

## REVIEW

# Jaundice in low birthweight infants: pathobiology and outcome

J F Watchko, M J Maisels

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.

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neonate, how to quantify that risk, and when to intervene with phototherapy or exchange transfusion.<sup>14–16</sup> 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,<sup>17–19</sup> who established clear anatomical, cytological, and histological criteria for the post-mortem diagnosis of kernicterus in prematures. More specifically, kernicterus was defined by (a) macroscopic yellow staining of specific subcortical nuclei—for example, globus pallidus, subthalamic nuclei, and brainstem cranial nuclei—and (b) 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<sup>17–19</sup>; only neuronal damage in association with the presence of yellow pigment is diagnosed as kernicterus.<sup>17–19</sup>

Compared with their term counterparts, infants born prematurely are considered to be at increased risk for developing kernicterus.<sup>9</sup> 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.<sup>21–22</sup> 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).<sup>23–28</sup> Consistent with these post-mortem 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.<sup>23–28</sup> 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.

## PATHOBIOLOGY

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,<sup>1–3</sup> 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.<sup>4</sup> 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 colonisation resulting in further enhancement of bilirubin enterohepatic circulation.<sup>4</sup> 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,<sup>5–7</sup> and post-kernicteric bilirubin encephalopathy and central neural hearing loss related to neonatal hyperbilirubinaemia have not emerged as important clinical sequelae in neurodevelopmental follow up of premature infants.<sup>4</sup> Yet kernicterus has occurred in preterm infants at low bilirubin levels and in the absence of acute neurological signs,<sup>8–10</sup> 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.<sup>11–13</sup> Thus there remains considerable debate on the risk neonatal hyperbilirubinaemia poses for neuronal injury in the VLBW

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**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  $\mu$ mol/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  $\mu$ mol/l).<sup>8–9, 29–32</sup> 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.<sup>15, 33</sup> 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.<sup>34, 35</sup>

It is likely that there are some hitherto unknown clinical conditions that enhance the risk for the development of kernicterus. An excellent 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.<sup>5</sup> 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%.<sup>17</sup> Benzyl alcohol increases membrane fluidity and may facilitate the passage of bilirubin into the brain.<sup>36</sup> 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.<sup>7</sup> Of the 69 newborns who did not have kernicterus, the peak TSB level ranged from 6.3 to 20.6 mg/dl (108–352  $\mu$ mol/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.<sup>7</sup> 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.<sup>5–7</sup>

### 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.<sup>37–42</sup> Graziani and coworkers<sup>40</sup> reported that bilirubinaemia in the range 2.3–22.5 mg/dl (39–382  $\mu$ mol/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 (a) neurologically normal (mean serum bilirubin 8.9 mg/dl (151  $\mu$ mol/l); range 4.1–25.3 mg/dl (70–430  $\mu$ mol/l)), (b) neurologically equivocal (mean serum bilirubin 9.1 mg/dl (155  $\mu$ mol/l); range 4.7–25.3 mg/dl (80–430  $\mu$ mol/l)), (c) neurologically abnormal (mean serum bilirubin 9.1 mg/dl (155  $\mu$ mol/l); range 2.7–19.9 (46–338  $\mu$ mol/l)), and (d) the subset of abnormal infants with sensorineural hearing loss (mean serum bilirubin 9.0 mg/dl (153  $\mu$ mol/l); range 5.9–12.7 mg/dl (100–216  $\mu$ mol/l))<sup>41</sup> and concluded that bilirubinaemia was not predictive of neurodevelopmental handicap in this

high risk group. Although van de Bor *et al*<sup>11</sup> found a relation between maximal TSB concentrations in the neonatal period and cerebral palsy (not of the type characteristically found with kernicterus) at a corrected age of 2 years, no relation was found between maximal TSB concentrations and hearing defects, and in follow up of the same population at five years, no significant difference was found in mean maximal TSB concentrations between children with and without handicaps.<sup>37</sup> The investigators did find, however, that children who suffered a grade 1 intracranial haemorrhage were at significantly greater risk of handicap. This effect was not seen in the more severe haemorrhages, but the number of infants with severe haemorrhages was small.

O’Shea and coworkers<sup>39</sup> were also unable to show a significant association between peak TSB and risk for developmental problems at 1 year of age in VLBW neonates when their multivariate analyses controlled for intracranial haemorrhage. Yeo and coworkers<sup>38</sup> similarly failed to show an association between peak TSB levels > 11.7 mg/dl (199  $\mu$ mol/l) and neurodevelopmental impairment, yet interestingly did observe an association in multivariate analysis between low serum bilirubin levels and risk for severe visual loss attributable to retinopathy of prematurity. More recently, Hack and coworkers<sup>43</sup> were unable to identify an association between TSB levels of greater than 10 mg/dl (170  $\mu$ mol/l) and a mental developmental index of < 70 or neurological abnormality indexed by cerebral palsy, hypotonia, hypertonia, and/or shunt dependent hydrocephalus. Although Hack and colleagues did report a significant association between peak TSB levels > 10 mg/dl (170  $\mu$ mol/l) and deafness, others have failed to identify a link between sensorineural hearing loss and bilirubinaemia in VLBW neonates.<sup>42</sup> The results of these observational studies are important but limited by the multifactorial nature of the causes of adverse neurological sequelae and the difficulty inherent in fully controlling for them even using careful study design and multivariate analyses.

Few randomised studies have been performed that shed light on the risk of hyperbilirubinaemia for VLBW neonates. The NICHD 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  $\mu$ mol/l)) in high risk newborns with birth weights less than 1250 g.<sup>15</sup> Kernicterus was found in four of 76 autopsied infants whose birth weights ranged from 760 to 1270 g. Their peak TSB levels ranged from 6.5 to 14.2 mg/dl (111 to 243  $\mu$ mol/l). The four affected infants were asphyxiated or had hyaline membrane disease, and all had some degree of intraventricular haemorrhage. Two had periventricular leucomalacia.<sup>15</sup> In this regard, some studies have suggested an association between hyperbilirubinaemia and cystic periventricular leucomalacia in low birthweight infants,<sup>44–46</sup> but others have not found this.<sup>40</sup> 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 leucomalacia. Periventricular leucomalacia 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 NICHD 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.<sup>47</sup> Scheidt and colleagues<sup>48</sup> 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 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.<sup>48</sup>

Although these observational and randomised study data are reassuring, few of the infants in the investigations had appreciably raised bilirubin levels.<sup>37-43</sup> 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.<sup>10</sup>

**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 relation between hyperbilirubinaemia and neuronal damage,<sup>19</sup> 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.<sup>6-8 49</sup> 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.<sup>50</sup> 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.<sup>50</sup>

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