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Current Drug Treatment Options in Neonatal Hyperbilirubinaemia and the Prevention of Kernicterus

Firmino F. Rubaltelli

Division of Neonatology and Neonatal Intensive Care Unit, Department of Paediatrics, University of Florence School of Medicine, Florence, Italy

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Abstract

Neonatal jaundice is a frequent problem in neonatology, but with the advent of phototherapy which has simplified its treatment, it no longer represents a major concern. Early hospital discharge of neonates has now resulted in a re-emergence of kernicterus.

Neonatal jaundice is principally the result of a transient deficiency of bilirubin conjugation, of a partial deficiency of hepatic bilirubin uptake and intracellular transport and of an increased enterohepatic circulation of the pigment. The fact that bilirubin production in the neonate is 2 or more times greater than in the adult per kilogram of bodyweight represents the mainstay of this condition.

Prevention of kernicterus in full term infants is based on the detection of neonates at risk for developing hyperbilirubinaemia, and can be accomplished with simple tests performed on umbilical cord blood such as blood type, Rh, Coombs' test and glucose-6-phosphate dehydrogenase, in order to detect haemolytic diseases. The daily evaluation of transcutaneous bilirubin measurement gives additional information on the rise of serum bilirubin level, and can help to distinguish physiological from nonphysiological hyperbilirubinaemia. A signifi-

cant hyperbilirubinaemia is more frequent in infants born before term, and in neonates who do not feed well and lose more than 10% of bodyweight.

In preterm infants the typical clinical feature of kernicterus is seen very rarely, and kernicterus is now a very infrequent postmortem observation. Since it is very difficult to distinguish the effects of bilirubin from other potentially toxic factors, it is difficult to give guidelines for the treatment of jaundice in very low birthweight infants other than to keep the serum bilirubin levels to a lower level than in full term infants (e.g. 10 mg/dl lower than in full term babies).

The intramuscular administration of a single dose of Sn-mesoporphyrin (6 μmol/kg bodyweight) in healthy term or near-term infants seems to be a promising treatment modality for controlling hyperbilirubinaemia.

Kernicterus[1] is an encephalopathy resulting from the deposition of unconjugated bilirubin in the nervous system at any age, but it is rather rare after the neonatal period. Infants with kernicterus present with athetoid cerebral palsy, severe motor delay, severe sensoneuronal hearing loss, dysarthria and mental retardation in about one-fourth of patients.

The most characteristic pattern of the neuropathological lesions involves the globus pallidus, subthalamic nucleus and hippocampus. Magnetic resonance imaging shows abnormally high intensity areas in T2-weighted images of the posteromedial border of the globus pallidus bilaterally.[2]

Abnormalities in auditory brainstem response might precede clinically symptomatic bilirubin encephalopathy.[3] However, kernicterus shows its complete clinical feature in term infants. In preterm infants, bilirubin encephalopathy has less definite clinical manifestations, and it is very often difficult to attribute neurological signs to intraperiventricular haemorrhage, periventricular leukomalacia or bilirubin toxicity. In addition, it is important to note that most children who are deaf or have athetoid cerebral palsy do not have bilirubin encephalopathy.[4]

1. Types of Treatment

There are currently 2 mainstays of therapy for neonatal hyperbilirubinaemia: phototherapy (PT) and exchange transfusion (ET) [table I]. In the search for pharmacological therapies and preventive measures for neonatal jaundice, metalloporphyrins (haem analogues that inhibit haem oxygenase, the rate-limiting enzyme in the formation of bilirubin from haem) have been synthesised and studied. Tin-mesoporphyrin (SnMP) has proven to be a very powerful inhibitor of haem oxygenase, and is being used clinically (see also section 2.4).[12-14]

The ET, performed when serum bilirubin concentration approaches or reaches 20 mg/dl in all cases of unconjugated hyperbilirubinaemia, almost totally eliminates the kernicterus, a well known clinical manifestation resulting from such high bilirubin levels. After the advent of PT, the number of ETs performed has decreased considerably; thus today, many paediatric residents have never performed an ET.

