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A Review article about

(hyperbilirubinemia in preterm infant)

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ABSTACT

Jaundice is the most well-known condition that requires clinical consideration and emergency clinic readmission in newborns.The yellow hue of the skin and sclera in babies with jaundice is the consequence of amassing of unconjugated bilirubin., serum bilirubin levels may rise unreasonably, which can be cause for concern in light of the fact that unconjugated bilirubin is neurotoxic and can cause passing in infants and long lasting neurologic sequelae in newborn children who endure (kernicterus). Preterm youngsters with expanded bilirubin creation loads are bound to support antagonistic results due to either neurotoxicity or overtreatment with phototherapy and additionally trade bonding. Clinicians ought to depend on master agreement sentiments to control ideal and powerful intercessions until there is better proof to refine bilirubin-actuated neurologic brokenness or advantages of bilirubin

Keywords

Introduction , Pathophysiology,ateiology , Predictors of Significant Jaundice in Late Preterm Infants, Natural bilirubin profile in preterm infant, Clinical profile of subtile posticterus sequelae,Emergency Interventions for Rapid Reduction of Bilirubin Concentrations, Follow up of preterm infans at risk for bilirubin induced neurological dysfunction ,summary.

Introduction

Most preterm newborn children under 35 weeks gestational age (GA) have raised all out serum/plasma bilirubin (TB) levels, which frequently present as jaundice, the yellowish staining of the skin because of bilirubin statement. At the point when left unmonitored or untreated in these

newborn children, a raised TB level (hyperbilirubinemia) can advance to quiet or suggestive neurologic indications. Intense bilirubin encephalopathy (ABE) is intense, reformist, and regularly reversible with forceful mediation, while kernicterus (or constant bilirubin

encephalopathy [CBE]) is the condition of ongoing, post-icteric and perpetual neurologic sequelae that is related with more genuine and normally irreversible appearances. [1] The current administration of a preterm newborn child with hyperbilirubinemia, who has an improved probability of creating bilirubin-incited neurologic harm, is under extreme investigation. Clinicians have been told to utilize the hour-explicit TB levels (Bhutani nomogram).[2] just as thinking about the simultaneousness with the level of a newborn child's youthfulness, ailment, or potentially hemolytic infection, the most widely recognized reason for expanded bilirubin creation, to manage the commencement of treatment.

Indeed, expanded bilirubin creation in preterm children adds to the danger of mortality or long haul neurodevelopmental disability (NDI) because of bilirubin neurotoxicity[3–4] and can be showed as the condition of bilirubin-instigated neurologic brokenness (BIND).[5-6] Universal screening and the avoidance of Rh infection, composed perinatal-neonatal consideration, neonatal mediations with early taking care of, and viable utilization of phototherapy has for all intents and purposes wiped out the danger of kernicterus in most developed nations .

Among the infants who died due to kernicterus, 100%, 89%, 54%, and 81% were of birthweight (BW) less than 1500 g, 1500 to 2000 g, 2001 to 2500 g, and >2500 g, respectively. Overall, 60 (2.8%) of 2181 survivors of 2608 admissions to the neonatal nursery sustained kernicterus. Mortality was 73% for these 60 infants. Since 1985, phototherapy initiated at 24-12 hours of life has effectively prevented hyperbilirubinemia in infants weighing less than 2000 g even in the presence of hemolysis.**7** This approach (introduced in 1985) reduced

exchange transfusions from 23.9% to 4.8%. Now with 3 decades of additional experience in implementing effective phototherapy, the need for exchange transfusions has virtually been eliminated and the side effects of phototherapy in extremely low birthweight (ELBW) infants are now under active investigation. Nevertheless, bilirubin neurotoxicity continues to be associated with prematurity alone.

Pathophysiology

Preterm and full term infants become jaundiced by similar mechanisms Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates. [8, 9]
Hepatic excretory capacity is low both because of low oncentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).

Bilirubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes.
In the first oxidation step, biliverdin is formed from heme through the action of heme oxygenase, the rate-limiting step in the process, releasing iron and carbon monoxide. The iron is conserved for reuse, whereas carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production.
Next, water-soluble biliverdin is reduced to bilirubin, which, because of the intramolecular hydrogen bonds, is almost insoluble in water in its most common isomeric form (bilirubin IXα Z,Z). Because of its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly bound to albumin. Binding to other proteins and erythrocytes also occurs, but the physiologic role is probably limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill.

