What's new in neonatal jaundice?

This article reviews current issues in the risk management of neonatal jaundice. These include discussion of challenging aspects of the recent National Institute for Clinical Excellence (NICE) guideline, an account of an evidence update for this guideline and consideration of possible future developments, including screening for bilirubin encephalopathy, audit of current practice and surveillance for severe hyperbilirubinaemia.

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Key points

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1. Controversial and challenging features of the NICE neonatal jaundice guideline (2010) include the recommendation to measure bilirubin in all visibly jaundiced neonates, risk assessment of neonates for jaundice and the recommended treatment thresholds.
2. The use of bilirubin nomograms has not been shown to reduce the incidence of bilirubin encephalopathy.
3. A recent Jaundice Evidence Update found no new evidence to suggest changes to NICE guidance.
4. There is insufficient evidence currently to support screening of neonates for hyperbilirubinaemia.

There have recently been several important developments in the understanding of neonatal jaundice, and refinements in monitoring and treatment. This paper reviews some of these developments and makes suggestions for further initiatives to help improve practice in neonatal jaundice in the hope of reducing the incidence of the rare but devastating sequelae of bilirubin encephalopathy and kernicterus.

Here, the term 'bilirubin encephalopathy' is used to refer to acute neurological dysfunction associated with hyperbilirubinaemia. While 'kernicterus' is strictly speaking a pathological term, it is often used to refer to the long-term neurodevelopmental effects of bilirubin encephalopathy, and it is in this latter sense that the term is used in this paper.

Neonatal jaundice has been the subject of much interest in the past 15 years following reports, initially from North America[1] and later from Europe[2], of the apparent re-emergence of bilirubin encephalopathy and kernicterus in term and near term infants. While there is some dispute as to whether this problem had ever disappeared[3], these reports generated concern among neonatologists. This was related in part to concern that control of rhesus disease had led to a complacent approach to the recognition, investigation and management of neonatal jaundice. For example, the UK surveillance study of severe hyperbilirubinaemia, supported by the British Paediatric Surveillance Unit (BPSU), reported 108 babies in two years with severe hyperbilirubinaemia (unconjugated serum bilirubin (SBR) ≥510μmol/L)[4]. Fewer than half of these babies underwent exchange transfusion despite some showing symptoms consistent with bilirubin encephalopathy, and 14 showed clinical features, brain MRI changes, post-mortem findings or sequelae clearly consistent with bilirubin encephalopathy/kernicterus. Other national surveillance studies have reported similar findings, both clinical and demographic – many babies with severe jaundice are readmitted to hospital following 'early' neonatal discharge, many are near term and babies from ethnic minorities are represented disproportionately[5-7]. Perhaps a surprising proportion of affected babies, including some who developed bilirubin encephalopathy, were still in hospital when severe jaundice was eventually recognised. The vast majority of affected babies have been breastfed, some showing clinical and biochemical evidence of lactation failure.

These observations have given rise to concern about risk management of neonatal jaundice, for example:

- Are babies who are at particular risk being identified and monitored appropriately?
- Regardless of risk, is jaundice in neonates identified in a timely manner?
- When jaundice is identified, is treatment timely and effective?
- Is sufficient support offered to lactating mothers and their babies before and after discharge?

Concern about these questions was heightened by the findings of a survey of UK treatment of neonatal jaundice[8]. The survey showed wide variation in practice, with almost as many treatment schemes as units surveyed. Some regimes appeared lax, with high SBR thresholds for phototherapy and exchange transfusion, and some made no allowance for differential treatment of preterm babies. Some of this wide

variation in practice probably reflected variation in risk perception and tolerance among clinicians and, more importantly, the relative paucity of evidence to inform treatment of neonatal jaundice.

In light of these concerning findings and such variation in practice, the National Institute for Health and Clinical Excellence (NICE) commissioned a Guideline Development Group (GDG) for neonatal jaundice in 2007. The group comprised clinicians with experience and expertise in jaundice, clinical and academic midwives, a health visitor, a biochemist, a general practitioner and lay members. The brief was to consider jaundice in the first month of life, to give recommendations on recognition, investigation and treatment and to provide written information for patients and carers.

