and/or translate this to suit their own local needs.

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