The presence of endogenous and exogenous binding competitors, such as flawless drugs, exclusive of decreases the binding affinity of albumin for bilirubin. A iota braids of unconjugated bilirubin in prevention is whoop circumscribe to albumin. This Bohemian bilirubin is accomplished to wicked lipid-containing membranes, into the bargain the blood-brain barrier, leading to neurotoxicity. In fetal dynamism, casual bilirubin crosses the placenta, occasion likelihood by a carrier-mediated conduct, [10] and fulfil of bilirubin distance from the fetus occurs primarily through the maternal organism. Tout de suite it reaches the liver, bilirubin is joyful into liver cells, swivel it binds to ligandin.

Grasp of **bilirubin** into hepatocytes increases to increasing ligandin concentrations. Ligandin concentrations are pedestal at origination but like a bat out of hell hoard turn over the first few weeks of life. Ligandin concentrations may be increased by the provision of pharmacologic agents such as phenobarbital. Bilirubin is bound to glucuronic caustic (conjugated) in the hepatocyte endoplasmic grater in a boomerang catalyzed by uridine diphosphoglucuronyltransferase (UDPGT.Bilirubin conjugation is biologically grave for the benefit of it transforms a water-insoluble bilirubin molecule into a water-soluble molecule. Water-solubility allows conjugated bilirubin to be excreted into bile. UDPGT remedy is evil-minded at opening but increases to mature self-possession by age 4-8 weeks. In supplementary, unconditional drugs (phenobarbital, dexamethasone, clofibrate) duff be administered to increase UDPGT activity. Infants who venture Gilbert warning sign or who are pollute heterozygotes for the Gilbert supporter and coherent mutations of the UDPGT1A1 coding region are at an increased risk of significant hyperbilirubinemia.

Interactions between the Gilbert genotype and hemolytic anemias such as glucose-6-phosphatase dehydrogenase (G-6-PD) lack, traditional spherocytosis, or Native hemolytic disease also appear to increase the risk of severe neonatal jaundice.

Once excreted into bile and transferred to the intestines, bilirubin is eventually reduced to colorless tetrapyrroles by microbes in the colon. However, some deconjugation occurs in the proximal small intestine through the action of B-glucuronidases located in the brush border. This unconjugated bilirubin can be reabsorbed into the circulation, increasing the total plasma bilirubin pool. This cycle of uptake, conjugation, excretion, deconjugation, and reabsorption is termed 'enterohepatic circulation'. The process may be extensive in the neonate, partly because nutrient intake is limited in the first days of life, prolonging the intestinal transit time.

In mother-infant dyads who are experiencing difficulties with the establishment of breast feeding, inadequate fluid and nutrient intake often leads to significant postnatal weight loss in the infant. Such infants have an increased risk of developing jaundice through increased enterohepatic circulation, as described above. This phenomenon is often referred to as breastfeeding jaundice and is different from the breast milk jaundice described below.

Certain factors present in the breast milk of some mothers may also contribute to increased enterohepatic circulation of bilirubin (breast milk jaundice). β-glucuronidase may play a role by uncoupling bilirubin from its binding to glucuronic acid, thus making it available for reabsorption.**[11]**.

Neonatal jaundice, although a normal transitional phenomenon in most infants, can occasionally become more pronounced. Blood group incompatibilities (eg, Rh, ABO) may increase bilirubin production through increased hemolysis. Historically, Rh isoimmunization was an important cause of severe jaundice, often resulting in the development of kernicterus. Although this condition has become relatively rare in industrialized countries following the use of Rh prophylaxis in Rh-negative women, Rh isoimmunization remains common in low- and middle-income countries (LMICs).

Nonimmune hemolytic disorders (spherocytosis, G-6-PD deficiency) may also cause increased jaundice, and increased hemolysis appears to have

been present in some of the infants reported to have developed kernicterus in the United States in the past 15-20 years.. More recently, 3 novel mutations in genes encoding either alpha or beta spectrin (SPTA1 or SPTB) were found in 3 unrelated neonates with nonimmune hemolytic jaundice. **[12**].

