FETAL AND NEONATAL EDITION

ARCHIVES OF DISEASE IN CHILDHOOD

*The Journal of the British Paediatric Association*

# *Annotations*

## Neonatal jaundice – a lighter touch

Many paediatricians must have wondered, as I have, when observing yet another healthy active but yellow infant receiving phototherapy whether the dramatic effect on the baby's colour and serum bilirubin has actually prevented a long term neurological impairment, or simply produced a worried mother and baby. While those with experience in developing countries know only too well of the ravages of kernicterus, and some can recall a case in the distant past in the UK, for most the danger remains elusive.

It is against this background that the clinician has to balance the relative risks of under treatment and over treatment. In the USA investigation and treatment of jaundice are presently more aggressive than in the UK, perhaps reflecting a greater anxiety concerning litigation than an innate caution. However views are changing and in a recent special article Newman and Maisels challenge current practice and propose a 'kinder gentler approach to jaundice in the term infant'.[1] The article based on an earlier review[2] and accompanied by commentaries from eight invited experts, tackles two important issues in the management of jaundice in term infants – evaluation and treatment.

### Evaluation of jaundice

DO WE NEED TO FIND A CAUSE?

At present the standard recommendations in the USA are that neonatal jaundice be evaluated and treated aggressively.[3–5] Measurement of serum bilirubin concentration in all infants with significant jaundice is followed by complete blood count, blood group, Coombs' test, reticulocyte count, direct bilirubin estimation, and blood smear in infants with a serum bilirubin rising by >85 μmol/l per day, or exceeding 222 μmol/l. However most laboratory tests do not help to guide management, a recent study showing a low diagnostic yield in 5000 jaundiced infants weighing >2500 g, polycythaemia being found in three infants and ABO incompatibility or rhesus immunisation in 14%.[6 7]

Rhesus immunisation would normally be detected anyway through maternal blood typing for rhesus group and subsequent cord blood analysis, and the relevance of ABO incompatibility is uncertain. Although moderate jaundice is more common in ABO incompatible infants,[8] severe jaundice is uncommon and cannot be predicted by the presence of elution tests for haemolysis.[9] A further justification for investigation of jaundiced infants has been to look for possible sepsis, but it is rare for jaundice to be the only sign of sepsis and no such case was identified in a recent study of 171 newborn infants with severe jaundice.[10]

NEW RECOMMENDATIONS

Newman and Maisels recommend that jaundice should be evaluated clinically rather than with laboratory tests. Where community follow up is difficult to arrange, blood group and Coombs' tests should be performed routinely on cord blood and where isoimmunisation is suggested, follow up for jaundice and anaemia is advised. Infants with jaundice in the first 24 hours, moderate jaundice with a positive Coombs' test, anxious parents, illness in the baby or those with marked jaundice or a family history of litigation should also be closely followed up.

Alternative strategy, which is more applicable to the UK where community services are well developed, is that all infants are followed up closely for jaundice and tests for isoimmunisation are done only on those in whom significant jaundice develops. This approach offers more selective use of laboratory tests and better detection of infants with jaundice not due to isoimmunisation. Additional laboratory tests would be performed as clinically indicated.

### Treatment

HISTORY

Hsia *et al* showed in 1952 the strong correlation between serum bilirubin concentration and clinical kernicterus in infants with severe haemolytic disease.[11] The incidence of kernicterus was 30–50% in those with the highest concentrations. Exchange transfusion produced a dramatic reduction in serum bilirubin and effectively abolished kernicterus when the serum bilirubin was kept below 342 μmol/l. The incidence of clinical kernicterus in markedly jaundiced babies without haemolytic disease is much lower.[12–14]

In preterm infants without rhesus isoimmunisation there is considerable disagreement over the importance of hyperbilirubinaemia, some studies reporting clinical and pathological kernicterus in infants with a serum bilirubin concentration well below 342 μmol/l and others indicating no risk unless concentrations were well over 342 μmol/l.[15–17] More recent studies have shown no correlation between yellow staining of the brain in preterm infants and serum bilirubin and it is most likely that pigmentation occurs secondary to neuronal damage.[18]

The large American collaborative perinatal project linked moderate increases of serum bilirubin concentration in the newborn period to lower developmental scores, lower IQs, and increased risk of neurological abnormalities at bilirubin concentrations previously considered safe.[19 20] These findings led to a belief in a spectrum of bilirubin toxicity. The advent of an apparently harmless treatment, phototherapy,

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encouraged the treatment of jaundice to be undertaken at much lower concentrations of serum bilirubin than were ever considered safe for treatment by exchange transfusion. The use of phototherapy has become widespread and very frequent, rates of up to 25% being reported in breast fed term infants in one study.[21]

BILIRUBIN AND THE BRAIN

A review of the relationship between serum bilirubin and 'brain damage' in term infants without haemolysis, found no evidence of an effect on cognitive impairment (IQ or development), neurological abnormality, or hearing loss.[2] This review of several large studies concentrated on estimating the magnitude of the effect of a single risk factor, peak total serum bilirubin concentration, on cognitive development, abnormality on neurological examination, and hearing in full term infants without haemolytic disease.