Complications from ET are not rare. They occur in 1 to 5% of patients, while mortality directly as-

Table I. Historical records of mainstays of therapy in neonatal hyperbilirubinaemia

First exsanguination transfusion of the neonate (exsanguination from the anterior fontanelle and transfusion into the internal saphenous vein)	1925	Hart[5]
First exchange transfusion through the umbilical vein	1947	Diamond[6]
Phototherapy	1958	Cremer et al.[7]
First double phototherapy	1973	Rubaltelli[8]
First fibre optic phototherapy	1990	Gale et al.,[9] Rosendfel et al.[10]
First clinical use of metalloporphyrins in Crigler-Najjar disease type 1	1989	Rubaltelli et al.[11]
First clinical use of Sn-mesoporphyrin in neonates	1995	Kappas et al.[12]

cribed to ET is approximately 0.3%.[4] PT is generally used (a) to control the rise of serum bilirubin in developmental and haemolytic jaundice in full term neonates, and especially in preterm infants who may develop bilirubin encephalopathy at relatively low serum bilirubin concentrations, and (b) to lower the bilirubin level in otherwise healthy near-term neonates before they are discharged from the hospital.

It is now accepted that the old value of 20 mg/dl (342 μmol/L) of serum (or plasma) total bilirubin concentration (STB) recorded in the 1960s corresponds to the actual value of 25 mg/dl (428 μmol/L) obtained by direct spectrophotometry (bilirubinometer).[15] However, there are substantial differences between plasma bilirubin concentrations determined by high performance liquid chromatography and spectrophotometry.[16] Moreover, for clinical purposes, the determination of total plasma bilirubin concentration by spectrophotometry (bilirubinometer) in nonhaemolysed samples is considered correct.

1.1 Phototherapy

After the first observation by Cremer et al.[7] on the effect of blue light in reducing serum bilirubin level, PT became very popular, first in Europe and South-America and later in the US and Canada. Under the effect of light, bilirubin is rapidly transformed in a configurational photoisomer (4*Z*,15*E* bilirubin), which is water soluble, bound to albumin and slowly excreted with the bile through the gastrointestinal tract, where it can spontaneously reisomerise to native bilirubin. Between rings A and B of bilirubin, an irreversible intramolecular cyclisation can occur resulting in lumirubin or cyclorubin, which seems to be the major route by which bilirubin is eliminated with PT. The excretion (without conjugation) in bile and urine is very rapid.[17] Blue lamps (Philips F20T12/BB) are the most efficient source of light for PT. The irradiation can be measured at skin level with a radiometer and should be between 5 and 15 $\mu W/cm^2$ at 425 to 475nm. Double or pan-phototherapy is a more efficient way to administer PT.[8]

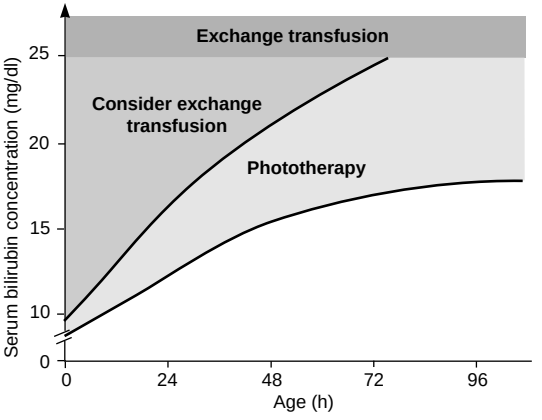

Fig. 1. Guidelines for the management of hyperbilirubinaemia in the healthy term infant according to the Italian Society of Neonatology (modified from Rubaltelli et al.[18])

1.2 Exchange Transfusion

Before the advent of PT, the indication for ET was a bilirubin level of 20 mg/dl. Today, ET is indicated when it is urgent to correct both severe anaemia (cord haemoglobin level ≤11 g/dl) and hypoalbuminaemia at the same time, and to stop haemolysis due to antibodies against blood red cells.

If the bilirubin level is rising at a rate greater than 1 mg/dl/h despite intense PT, ET (double-volume) is indicated (fig. 1).