The group met over a period of two years to review evidence and prepare its guidance. Following a draft publication and feedback from stakeholders, the full guidance was published in 2010. The full and abridged versions are available on the NICE website[9], and comprehensive summaries and reviews of the guidance have been published recently[10-12]. This article will list the main components of the NICE guideline, consider some aspects that may offer the greatest challenge to health professionals, discuss developments since the publication of the guideline, and recommend further developments in risk management of neonatal jaundice.

- Provision of a pathway for the approach to jaundice in all neonates.
- Advice for greater vigilance (and early review) of neonates with the following factors:
  - gestation <38 weeks
  - previous sibling with jaundice requiring phototherapy
  - mother's intention to breastfeed exclusively
  - visible jaundice in the first 24 hours
- Recommendation that bilirubin must be measured in all babies with visible jaundice.
- Endorsement of transcutaneous bilirubinometry in clearly specified circumstances.
- Generation of pathways for phototherapy and exchange transfusion, reinforced by gestation-specific, consensus-based, treatment thresholds.
- Practical advice for managing standard and intensified phototherapy.
- Production of an information leaflet for parents and carers.

TABLE 1 Important aspects of the NICE guideline on neonatal jaundice.

Summary of the NICE guidance

The most important aspects of the NICE guideline[9] are shown in **TABLE 1**.

Challenging and controversial aspects of the NICE guidance

Measuring bilirubin in visibly jaundiced babies

One of the most significant recommendations is the advice to measure bilirubin in all visibly jaundiced babies. This was based on a review of the evidence concerning visual assessment of jaundice. This indicated clearly that, while the absence of visible jaundice had good negative predictive value, even experienced health professionals are inaccurate in their visual estimation of hyperbilirubinaemia in jaundiced babies.

This recommendation has substantial implications for relevant health professionals, particularly a midwife working in the community. When a midwife encounters a jaundiced baby, according to the guideline, the bilirubin should be measured. If a transcutaneous bilirubinometer is available this can be used if the baby is mature and more than 24 hours old. If not, or there is no access to a bilirubinometer, or the bilirubinometer reading exceeds 250μmol/L, arrangements should be made for laboratory SBR measurement. Ideally this should be measured as soon as possible, so taking a blood sample and taking it back to the laboratory at the end of rounds is inappropriate. However, returning immediately to the hospital with the sample will inevitably, and repeatedly, disrupt the midwife's rounds.

Some of these problems can be allayed by providing bilirubinometers to midwives, particularly those who work in the community. This carries substantial resource and training implications – bilirubinometers are not cheap. Should they be provided to all community midwives, or should the training and resource be concentrated on a smaller group? Different arrangements may be appropriate in different districts. In one of the authors' districts (DM), the latter approach has been adopted, with three 'locality' community midwives who have had training in routine neonatal examination being trained in the use of, and provided with, bilirubinometers. This may work in a geographically small or defined district, but there are problems when the locality midwife is not available, and the arrangement carries the risk of de-skilling the other midwives. Yet, to provide all midwives with bilirubinometers, and to train them in their use, may be prohibitively expensive. While the health economic analysis accompanying the NICE guideline suggested that preventing one to two cases of kernicterus per year would pay for the rollout of transcutaneous bilirubinometry, nonetheless for individual units the required investment is substantial.

Enhanced surveillance of neonates at greater than average risk for jaundice

Risk assessment, to offer enhanced monitoring of babies at greater than average risk for neonatal jaundice, is also controversial and challenging. In the days before early discharge of mothers and babies this was not an issue, since most remained in hospital long enough for jaundice to present itself. Now, however, most mothers and babies are discharged before jaundice has appeared and this may well be a factor in the apparent resurgence of severe hyperbilirubinaemia. A universal system of community surveillance in which neonates received daily review in the first week of life could accommodate this challenge, particularly if informed by the need to measure bilirubin in all jaundiced babies.