It also analysed results from the collaborative perinatal project, concluding they were biased by inclusion of preterm infants and those with haemolytic disease in whom the risks of hyperbilirubinaemia are considerably greater. Further, of 15 000 subjects with complete hearing evaluations at the age of 8 years, those with the highest risk of sensorineural hearing loss were those with the lowest bilirubin concentrations.

With regard to IQ, a more recent study of 1948 17 year old draftees showed an association between IQ <85 and serum bilirubin over 342 in term males but neither mean IQ, physical or neurological abnormality, nor hearing loss were related to serum bilirubin concentration. The result may be due to chance as it was one of many outcome variables analysed for statistical significance. Its clinical significance is unclear.

Other important studies in this area include the relationship between bilirubin binding capacity and adverse outcome, some finding a positive association and others not. Unfortunately the test for bilirubin binding capacity is not readily available.

Studies of brain stem auditory evoked responses and visual evoked potentials have shown 'improvements' after exchange transfusion in both term and preterm infants.[22 23] While these provide a direct measure of reversible bilirubin toxicity they do not indicate at what level the effect is irreversible and hence are of uncertain clinical value.

Newman and Maisels' review concluded that the risk of bilirubin induced damage is low in term infants without haemolysis.

TREATMENT EFFICACY

Early studies strongly suggest that exchange transfusion is effective in preventing kernicterus in infants with severe haemolysis, however the relevance of these studies to present practice is questionable as these infants were often seriously ill, asphyxiated, or preterm.[11] The tremendous changes in neonatal care and pharmacological practice since then might well have reduced the risk of kernicterus, for example better treatment of hypoxia and acidosis and avoidance of the dangers associated with sulphisoxazole and high dose vitamin K.

The risks of exchange transfusion are well known. Phototherapy is effective in reducing serum bilirubin concentration and appears to be safe as judged by neurodevelopment outcome.[24] However the separation of mother and infant by the barrier of phototherapy, together with fear and anxiety engendered in the parents and their effects on bonding and feeding, are likely to produce a negative impact on the nursing mother. Loose stools due to excretion of Z-lumirubin is a well recognised problem of phototherapy.

A further potential hazard is the effect of high intensity light on the retina.[25] While this can effectively be countered by the use of eye patches, the possible adverse effect of continuous visual occlusion, sometimes for several days, is worthy of consideration.

TREATMENT RECOMMENDATIONS

In aiming for 'a kinder, gentler approach' Newman and Maisels recommend a relaxation in treatment schedules as follows: phototherapy when the serum bilirubin concentration is 225–330 μmol/l in babies who are sick or have haemolysis and at serum bilirubin 300–375 μmol/l in well babies without haemolysis. They recommend exchange transfusion at a serum bilirubin concentration of 300–400 μmol/l in sick babies or those with haemolysis and at 425–500 μmol/l in well babies without haemolysis. A recommendation that will surprise many British paediatricians is that breast feeding be interrupted in well infants without haemolysis when the serum bilirubin is 275–425 μmol/l.

## Commentary from the US

Newman and Maisels' review is accompanied by commentaries written by eight eminent American authorities. The tenor of most of their comments suggests agreement with a cautious move towards the new recommendations. However, several express the fear, voiced by Valaes 'What happened to the dreaded dragon?' (kernicterus). Were our fears unjustified or have we simply tamed the beast and need to continue our efforts lest it be again unleashed on our babies? Another expresses serious concern that the review 'almost completely downplays the toxic potential of bilirubin' and about the effects of moderate hyperbilirubinaemia on IQ, a view discounted by most of the other commentators.

The prevention of jaundice by good breast feeding strategies and support for the nursing mother as well as the avoidance of water supplementation are suggested by one, and another makes a plea for early use of phototherapy, stressing it is more effective and reduces prolonged exposure to raised serum bilirubin concentrations.

While cautiously agreeing with the new recommendations of Newman and Maisels two commentators stress the importance of undertaking a national evaluation of the outcome of these proposals.

## Practice in the UK

OMISSIONS

For those working in the UK there are several surprising omissions from both the review and commentaries. First none mention the value of the Hillingdon Hospital chart, relating serum bilirubin to age with an action line for phototherapy.[26] The aim of Finlay and Tucker when introducing it was to restrict the use of phototherapy and to emphasise the importance of early phototherapy for early onset jaundice.

There is no mention of the value of intermittent phototherapy, which when given for one hour out of every four has been shown to be as effective as continuous phototherapy.[27] Not only does this reduce the irradiance to the infant and separation from the mother, but it makes sound economic sense in developing countries with a limited supply of phototherapy equipment.

