Jaundice in preterm, as well as full term, infants results from (a) an increased bilirubin load in the hepatocyte, (b) decreased hepatic uptake of bilirubin from the plasma, and/or (c) defective bilirubin conjugation. Hyperbilirubinaemia in preterm infants is more prevalent, more severe, and its course more protracted than in term neonates.

**PATHOBIOLGY**

Preterm and full term infants become jaundiced by similar mechanisms. There is: (a) an increased bilirubin load in the hepatocyte as a result of decreased erythrocyte survival, increased erythrocyte volume, and increased enterohepatic circulation of bilirubin; (b) decreased hepatic uptake of bilirubin from plasma; (c) defective bilirubin conjugation. Hyperbilirubinaemia in preterm infants is more prevalent, more severe, and its course more protracted than in term neonates, as a result of exaggerated neonatal red cell, hepatic, and gastrointestinal immaturity. The postnatal maturation of hepatic bilirubin uptake and conjugation may also be slower in premature infants. In addition, a delay in the initiation of enteral feedings so common in the clinical management of sick premature newborns may limit intestinal flow and bacterial colonization resulting in further enhancement of bilirubin enterohepatic circulation. These developmental and clinical phenomena contribute to the greater degree and duration of neonatal jaundice in premature infants.

Despite the near universal finding of clinical jaundice in the very low birthweight (VLBW) infant, kernicterus has virtually disappeared in postmortem series of premature neonates, and post-kernicteric bilirubin encephalopathy and central neural hearing loss associated with neonatal hyperbilirubinaemia have not emerged as important clinical sequelae in neurodevelopmental follow up of premature infants. Yet kernicterus has occurred in preterm infants at low bilirubin levels and in the absence of acute neurological signs, and investigators have suggested that moderate hyperbilirubinaemia (total serum bilirubin (TSB) levels higher than 10–14 mg/dl (170–239 µmol/l)) may be associated with milder forms of central nervous system dysfunction and sequelae. Thus there remains considerable debate on the risk neonatal hyperbilirubinaemia poses for neuronal injury in the VLBW neonate, how to quantify that risk, and when to intervene with phototherapy or exchange transfusion. In the remaining sections of this review, we review the relevant literature on kernicterus and the neurodevelopmental outcome of the hyperbilirubinaemic preterm neonate.

**KERNICTERUS IN PRETERM INFANTS**

Kernicterus is a pathological diagnosis characterised by bilirubin staining of the brainstem nuclei. Clarification of the neuropathological definition of bilirubin associated brain damage in the preterm infant was provided by Ahdab-Barmada, who established clear anatomical, cytological, and histological criteria for the postmortem diagnosis of kernicterus in prematures. More specifically, kernicterus was defined by macroscopic yellow staining of specific subcortical nuclei—for example, globus pallidus, subthalamic nuclei, and brainstem cranial nuclei—and microscopic evidence of neuronal damage in those nuclei. Yellow staining alone was not considered sufficient for the diagnosis of kernicterus, as this may occur as a terminal event in premature neonates; only neuronal damage in association with the presence of yellow pigment is diagnosed as kernicterus.

Compared with their term counterparts, infants born prematurely are considered to be at increased risk for developing kernicterus. This was apparent to clinical investigators as early as the 1950s when kernicterus was first reported in preterm newborns and its occurrence demonstrated in the absence of isoimmunisation. 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 µmol/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.

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.

**Abbreviations:** TSB, total serum bilirubin; VLBW, very low birthweight
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). 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. 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.

It is likely that there are some hitherto unknown clinical conditions that enhance the risk for the development of kernicterus. An example of this possibility was the report from one neonatal intensive care unit of an abrupt temporal decrease in kernicterus at autopsy in premature infants. The incidence of kernicterus fell from 31% to 0% when the practice of flushing intravenous catheters with bacteriostatic saline containing benzyl alcohol was stopped.

In an earlier study from the same neonatal intensive care unit, the incidence of kernicterus diagnosed post mortem among neonates of 25–32 weeks gestation was a remarkably high 25%. Benzyl alcohol increases membrane fluidity and may facilitate the passage of bilirubin into the brain. At the same institution, only three cases of kernicterus were found in 72 autopsies performed from 1984 to 1991 on newborns of less than 34 weeks gestation who lived for at least 48 hours.