Unfortunately, constraints on resources, particularly numbers of midwives, render this ideal system unattainable, and midwives increasingly have to prioritise their work. This entails offering enhanced input, with earlier and more frequent visits to mothers of babies at greater than average risk for hyperbilirubinaemia. Community midwives, of course have responsibilities other than dealing with neonatal jaundice. The guideline advice on risk assessment is intended to assist hospital and community midwives in providing enhanced input to babies at greater than average risk. It is, however, not without problems and controversy. It has been criticised as being too broad to be useful, for example one of the risk factors – mother's intention to exclusively breastfeed – may apply to up to 70% of mothers of newborn babies. How can this help

midwives to prioritise their work?

Systematic attempts have been made to assign risk for later hyperbilirubinaemia before discharge of newborn babies. These attempts have included plotting pre-discharge bilirubin on a nomogram, since high pre-discharge bilirubin measurements may 'track' for later hyperbilirubinaemia. The best-known example, the Bhutani nomogram, was devised from bilirubin measurements in a population of neonates in Philadelphia and excluded babies with known haemolysis[13]. Bilirubin nomograms have shown moderate predictive value, particularly when pre-discharge bilirubin is combined with clinical risk factors similar to those in the NICE guideline. They have not been shown, however, to convincingly reduce the incidence of important outcomes such as extreme hyperbilirubinaemia or bilirubin encephalopathy[14]. This is perhaps not surprising since these are still relatively infrequent adverse outcomes and they are often unpredictable, being associated, for example, with sepsis, lactation failure and glucose-6-phosphate dehydrogenase (G6PD) deficiency as well as hyperbilirubinaemia.

The main value of highlighting risk factors is to raise awareness among health professionals (and parents) and to encourage particular vigilance about jaundice when the factors are present.

Treatment thresholds for phototherapy and exchange transfusion

The treatment thresholds in the guideline have been another area of controversy. Some stakeholder feedback during the consultation period before final publication expressed concern that the thresholds were too aggressive and might lead to overtreatment of neonatal jaundice. The GDG was well aware of the lack of evidence to inform these thresholds and that previous guidelines included consensus, not firmly evidence-based, thresholds. In the 2004 American Academy of Paediatrics guideline, for example, the treatment graphs for phototherapy and exchange transfusion were accompanied by a qualification that the advice was indeed a consensus and that there was not universal agreement about them among their expert group[15]. The NICE GDG recommended treatment thresholds that were intended to offer a reasonable balance between thresholds acceptable both to 'hawks' and 'doves' and there was substantial unanimity about the thresholds debated and agreed. Also, there was a conscious attempt to produce advice that was practical and attainable, particularly when designing the early slope of SBR thresholds. Treatment advice has been produced as a series of charts, one for full term babies (gestation ≥ 38 weeks) (**FIGURE 1**), and one for each week of gestation down to 23 weeks. These charts are readily available, and can be downloaded for clinical use, from the NICE website.

Undue emphasis should not be placed just on SBR levels when making treatment decisions about neonatal jaundice. Other important variables include the baby's age and maturity (accommodated by the graphs), co-morbidity such as haemolytic disease, sepsis, dehydration and acidosis, the mode of feeding and the success of establishing lactation. One of the main potential benefits of the treatment advice is to encourage consistency in treatment, which must be an improvement on the pre-guideline situation. Since, at least in term babies, bilirubin encephalopathy typically occurs at SBR levels well above the treatment thresholds[16] their use, in association with timely recognition and assessment of neonatal jaundice, may help to reduce the incidence of this potentially preventable disaster. This may not reassure the 'doves', who fear that compliance with the guideline will result in overtreatment of neonatal jaundice. In the absence of evidence for or against this, since phototherapy used according to the guideline is safe and effective and may help prevent the disaster of bilirubin encephalopathy, perhaps the burden of proof, to show that higher treatment thresholds are safe, rests with the doves.