1.3 Intravenous Immune Globulin

Intravenous immune globulin (IVIG) reduces jaundice in many cases of neonatal isoimmunisation.[19,20] The mechanism of IVIG is probably similar to that found in neonatal isoimmune thrombocytopenia, such as the blockade of immunoglobulin constant fragment (Fc) receptors and resultant inhibition of haemolysis of antibody-coated erythrocytes. The recommended dose is 500 mg/kg bodyweight of human virus inactivated IVIG, infused over a 2-hour period. The infant must be closely monitored for possible adverse effects, with particular attention to heart rate and blood pressure. Informed consent must be obtained from parents since this treatment is still experimental.

This type of treatment is not always successful; infants with a bilirubin rate of rise of ≥1 mg/dl/h are at risk for not responding to IVIG administration.

1.4 Pharmacological Approaches

There are many pharmacological approaches to the prevention and/or treatment of neonatal hyperbilirubinaemia. Many of these, such as agar, cholestyramine and activated charcoal to interrupt the enterohepatic bilirubin circulation, and phenobarbital to induce UDP-glucuronosyltransferase, are no longer used (with the exception of patients with Crigler-Najjar disease).

Bilirubin oxidase, an enzyme that degrades bilirubin to biliverdin, dipyroles and other products, administered by enteral feeding or intravenously, is still experimental.[21,22]

A different approach, intended to reduce bilirubin production rather than increasing bilirubin elimination, is to block haem oxygenase, the key enzyme in bilirubin synthesis. Various metalloporphyrins have been studied, in particular tin-protoporphyrin and SnMP (Stanate®) [6 μmol/kg bodyweight, given intramuscularly].[11-14]

In a series of clinical trials it has recently been demonstrated that a single small dose of SnMP, administered shortly after birth, can significantly moderate the severity of hyperbilirubinaemia and reduce the need for PT.[12] The only dose-limiting adverse effect is a transient, cutaneous photosensitivity.[12]

2. Therapeutic Strategies in the Treatment of Hyperbilirubinaemia Due to Different Clinical Situations

2.1 Breast-Feeding Jaundice

The association between neonatal hyperbilirubinaemia and breast-feeding has been reported by numerous authors but not confirmed in large series of full term neonates.[23] It is possible that jaundice in breast-fed infants is not associated with breast-feeding but rather with the caloric deficiency that is sometimes found in neonates who are breast-fed in accordance with a rigid time schedule rather than on demand[23] (tables II to IV).

Severe unconjugated hyperbilirubinaemia in breast-fed neonates who have been discharged from hospital very early raises concern among paediatricians. The possible explanation for a rather severe and unexpected jaundice is the fact that an insufficient intake of breast milk (caloric deprivation) increases the activity of the haem oxygenase, the key enzyme in bilirubin biosynthesis. In the author's opinion, it is mandatory to organise a serum bilirubin check at least the day after discharge in order to decide if further controls are necessary.

Maisels and Newman[4] documented the occurrence of classical kernicterus in 6 near-term, otherwise healthy, breast-fed infants. The recorded peak of bilirubin levels occurred 4 to 10 days after birth and ranged from 39 to 49.7 mg/dl. It is worthy of note that within their study one patient developed opisthotonos, high-pitched cry, hypotonia and poor head control after the exchange transfusion. Another infant presented to the physician's office at age 10 days because of jaundice. After the first exchange he had seizures, and later opisthotonos. A third patient also had seizures after 2 exchange transfusions even though neurological signs were present at the admission to the hospital on day 4. Another patient, whose bilirubin serum concentration was 41.4 mg/dl, received 3 exchange transfusions; subsequently he had a high-pitched cry, increased muscle tone and a stiff neck.[4]

Table II. Influence of breast-feeding on neonatal hyperbilirubinaemia: characteristics of study groups. The figures given are mean± SD; none achieved statistical significance (from Rubaltelli,[23] with permission)