Predictors of Significant Jaundice in Late Preterm Infants

Significant jaundice defined as requirement of phototherapy/exchange transfusion as per hour specific total serum bilirubin (TSB) nomogram of AAP guidelines.[13].

TcB values at 48–54 hours and infant gestational age were the best clinical predictors of subsequent extreme hyperbilirubinemia. TcB levels at 48–54 hours of life were divided into three categories: 10 mg/dL, 10–12 mg/dL, and > 12 mg/dL. The gestational age was divided into five categories. [**14**,**15**]

In three risk classes, strong, moderate, and low, the AuROC curve was 81.0 percent. With a specificity of 87.1 percent, the positive probability ratio for subsequent extreme hyperbilirubinemia in the high-risk population (score > 5) was 4.53. The low-risk group's negative predictive value (score 3) was 81 percent**[16]**.Final Thoughts,A simple predischarge prediction score was established based on gestational age and TcB values at 48–54 hours of life. This score divided late preterm and term newborn babies into three risk categories, and it could be used to classify high-risk infants for outpatient follow-up with serious hyperbilirubinemia in the future.

Natural bilirubin profile in preterm infant

Previous research suggests that preterm infants with low TB levels can maintain long-term NDI at 18 to 22 months,**[17**,**18**–**19]** and that preterm infants with high TB levels can experience increased mortality and NDI

linked to auditory neuropathic or visuomotor processing disorders (now known as BIND). [**7-20**]However, due to efficient bilirubin removal and adequate BBC, some preterm infants are immune to relatively high bilirubin loads in the absence of increased development rates.[**21]** Phototherapy that is either unnecessary or overprescribed can compromise bilirubin's ability to function as a protective antioxidant from bilirubin neurotoxicity, which may occur at even very low TB levels**.[22].**

Clinical profile of subtile posticterus sequelae

KERNICTERUS IN PRETERM INFANTS

Kernicterus is a pathological diagnosis characterised by bilirubin staining of the brainstem nuclei. Compared with their term counterparts, infants born prematurely are considered to be at increased risk for developing kernicterus**.[22,23].**

This was apparent to clinician investigators as early as the 1950s when kernicterus was first reported in preterm newborns and its occurrence demonstrated in the absence of isoimmunisation.[**23,24**] The latter was a novel observation: hitherto, cases of kernicterus were associated with haemolysis secondary to Rh incompatibility. The risk of developing kernicterus was generally confined to neonates whose TSB concentrations rose to values greater than 20–24 mg/dl (340–408 μmo/l).Consistent with these postmortem findings were several follow up studies from this time period that failed to show an association between TSB levels of less than 18–20 mg/dl (306–340 μmol/l) and adverse neurodevelopmental sequelae in the premature neonate.23–28 Premature infants described in these investigations were significantly larger (> 1500 g) and more mature (32–36 weeks gestation) than the extremely low birthweight premature infants cared for in today's neonatal intensive care units.

In the decade that followed, premature infants were observed to develop kernicterus at TSB levels considerably lower than 20 mg/dl (340 μmol/l)—the so called "low bilirubin kernicterus". In a series of studies published from 1958 to 1972, kernicterus was described in premature

infants at TSB levels ranging from 10 to 18 mg/dl (170–306 μmol/l). **[25,26,27].**

This was a time of emerging new technologies in the management of smaller and more premature neonates and included, for the first time, appreciable numbers of newborns with birth weights of less than 1000 g and gestational ages of less than 28 weeks. It was also suggested that various clinical factors, such as hypothermia, asphyxia, acidosis, predisposed premature infants to kernicterus, and should be considered in determining exchange transfusion levels for a given infant.[28,29].

However, two studies published in the early 1980s evaluated the predictive nature of such clinical conditions and failed to identify any risk factor or group of factors that was associated with the development of kernicterus in the premature neonate, including birth weight less than 1500 g, hypothermia, asphyxia, acidosis, hypoalbuminaemia, sepsis, meningitis, drug therapy, and TSB level.[30,31].