Evidence update

In January 2012, NICE commissioned an Evidence Update Advisory Group to review evidence published since the production of the guideline and to consider whether any such evidence justified change in the guidance. A professor in neonatal medicine chaired the group; it included the three consultants in the original GDG and another consultant neonatologist. It

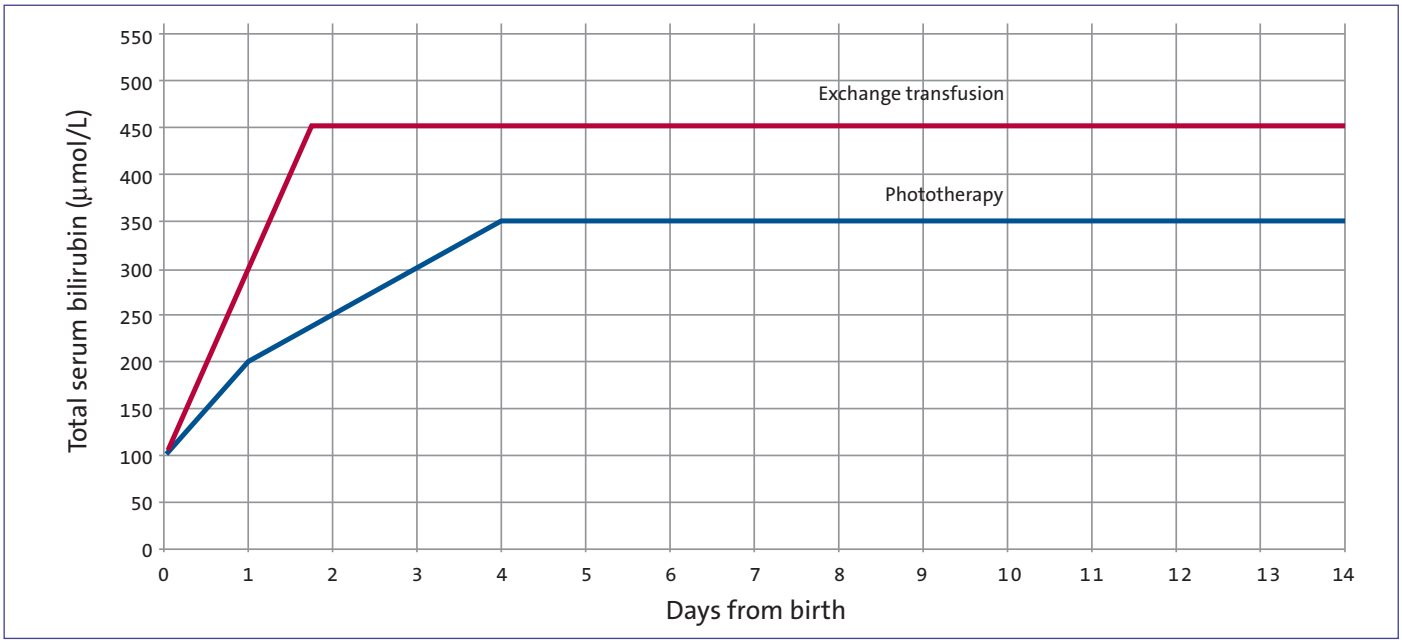

FIGURE 1 Treatment threshold graph for baby with neonatal jaundice, born at or greater than 38 weeks' gestation. Adapted from the NICE guideline[9].

received evidence appraisal and editorial support from a NHS Evidence project team.

The NHS Evidence project team conducted searches for relevant studies from June 2009 (the end of the search period for the full guideline) to November 2011. Databases searched included CINAHL, the Cochrane Database of Systematic Reviews, Embase, Medline and the Database of Abstracts of Effects. The main, but not the exclusive, focus of the search was management of jaundice. In all, 131 studies were identified and after sifting, eight studies were considered in the published update[17].

In short, most of the studies reviewed provided no substantive evidence to suggest that the full guideline recommendations need to be changed. Transcutaneous bilirubinometry was accompanied by the need for fewer blood tests for jaundiced babies than visual assessment[18]. Prone positioning provided no advantage during phototherapy compared to supine positioning[19]. LED for providing blue light was no more effective than fluorescent tubes[20]. Triple was no more effective than double phototherapy[21], and in a small study the mean decrease in SBR after 24 hours was non-significantly greater in babies randomised to double compared to single phototherapy[22]. In a larger study this difference may have reached statistical significance. White curtains, as noted in the original NICE guidance, offer no advantages[23] over phototherapy alone (**FIGURE 2**).