	Bilirubinaemia	
	≤12.9 mg/dl	>12.9 mg/dl
Weight at birth (g)	3378 ± 411.08	3303.02 ± 497.4
Weight loss		
third day (g)	139.08 ± 68.1	153.30 ± 51.96
fifth day (g)	127.91 ± 77.68	155.75 ± 72.67
Apgar score		
after 1 min	7.81 ± 0.75	7.69 ± 0.80
after 5 min	9.51 ± 0.48	9.23 ± 0.54
Gestational age (wk)	39.7 ± 3.3	38.9 ± 1.40

Table III. Influence of breast-feeding on neonatal hyperbilirubinaemia: occurrence in relation to selected neonatal and maternal characteristics (from Rubaltelli,[23] with permission)

	No. of patients evaluated		Patients with bilirubinaemia >12.9 mg/dl		p-Value
	n	%	n	%	
Total	1454	100.0	70	4.88	
Breast-fed	605	41.55	28	4.62	NS
Formula-fed	226	15.54	8	3.54	NS
Supplementary feeding	623	42.92	34	5.45	NS
Maternal diabetes	17	1.17	2	11.76	<0.0514
Positive Coombs' test	20	1.37	7	35.00	<0.0001
Cephalohaematoma	17	1.17	3	17.46	<0.0001
Hypertension	63	4.33	7	11.11	<0.0040
Caesarean section	223	15.34	8	3.58	NS
Smoking mother	116	7.98	4	3.45	NS
Oxytocin administration	455	31.29	19	4.17	NS
Male	749	51.52	42	5.60	NS
Female	705	48.48	32	4.54	NS

NS = not significant.

From the author's own experience and from anecdotal cases it seems that the neurological signs become more prominent after exchange transfusion. It is possible to conceive that during ET the blood albumin concentration decreases, due to the relative dilution of blood with dextrose-citrate (CDP or ACD), and/or blood pH decreases; these factors enhance the deposition of unconjugated bilirubin in the CNS. Since ET is not effective on neurological outcome when bilirubin is in the region of 35 to 40 mg/dl, it seems reasonable, in the absence of overt neurological signs, to treat hyperbilirubinaemia with albumin infusion and with an intense double (fibre optic and conventional blue-light) PT. Plasma bilirubin decrement, blood pH and albumin concentration must be strictly followed during the procedure. Since there are no demonstrations that this treatment is more effective than an urgent ET, informed consent of the parents is mandatory.

2.2 Breast-Milk Jaundice

Breast-milk jaundice, which must be differentiated from so-called breast-feeding jaundice, can be defined as prolonged unconjugated hyperbilirubinaemia that disappears very slowly and is sometimes still evident at 3 months of age. It is not yet evident which factor is responsible for breast-milk jaundice, but it seems that at the basis of this prolonged hyperbilirubinaemia is an increased enterohepatic recirculation of bilirubin. The role of β-glucuronidase in maternal milk or in the intestines has not been definitively ascertained. A brief interruption of breast-feeding (24h) often results in a significant reduction of serum bilirubin concentration. However, since breast-feeding jaundice is not a cause of neurodevelopmental or hearing defects, continuation of breast-feeding must be encouraged.[24]

2.3 Developmental Jaundice

We define the so-called physiological or developmental jaundice as the disorder consequent on neonatal indirect hyperbilirubinaemia which is not due to haemolysis, but to a reduced bilirubin conjugation in spite of normal bilirubin production. Jaundice is now the most common cause for hospital readmission in near-term infants who undergo

Table IV. Influence of breast-feeding on neonatal hyperbilirubinaemia: mean (± SD) weight loss (g) in breast-fed and formula-fed neonates (from Rubaltelli,[23] with permission)