The potential dangers to the baby's eyes both from the high irradiance and possibly from prolonged occlusion must also be questioned in the context of a treatment which may not be needed.

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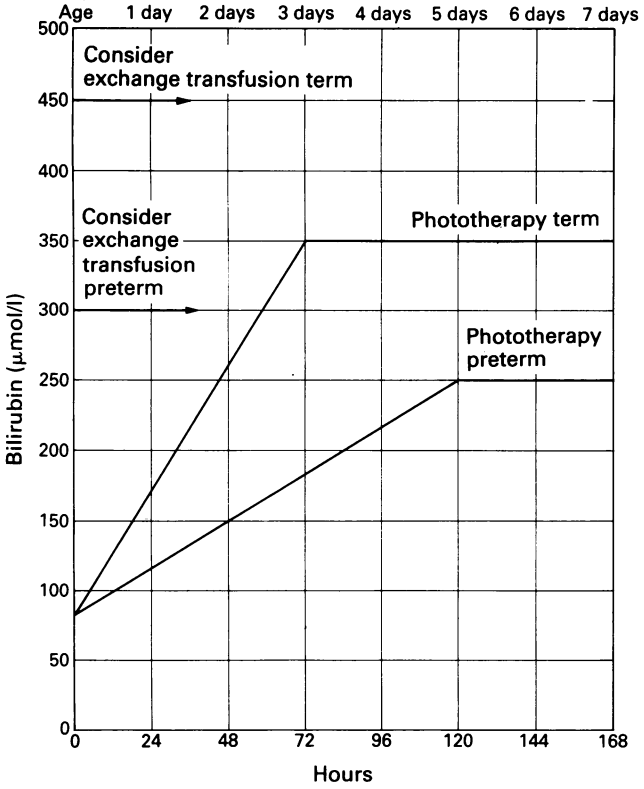


*Bilirubin chart modified from that used at Hillingdon Hospital (see Finlay and Tucker[26])*

SURVEY OF PRACTICE

In an attempt to sample current views, a postal questionnaire was sent to 60 paediatricians in the UK whose experience ranged from 10–38 years. Of the 49 replies, one third had seen a case of clinical kernicterus in the UK in a rhesus baby, and one third in a non-rhesus infant, many indicating the severity of the infants' neonatal illness evident many years ago. Very few believe an increased serum bilirubin concentration can affect IQ in the absence of kernicterus in term infants, but some had doubts about preterm infants. The ranges of serum bilirubin at which phototherapy and exchange transfusion would always be used in term infants, 250–400 and 350–500 μmol/l respectively, are similar to the new recommendations of Newman and Maisels. All expressed some caution in preterm infants and most in infants with rhesus disease.

About one half used the Hillingdon Hospital chart or a local modification to guide phototherapy use and many others took account of postnatal age and gestational age. Over two thirds would not interrupt breast feeding and most others would do so only occasionally or for less than 24 hours. Most would not normally offer extra fluids, but those who would often felt strongly about it.

With regard to obstructive jaundice, an overwhelming majority felt the screening at 6 weeks of age should not be brought forward as has recently been suggested.[28] Better education is needed of parents, midwives, and general practitioners in the importance of detecting obstructive jaundice. Finally, 60% feel their present policies could safely be liberalised (that is adopt a less aggressive approach to management), caution being expressed regarding preterm infants.

## My future practice

The virtual disappearance of clinical kernicterus from UK practice in recent years and the accumulating evidence that in infants who are otherwise well there is no relationship between a high serum bilirubin concentration and adverse neurodevelopmental outcome strongly suggests a need to reconsider our approach to treatment of jaundice.

WHEN IS JAUNDICE IMPORTANT?

It is helpful first to decide when jaundice is important and then when and how to treat it.

- Jaundice in the first 24 hours suggests haemolysis and requires investigation and early treatment.
- Marked jaundice at any age requires investigation and consideration of treatment.
- Prolonged jaundice beyond 2 weeks of age in term infants (approximately 2·4% of breast fed infants),[29] and beyond 3 weeks in preterm infants may indicate serious disease such as hypothyroidism, urinary tract infection, obstructive jaundice, and rarely galactosaemia. It demands clinical assessment and investigation but rarely needs to be treated.

WHEN AND HOW TO TREAT

A modification of the Hillingdon Hospital chart[26] is helpful in guiding and limiting the use of phototherapy (figure). In well term infants I would advocate phototherapy if serum bilirubin exceeded 350 mmol/l by 72 hours, but at lower concentrations before that age, and would consider exchange transfusion if bilirubin exceeded 450 μmol/l and proceed to exchange transfusion if >500 μmol/l. Corresponding figures for preterm infants would be phototherapy if the serum bilirubin was >250 μmol/l at 120 hours (allowing for the later physiological peak), considering exchange transfusion if it was >300 μmol/l, and proceeding if it was >350 μmol/l. In sick infants treatment would start at lower concentrations of serum bilirubin.