Auditory Dysfunction In preterm infants

The concern between hyperbilirubinemia and tag degeneration is tremendous and substructure be regulated by other hazard factors.35 Preterm infants concerning brazen TB levels 14 mg/dL), and those upon BW forth than 1500 g venture a higher feat of deafness than their healthy counterparts near BW more than 1500 g. Summation, midst high-risk patients, the parsimonious majority of hyperbilirubinemia was much longer in insensitive infants, who appeared to endeavour a greater number of acidotic episodes while they were hyperbilirubinemic. Hyperbilirubinemia appears to emissary lop vilify to the brainstem auditory nuclei and may as well as damage the auditory nerve and spiraLganglion.[32] In against, the fortnightly of Corti and thalamocortical auditory pathways act to be unaffected by bilirubin. Clinically, a usual hint of chastise diminish caused by hyperbilirubinemia is auditory neuropathy spectrum disorder (ANSD).[33,34]. Appropriately,

tests of auditory transduction and alien furious apartment do favoured the cochlea, such as the curl microphonics and OAEs, may be normal while ABR testing is abnormal. Miscellaneous experts try on meander ANSD is united hither regard to a more subtle neurologic manifestation (BIND).[35,36] Examination of ANSD is energetic befitting to behind time clinical onset and nonspecificity. In a break down of 260 patients nigh ANSD, recorded risk of hyperbilirubinemia was 47.7% in ahead of time infants, and 20.3% in those who received exchange transfusion.[37] A Cheer up analyse of 9419 infants whose apostrophize b supplicate faculty was puzzling or who had risk factors for hearing loss, 352 were diagnosed with sensorineural hearing loss.35 Of these, 18 (5.1%) were diagnosed with ANSD united with prematurity and wretched BW (n 5 5), pharmacologic ototoxicity (n 5 8), and hyperbilirubinemia (n 5 7), and 4 had scrap risk factors. Nolens volens these firm are fleeting and have no weight on approach devote and language development has to yet be proven.

Visuocortical Dysfunction

Beside the exemplary visuo-oculomotor signs of kernicterus, fundamental information have exhibited various intriguing and possibly troubling discoveries when the visual cortex work in solid, bilirubin-uncovered newborn children was studied.[38] By utilizing a quantitative proportion of neural movement, the cleared boundary visual evoked potential (sVEP) reaction capacities over a wide scope of difference, spatial recurrence, and vernier balance sizes in 16 full-term babies with high TB levels (>10 mg/dL) and 18 age-coordinated with babies with no noticeable neonatal jaundice. The impact of bilirubin on the visual cortex endures well past the time of openness and more than one sort of vision is influenced, proposing boundless impact of bilirubin on the visual cortex .

Integrity of Brainstem Function and Structure

The incidence and superintendence of irregular crowded apnea events of respecting than 20 hastily requiring unalloyed surround ventilation try on been supposed by Amin and colleagues[39] as signs of intractable apnea and possible signs of BIND. Model intellectual fashionable temper insight for kernicterus try been going round, relative to unescorted descriptive of term infants, and demonstrating vulnerability of the basal ganglia.[40] Anciently, entrails generation of a hyperbilirubinemia-related maligning, T1-weighted planner imaging shows hyperintensity of the globus pallidus with or without queer signal in the subthalamic nuclei. Weeks or months at the end of the day, T2-weighted and fluid-attenuated inversion increase (FLAIR) images mature hyperintense, and hyperintensity is no longer seen on T1-weighted images. A traditional celebrity does bawl terminate the different of bilirubin-related wisdom welt; paper images may permit an anciently abnormal D , followed by discernible resolution, then later, an abnormal T2-weighted series at a time cruise fundament be variable. Akin representative discretion attempt been supposed in a restrain of preterm infants of nearly than 30 weeks estimated gestational age (EGA).[41] In these infants, BAMRs, but groan TB levels, were in the air on the rotation transfusion 6 Bhutani et al thresholds recommended in the 1990s,[42] although all had evidence of clinical instability during their hospitalization. Hence, it has been supposititious that this constellation of intellect may be underrecognized among preterm infants. Conspicuously, the bilirubin-related harm pattern can be differentiated outlandish the finery common stamp of preterm brain injury of white matter injury alone.[43,44].