	Breast-fed	Formula-fed	Breast + formula
Third day	139.83 ± 66.39	138.19 ± 69.56	139.85 ± 70.39
Fifth day	129.62 ± 74.77	133.63 ± 72.45	125.88 ± 83.07

early discharge.[25] Hansen[26] has recently reported 4 cases of severe hyperbilirubinaemia in infants discharged early, 3 of whom did not present signs of haemolysis, while in one, unrecognised Rhesus immunisation was the main cause of the hyperbilirubinaemia. In the first 3 infants indirect serum bilirubin ranged from 550 μmol/L (32.1 mg/dl) to 620 μmol/L (36.3 mg/dl), while in the Rhesus immunised infant the value was 605 μmol/L (35.5 mg/dl). Intense PT (fibre optic mat plus 2 Air-Shields Phototherapy Systems 7850 and an Air-Shields Fluoro-Lite Phototherapy unit placed at 45° angles on both sides) plus *ad libitum* feeding (breast-feeding and formula) was employed; after 2h, serum bilirubin was reduced by 170 to 185 μmol/L (10 to 11 mg/dl) in 3 patients, while in the fourth a reduction of 195 μmol/L (11.3 mg/dl) was seen in the 5h interval. This was the only patient treated also with ET. In all, brainstem auditory evoked responses done before discharge were normal.[26]

Intensive PT and *ad libitum* feeding are recommended as first treatment in any case of developmental jaundice if serum bilirubin value is ≥17 mg/dl at ≥48 hours of life (fig. 1). If a high STB level is found at less than 48h the diagnosis of developmental jaundice is not certain. PT will be discontinued after at least 24h of treatment if STB is ≤13 mg/dl at >72h of life, or has decreased by more than 2 mg/dl. For PT-treated infants a new determination of STB is recommended 24h after discontinuation of PT in order to evaluate a possible rebound.

2.4 Haemolytic Jaundice

Newborn infants can develop hyperbilirubinaemia due to blood group incompatibility; in such cases the mother is generally group O and the infant group A or B. Direct Coombs' test shows the presence of anti-A or anti-B antibodies on the erythrocytes. The risk of kernicterus is considered to be much higher with haemolytic jaundice than with developmental jaundice, the serum bilirubin concentration being equal. It is possible, but has not been demonstrated, that during a rapid breakdown of erythrocytes the binding capacity of albumin for bilirubin can be outpaced. Rh haemolytic disease is now rare due to the advent of Rho(D) immune globulin (RhoGAM) administration to Rh^- mothers who deliver Rh^+ infants, with ensuing decrease in haemolytic Rh disease. However, since the risk of kernicterus is higher, an early ET must be considered in order to remove sensitised red blood cells, correct anaemia and remove bilirubin when cord STB is ≥4 mg/dl and cord haemoglobin level is ≤11 g/dl. In less severe cases a combined treatment employing high intensity PT and IVIG can be tried.

Nevertheless, if the bilirubin level is rising over 1 mg/dl/h despite intense PT, there is an indication for ET (double-volume) (fig. 1).

Neonatal jaundice associated with glucose 6-phosphate dehydrogenase (G-6-PD) deficiency is very frequent in diverse population groups, including a large number of people in Africa (G-6-PD A-variant), many in a broad band stretching from Italy to India (G-6-PD Mediterranean), and further population groups in the Far East. The pathogenesis of the jaundice is not clear.[27] In some instances, G-6-PD–deficient neonates – under conditions of oxidative stress – become subject to acute haemolysis. However, haematological indices of haemolysis such as decreasing haemoglobin or haematocrit, or increasing reticulocyte count, have not always supported haemolysis in the aetiology of the jaundice.

It has been recently shown that there are 2 subgroups of G-6-PD–deficient neonates: one of neonates with no conjugation defect, who remain non-jaundiced, the other with a conjugation defect, who subsequently become jaundiced, and are at risk of developing kernicterus.[27] It has been found recently that among G-6-PD–deficient infants the incidence of hyperbilirubinaemia is greater in those with the heterozygous or variant homozygous *UDPGT1* genotype [the variant promoter contains a 2-base-pair addition (TA) in the TATAA sequence element of the promoter, and this polymorphism is associated with Gilbert's syndrome] than in normal homozygotes.[28] If a G-6-PD–deficient neonate

has an STB level of ≥15 mg/dl at ≥48h of age, he or she must be treated with PT or, if SnMP is available, with a single dose of 6 μmol/kg bodyweight given intramuscularly.