Two studies reported findings that might in future lead to changes in the guidance. A pilot study was conducted to determine whether phototherapy could safely be stopped at a higher SBR level (17μmol/L less than the treatment threshold compared to 51μmol/L below the threshold as recommended in the current guidance). The duration of phototherapy was significantly shorter in the 'high threshold' group, and length of hospital stay was significantly reduced[24]. There was no significant difference in the need for further phototherapy between the groups. Thus, using the higher stopping threshold appeared to be safe and to reduce the duration of intervention. The authors stated their intention to complete a definitive study based on the findings of this pilot study. Should their findings be replicated in a larger study, guidance might need to be changed to accommodate the clinical and health economic attractions of shorter treatment duration and hospitalisation, with no compromise of safety.

FIGURE 2 Phototherapy: the mainstay of treatment for significant jaundice.

The second study offering promise was a randomised controlled trial of albumin infusion before exchange transfusion compared to exchange transfusion alone in babies with non-haemolytic jaundice[25]. Babies randomised to albumin received 1mg/kg albumin one hour before exchange transfusion. Compared to controls, their SBR levels were significantly and substantially lower both six and 12 hours after the intervention. No babies in the albumin group needed a second exchange transfusion, whereas four babies in the control group did. These findings may lend support to the intuition of some clinicians that albumin priming is beneficial in hyperbilirubinaemia at or approaching exchange transfusion levels. It was not recommended in the original guidance because of lack of evidence for such benefit. If further studies replicated these findings, this might inform a change in guidance.

Screening for bilirubin encephalopathy/kernicterus

Is there a case for screening for bilirubin encephalopathy/kernicterus? In 2007, the National Screening Committee (NSC) judged that, according to its criteria, such a case had not been made[26], and in 2009 the United States Preventive Services Task Force concluded that there was insufficient evidence at the time to recommend screening of neonates for hyperbilirubinaemia[27]. While the condition is of undoubted clinical and public health importance, there is no threshold of SBR above which the risk of kernicterus is clearly defined. As discussed above, pre-discharge screening, even when combined with clinical risk scores, has not convincingly been shown to reduce morbidity or mortality from bilirubin encephalopathy, and some cases present rapidly and unpredictably in the absence of definable risk factors. The NSC is currently reviewing its advice, taking account of new research. It is likely that further research on the natural history of bilirubin encephalopathy, the relationship between SBR and bilirubin encephalopathy and the utility of pre-discharge screening will be needed before a substantial change to universal screening in the UK occurs.

Future developments in neonatal jaundice

What of other developments in neonatal jaundice? One of the recommendations of the NICE GDG was to establish a national kernicterus registry, which would help in monitoring national trends and could facilitate sharing the findings of root cause analyses of individual cases. There are practical challenges to establishing and maintaining disease registries. The BPSU, while supporting surveillance of rare disease, does not consider establishing registries to fall within its remit. Reporting cases would be the primary responsibility of individual clinicians or neonatal units.

Hopefully, this would be a rare experience for such individuals and many cases may have medico-legal implications and be the subject of litigation. Individual clinicians or units may, therefore, be reluctant to report cases or share the findings of local root cause analyses. Reporting could, however, be triangulated and other sources could include medico-legal proceedings and even parents of affected babies. For a registry to be successful, clinicians and the public need to be persuaded of the anticipated benefits, and challenging issues relating to consent and confidentiality would have to be addressed.

Other measures could be taken to evaluate developments in neonatal jaundice. First, compliance with the NICE guideline could be determined. Clinicians are expected to audit their compliance with relevant NICE guidelines and NICE provide audit tools to facilitate this. It would be very interesting to survey national compliance with the jaundice recommendations, particularly with regard to the challenging issues discussed above, such as uptake of transcutaneous bilirubinometry and appropriate post-discharge follow-up of babies with 'risk factors'.

Second, the national surveillance study should be repeated to determine the current incidence of severe hyperbilirubinaemia and bilirubin encephalopathy. A reduction in these would not necessarily be causally associated with the implementation of the NICE guideline – other relevant factors could include heightened awareness and risk perception of jaundice. Nonetheless, for rare problems such as severe hyperbilirubinaemia and bilirubin encephalopathy, national surveillance can provide an invaluable snapshot of trends and associations.

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