Of the 69 newborns who did not have kernicterus, the peak TSB level ranged from 6.3 to 20.6 mg/dl (108–352 µmol/l), and 56% had peak TSB levels higher than those suggested for exchange transfusion by the National Institute of Child Health and Human Development (NICHD) phototherapy study guidelines. The substantial decrease in the incidence of kernicterus reported in these studies confirms the experience in most nurseries that kernicterus in premature newborns has disappeared almost completely from the neonatal intensive care unit.

**NEURODEVELOPMENTAL OUTCOME OF HYPERBILIRUBINAEMIC VLBW NEONATES**

Several neurodevelopmental follow-up studies have failed to show an association between peak TSB levels and later adverse outcomes in VLBW neonates. Graziani and coworkers reported that bilirubinaemia in the range 2.3–22.5 mg/dl (39–382 µmol/l) was not related to the development of cerebral palsy or early developmental delay. Similarly, Macgregor and coworkers in a large cohort (n = 213) of extremely low birthweight (< 1000 g) neonates observed comparable TSB levels across newborns with birth weights ranging from 760 to 1270 g. Their peak TSB levels ranged from 6.5 to 14.2 mg/dl (111 to 243 µmol/l). The four surviving infants in the NICHHD cooperative phototherapy study (1974 to 1976) included a low birthweight preterm cohort. Infants were randomly assigned to a control group that received no phototherapy or to a group that received phototherapy at predetermined TSB levels. The criteria for exchange transfusion for all infants mandated exchange transfusions at low levels of serum bilirubin (10 mg/dl (171 µmol/l)) in high risk newborns with birth weights less than 1250 g. Kernicterus was found in four of 76 autopsied infants whose birth weights ranged from 76 to 1270 g. Their peak TSB levels ranged from 6.5 to 14.2 mg/dl (111 to 243 µmol/l). The four affected infants were asphyxiated or had hyaline membrane disease, and all had some degree of intraventricular haemorrhage. Two had periventricular leukomalacia. In this regard, some studies have suggested an association between hyperbilirubinaemia and cystic periventricular leukomalacia in low birthweight infants, but others have not found this. Despite the associations described (all from multiple significance testing with the resultant possibility of spurious conclusions), it is unlikely that hyperbilirubinaemia is causally related to cystic periventricular leukomalacia. Periventricular leukomalacia is primarily an ischaemic lesion, probably caused by hypoperfusion of the periventricular white matter. Bilirubin normally is not deposited in the periventricular region and is primarily toxic to neurons and not the glial elements that predominate in the periventricular white matter.

Surviving infants in the NICHHD cooperative phototherapy trial (1974–1976) were followed and evaluated at 6 years of age with the Wechsler verbal and performance intelligence quotient (IQ) test. No differences were found between the...
control and phototherapy groups in the incidence of definite and suspected cerebral palsy, clumsy or abnormal movements, hypotonia, or an IQ lower than 70. There were no differences between the two groups in growth, speech, hearing loss, or evidence of hyperactivity. 57 Scheidt and colleagues 57 published a six year follow up of the 224 control children with birth weights lower than 2000 g. None of these infants received phototherapy, but bilirubin levels were maintained below specified levels by the use of exchange transfusion. No relation was found between serum bilirubin levels and the incidence of cerebral palsy, nor between maximum serum bilirubin level and IQ. IQ was not associated with mean bilirubin level, time and duration of exposure to bilirubin, or measures of bilirubin-albumin binding. 58

Although these observational and randomised study data are reassuring, few of the infants in the investigations had appreciably raised bilirubin levels. 17–41 Furthermore, a report of kernicterus in two infants at 31 and 34 weeks gestation, neither of whom were acutely ill and whose serum bilirubin levels were 13.1 mg/dl (224 μmol/l) and 14.7 mg/dl (251 μmol/l), has raised renewed concerns about low bilirubin kernicterus in the premature infant. 20

SUMMARY

The literature on bilirubin induced neurological injury in the jaundiced preterm neonate reveals a complexity that is far greater than suggested by a simple a priori cause and effect relationship between hyperbilirubinaemia and neuronal damage, 59 leaving neonatologists in a clinical quandary with respect to the management of neonatal hyperbilirubinaemia in the premature infant. There is, nevertheless, little doubt that kernicterus is currently a very rare event in premature infants in neonatal intensive care units. 60–62 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 erythroblastosisis fetalis or severe bruising. 60 Future randomised studies such as that proposed by the NICHD 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. 60

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