The incidence of jaundice may effectively be reduced by encouraging proper breast feeding practices, stimulating milk production by regular suckling, and avoiding fluid supplementation. The importance of inadequate energy intake and of fluid supplementation in raising the serum bilirubin concentration have been clearly demonstrated[21 30] but half the breast fed babies in a recent study in Newcastle had received water.[31] I would not stop breast feeding in a jaundiced infant unless exchange transfusion was being considered, and then only temporarily.

Separation of mother from baby should not be allowed to result from the use of phototherapy. Intermittent phototherapy has clear advantages for mother and baby and is as effective as continuous treatment.[27]

Finally, if we are to be less aggressive in managing jaundice we must ensure that outcomes are carefully monitored, perhaps using the British Paediatric Surveillance Unit as a means of ascertainment of cases of clinical kernicterus and its sequelae.

## Conclusion

Management of jaundice in the US is moving from an aggressive approach to a more liberal one. Paediatricians in the UK have already adopted the 'gentler' approach currently being proposed in the US and many wish to move even further in this direction. This approach is supported but demands careful surveillance of outcome.

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# Laryngo-tracheo-oesophageal cleft

A cleft larynx is a rare but significant cause of congenital respiratory distress and aspiration. Management of this defect is complex and despite recent advances the overall mortality remains unacceptably high. Although over 179 cases have been reported to date there continues to be significant delay in diagnosis, perhaps due to a reluctance to perform neonatal bronchoscopy, and appropriate intervention which contributes to increased morbidity and mortality. However these patients often have other significant abnormalities which may independently affect their outcome. Of these gastro-oesophageal reflux, microgastria, ventricular septal defect, bronchial and tracheal stenosis are among the most clinically significant.

The approximate incidence is one in 10 000 to 20 000 live births, although the true incidence may be higher.[1] There is no consistent pattern of inheritance but males are affected more commonly than females and sporadic familial occurrences have been described. Laryngeal clefts have also been reported with the G syndrome (X linked or autosomal dominant) and in the Pallister-Hall syndrome. Clefts are classified into four types based on the length of involvement of the trachea. The more extensive the defect the greater the potential for fatal pulmonary complications and poor outcome. The defect extends to the cricoid in type 1, involves the cricoid and/or proximal trachea in type 2, extends to the carina in type 3, and into one or both mainstem bronchi in type 4. Fortunately types 1 and 2 cleft constitute the most common abnormality seen.

A laryngeal cleft arises from abnormal separation of the larynx-trachea and the oesophagus. At 25 days the laryngotracheal septum develops and begins to fuse in a cephalad direction and so separate the distal trachea from the developing oesophagus. At the same time the cricoid cartilage develops as two lateral centres of chondrification from the sixth branchial arch. Dorsal fusion of the cricoid plate is complete by day 50–54 and laryngeal muscular development then ensues. The range of abnormalities seen results from defects in cricoid chondrification or fusion (types 1 and 2) and or failure of fusion of the laryngotracheal septum (types 3 and 4). This embryological difference is highlighted by the occurrence of isolated tracheo-oesophageal fistula that occurs in the absence of any laryngeal abnormality. The exact cause of the disorder is unknown but substance abuse in the first trimester and neural crest abnormalities have been cited as potential factors.[2]

The result is an abnormal communication between the larynx, trachea, and oesophagus. The infant is thus at risk from repeated aspiration of food and saliva, recurrent pneumonia and respiratory distress, although minor type 1 clefts may be asymptomatic. A laryngeal cleft should be considered in any infant who develops aspiration and cyanosis after feeding and respiratory distress, although other causes such as choanal atresia, tracheo-oesophageal fistula, tracheomalacia, and laryngopharyngeal dysmotility should also be considered. Typically, cleft patients are said to present with a classical triad of increased salivation, stridor, and a low soundless cry.[1] However this triad is rare and most infants develop aspiration and cyanosis after feeding and this combined with postpartum respiratory distress should stimulate urgent bronchoscopy. The cry is usually harsh and not silent and stridor is uncommon. Secretions are increased and there is significant difficulty with feeding. Contrast radiography may show the abnormal communication but this is often difficult to distinguish from simple spill over. A lateral neck *x* ray film may show an anteriorly displaced nasogastric tube or a posteriorly displaced endotracheal tube. Successful management of these infants requires a low threshold for bronchoscopy and thus early diagnosis, a secure and stable airway, and provision of adequate nutrition. Most require a tracheostomy and gastrostomy at the outset. A fundoplication may be required if there is troublesome gastro-oesophageal reflux. Other procedures such as gastric transection are not

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