Emergency Interventions for Rapid Reduction of Bilirubin Concentrations

Rapid bilirubin reduction strategies to reverse the rapid rate of TB rise include effective phototherapy (nearly the entire body surface area [>80%]), double-volume blood exchange transfusion, and occasional need for pharmacologic agents often used in combination.

Effective phototherapy is the current "drug" of choice to reduce the severity of neonatal unconjugated hyperbilirubinemia (regardless of etiology) in a matter of 2 to 4 hours. Optimum use of phototherapy has been defined by specific ranges of TB thresholds that have been correlated to an infant's postnatal age (in hours) and their potential risk for bilirubin neurotoxicity (see previously). Effective phototherapy implies its use as a drug with specific light wavelengths at a specific narrow peak (460 nm, blue) and a range of emission spectrum (that is minimized from the traditional range of 400–520 nm), preferably in a precise (narrow) bandwidth that is delivered at an irradiance (dose) of greater than or equal to 25 to 30 mW/cm2 /nm (measured specifically for the selected light wavelength) to 80% of an infant's body surface area.65,66 There are several commercial devices and delivery methods for phototherapy for use at both the hospital and home. Blue light-emitting diodes in the 425 to 475 nm range should be easily and rapidly accessible, and periodically inspected and maintained to ensure proper functioning. Shadows with multiple lights should be avoided. The efficacy is additionally influenced by the following: (1) optimization of light administration to achieve a minimum distance between the device and the patient such that the footprint of light covers maximum surface area with minimal physical barriers; (2) infant characteristics, such as the severity of jaundice, surface area proportions, as well as dermal thickness, pigmentation, and perfusion; and (3) the duration of treatment to a specific TB threshold**.[45,46].**

Exchange transfusion is a critical and invasive procedure that can significantly reduce TB levels in a matter of 1 to 2 hours. Trained personnel in neonatal/pediatric intensive care facilities with full monitoring and resuscitation capabilities should perform this procedure. Exchange transfusion should be considered and anticipated when there are any neurologic signs even if TB is falling, or there are significant concerns of neurotoxicity. Concerns for neurotoxicity in term infants are heightened in an asymptomatic infant when (1) TB level exceeds 25

mg/dL; (2) intensive phototherapy fails to produce a significant TB reduction in an infant with severe hyperbilirubinemia (a progressive TB decline of at least >0.5 mg/dL per hour or >2 mg/dL drop in 4 hours should be expected) without onset of neurologic signs; or (3) an infant who had an earlier successful hearing screen and fails an automated ABR screen.

Before an exchange transfusion is initiated, the health care team should review the risks and benefits of the procedure with the parents, so parents can provide informed parental consent.

The adverse effects of an exchange transfusion include neonatal morbidities such as apnea, anemia, thrombocytopenia, electrolyte and calcium imbalances, risk of necrotizing enterocolitis, hemorrhage, infection, complications related to the use of blood products, and catheter-related complications**.[47].**

Exchange transfusion also carries the risk of neonatal mortality, especially in sick infants. Exchange transfusion is ideally performed as an isovolumic procedure, preferably with concurrent withdrawal from an arterial line and infusion through a venous line. Double-volume exchange (170 mL/kg) is preferable, but in the event of technical difficulties, a single-volume exchange transfusion may be adequate if supplemented with intensive phototherapy. The entire process should be accomplished within 4 to 6 hours of the identification of the medical emergency.1 Pharmacologic options and chemoprevention strategies have been reviewed in recent articles**.[48,49],** but have a limited role in the emergency room management of a sick infant.

Intravenous Gamma Immunoglobulin

Intravenous gamma immunoglobulin (IVIG) may be administered when the hyperbilirubinemia is attributed to isoimmunization. IVIG has been shown, anecdotally, to reduce the need for exchange transfusions in Rh and ABO hemolytic diseases**.,[50,51]** Although data are limited, there is

no evidentiary basis for its use and there are concerns for significant side effects in preterm neonates.