PT should be discontinued after at least 24h of treatment if STB is ≤13 mg/dl at >72h of life or has decreased by more than 2 mg/dl. For PT-treated infants a new determination of STB is recommended 24h after discontinuation of treatment, in order to evaluate a possible rebound. Following SnMP administration, STB must be measured once daily until the level has peaked and then fallen to ≤13 mg/dl.

2.5 Jaundice Due to Polycythaemia or Extravascular Blood

The daily production rate of bilirubin is 6 to 8 mg/kg bodyweight/24h in healthy term infants. When the blood mass is increased, as in polycythemia, or there is presence of extravascular blood (bruising, cephalohaematoma, enclosed haemorrhages), the rate is increased. This is a condition frequently responsible for hyperbilirubinaemia, especially in the full term neonate.

2.6 Crigler-Najjar Disease

Crigler-Najjar (CN) disease is a rare disorder of bilirubin metabolism caused by a deficiency of hepatic UDP-glucuronyltransferase, and is characterised by high serum levels of unconjugated bilirubin which appear in the first days after birth and continue through life. Plasma unconjugated bilirubin may increase to levels that exceed the binding capacity of plasma albumin, thereby causing kernicterus. Based on the responsiveness of the serum bilirubin concentration to treatment with phenobarbital, CN disease can be distinguished as type 1, which does not respond to phenobarbital and is considered to be caused by a complete enzymatic defect, and type 2, which responds to phenobarbital and other drugs that induce enzyme synthesis.[29] Several different mutations have been described to date in the coding region of the *UGT1A* gene complex locus, accounting for a partial or total loss of bilirubin glucuronidating activity in Crigler-Najjar patients. Recently, 2 other mutations were identified in the TATAA box element of the *UGT1A* gene.[30]

Type 1 CN is treated with PT (about 10h every night), and in situations of increased bilirubin production such as fever, prolonged fasting or infectious diseases, SnMP (Stanate® 2 to 4 μmol/kg bodyweight) should be used as an adjunctive treatment in order to prevent the possible occurrence of neurological damage.[14]

Type 2 disease remains generally stable under phenobarbital treatment. However, the amount of bilirubin transferase activity, determined in COS-1 cells following transfection of the major bilirubin transferase, is variably reduced in type 2 patients accounting for the different phenotypes.[30] Notwithstanding the phenobarbital treatment, some patients have high STB values, and during situations of increased bilirubin production they may need treatment with SnMP.

3. Conclusions

The problem of neonatal jaundice was solved many years ago when the value of 20 mg/dl was identified as the threshold level for bilirubin toxicity in term neonates. Today there is general agreement that the old value of 20 mg/dl is identical to the actual value of 25 mg/dl which is now measured more accurately.[15]

There are two possible explanations for the current re-emergence of kernicterus: the lessening in concern about jaundice in term or near-term neonates without overt haemolysis, and shortened hospital stays due to financial rather than family or medical considerations.

Should we change the old approach to the treatment of neonatal hyperbilirubinaemia? For many decades, PT has been successfully used to prevent the need for exchange transfusion, which was considered the 'gold standard' for preventing kernicterus. We are now faced with infants rehospitalised for severe neonatal hyperbilirubinaemia. Is it true that the effect of phototherapy on bilirubin levels is not as immediate as that of exchange transfusion? We must consider that when we measure

STB, bilirubin photoisomers are not differentiated from native bilirubin; consequently, when we measure STB in a neonate under PT, we overestimate STB. In addition, it has recently been demonstrated that a very rapid reduction from extreme levels of hyperbilirubinaemia may be achieved by effective PT.[26]

Intense whole-body PT may be employed as first-line treatment of every infant admitted to hospital for severe jaundice, even when an exchange transfusion is planned.

SnMP seems to be a promising, though still experimental, new treatment, especially if very early (<24h) discharge from hospital is planned. Finally, the use of a noninvasive measurement of bilirubin (Bili*Check*®) in the hospital and at home can help in the assessment of jaundice.

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Correspondence and reprints: Professor *Firmino F. Rubaltelli*, Division of Neonatology, Careggi University Hospital, Viale Morgagni, 85, 50134 Firenze, Italy.
E-mail: rubaltelli@CESIT1.UNIFI.IT