Phenobarbital

Phenobarbital can accelerate bilirubin excretion by increasing hepatic clearance**.[52]** However, this drug is no longer recommended, as it has no clinical effect when administered to infants of less than 32 weeks GA and is ineffective when given before 12 hours of age. The adverse effects of this therapy include sedation, risk of hemorrhagic disease, and the potentially addictive nature of phenobarbital**.[53]** This drug has a slow onset of effect (usually several days) and a long duration of action (1–2 weeks) after its discontinuation. For all of these reasons, the use of phenobarbital is no longer recommended.

Metalloporphyrins

Synthetic heme analogs or metalloporphyrins can inhibit HO, the rate-limiting enzyme in the bilirubin production pathway.[**54]** Some have been noted to cause photosensitization (especially during exposure to intense fluorescent light). These drugs are being investigated in clinical pharmacologic and toxicologic studies and have been shown 12 Bhutani et al to reduce TB levels**.[55]** The Food and Drug Administration has not yet approved their use in the United States.

FOLLOW-UP OF PRETERM INFANTS AT RISK FOR BILIRUBIN-INDUCED

Posticteric sequelae are often unrecognized, mislabeled, or misdiagnosed in preterm infants. These errors have led to prolonged diagnostic and health-seeking odysseys for families. Follow-up studies of infants enrolled in the NICHD trial of 1979 to 1985 demonstrated the challenges of follow-up in this population as well as the residual morbidities identified at late childhood and in adults. Oh and colleagues**,[56]** through a retrospective observational analysis in infants with BW less than 1000 g, noted that TB concentrations during the first 14 days of birth are

directly correlated with death, NDI, sensorineural hearing loss, and other physical impairments. Confounding effects of modest hyperbilirubinemia or potential toxic effects of phototherapy could not be excluded. These have been supplemented by similar concerns for adverse outcomes at age 16 to 22 months for preterm infants weighing less than 1000 g**.[57]** Infants with TB levels that approach thresholds for an exchange transfusion should be followed through infancy until school age for awkwardness, gait abnormality, failure of fine stereognosis, gaze abnormalities, poor coordination, and exaggerated extrapyramidal reflexes. Follow-up should include neurologic and neurodevelopmental evaluation, neuroimaging with magnetic resonance, and ABRs.

SUMMARY

Bilirubin, a powerful antioxidant, also can act as a powerful but silent neurotoxin at the most vulnerable stage of preterm life. The impact is long-lasting with both functional and structural neurologic injury that alters the processing of afferent input and leads to disordered efferent function. Moreover, these perturbations can potentially arrest or retard the natural neural maturation and/or lead to disordered clinical extrapyramidal function, sensory processing of hearing, visual responses, and learning. At a cellular level, development of neurogenic niches and maturation of both vascular endothelial cells and glial cells are significant in the immediate postnatal period, which may be amplified by the concomitant stresses that can accompany these exposures, such as prematurity, inflammation/sepsis, and oxidative stress. Innovative rehabilitation techniques during early follow-up may promote plastic compensation for loss of function. Functional recovery would depend on the ability of the maturing brain to reestablish neuroplasticity as with most preterm neonates at risk for developmental sequelae. In the future, advances in neuroimaging techniques, comprehensive evaluation for the integrity of auditory and visual responses, and specific testing for extrapyramidal neuromotor performances may contribute to the increased recognition of bilirubin-related neurologic sequelae. In the meantime, as

better predictive biomarkers are validated, individualized clinical judgment is the key to balance the risks and benefits of preventive, effective, and timely interventions.kernicterus is currently a very rare event in premature infants in neonatal intensive care units.6–8,49 This may be the result of overall improvements in care and/or of the fairly aggressive use of phototherapy. Certainly phototherapy, if used appropriately, is capable

of controlling the bilirubin levels in almost all low birthweight infants, with the possible exception of the occasional infant with severe erythroblastosis fetalis or severe bruising.50 Future randomised studies such as that proposed by the NICHHD Neonatal Research Network designed to compare aggressive with conservative use of phototherapy and exchange transfusion in extremely low birthweight infants will help to more clearly define the risks of hyperbilirubinaemia in premature neonates and the indications for clinical interventions (B Morris, personal communication, 2002). Details of this continuing study are provided in the following review which deals with the treatment of the jaundiced low birthweight infant.

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