NICE National Institute for Health and Care Excellence

2023 exceptional surveillance of jaundice in newborn babies under 28 days (NICE guideline CG98)

Surveillance report

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Surveillance decision

December 2023: After initial scoping of this topic area, we decided not to proceed with the update. Because of local variations in assays used, it is more appropriate for local laboratories to calibrate bilirubin measurements against the threshold table instead of having different threshold tables at national level.

We will update the NICE guideline on jaundice in newborn babies under 28 days. The update will focus on total serum bilirubin (TSB) thresholds for starting phototherapy or exchange transfusion in term babies with neonatal hyperbilirubinaemia.

As an interim measure prior to update, we have amended the threshold table and the section on how to manage hyperbilirubinaemia, with this statement: Note that there is variability between assays from different manufacturers in reported bilirubin measurement. Healthcare professionals should consult their local pathology laboratory when interpreting threshold tables.

Reason for the exceptional review

NICE received 2 external communications that identified a potential safety issue around the TSB threshold values for the management of newborns with hyperbilirubinaemia in the threshold table in the NICE guideline:

- a letter from Synnovis and the chief medical officer of Guy's and St Thomas' NHS foundation trust
- a copy of a Situation-Background-Assessment-Recommendation (SBAR) report from the national external quality assessment service.

Both communications said that variability between assays from different manufacturers in reported TSB levels for an individual baby have led to serious clinical incidents, in which newborn babies have inappropriately received phototherapy, and/or unnecessary admission to hospital, and/or assessment for exchange transfusion.

Methods

The exceptional surveillance process consisted of:

- Considering the evidence used to develop the guideline in 2010 and 2016.
- Considering relevant information from the previous surveillance review of the guideline in 2020, which also covered evidence from previous surveillance in 2012 and 2014.
- Examining related NICE guidance and quality standards.
- Considering the new evidence and information that triggered the review.
- Considering new or updated Cochrane reviews and national policy (none identified).
- Examining the NICE event tracker for relevant ongoing and published events (none identified as of 13 March 2023).
- Assessing the new information against current recommendations to determine whether to update sections of the guideline.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

Guideline development

The bilirubin threshold table for the management of babies aged 38 weeks or more gestational age with hyperbilirubinaemia was developed in 2010 by consensus from the guideline development group (GDG). This was informed by the hour-specific percentile based predictive bilirubin nomogram reported in Bhutani et al. 1999 (see section 1.3 in the full guideline from May 2010). The study reported on the predictive ability of a universal predischarge serum bilirubin measurement to screen for risk of subsequent significant hyperbilirubinemia in healthy term and near-term newborns (n=2,840; median gestational age=39 weeks) during the first postnatal week. It found that hour-specific TSB levels before hospital discharge 'can predict which newborn is at high, intermediate or low risk

for developing clinically significant hyperbilirubinemia (specifically defined as TSB levels ≥95th percentile for age in hours).'

In the 2016 update of the NICE guideline, a systematic search was conducted for studies published up to 13 August 2015 that were relevant to the review question 'what are the optimal total serum bilirubin (TSB) thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia?' The population included term babies (≥37 gestational weeks) with hyperbilirubinaemia or suspected hyperbilirubinaemia. The intervention of interest was the use of different TSB thresholds for starting phototherapy or exchange transfusion based on the age of the babies, and the associated outcomes or consequences (for the full review protocol, see appendix C in the addendum from October 2016).

One cohort study met the criteria (Argent et al. 1985). This was rated according to GRADE criteria as very low quality. The study (n=92) compared 3 groups (with 3 different TSB thresholds for initiation of phototherapy) of term babies who had clinical jaundice. It found that the number of babies who subsequently had complications, such as readmission or exchange transfusion, was higher in the group in which phototherapy was initiated at a higher TSB threshold.

Three cross-sectional studies (including Bhutani et al.) and 1 survey study were considered as additional supportive information to assist the committee's discussion due to the scarcity of direct evidence (no formal quality assessment was conducted as these 4 studies did not qualify as direct evidence). However, only the Bhutani et al. study contributed towards the committee's discussion for this review question.

No economic evidence was identified for inclusion in the economic systematic review.

It was concluded that the clinical evidence base in this area had not improved since 2010, and to update the bilirubin thresholds for the management of hyperbilirubinaemia in babies 38 weeks or more gestational age, a consensus based on topic experts' expertise and opinion was required. A targeted consultation was conducted with midwives and clinicians working in neonatology to seek their views and opinion on the threshold table (for further details, see appendix P in the addendum from October 2016). Based on the consultation findings, the committee agreed to remove columns in the 2010 threshold table on TSB values that indicated when a repeat bilirubin measurement in 6 to 12 hours should be performed and TSB values that indicated 'consider phototherapy and repeat bilirubin measurement in 6 hours' as in practice, the testing requirements advised by these

columns were not being implemented. The committee highlighted that actions for when bilirubin levels fall below the phototherapy thresholds should instead be addressed in separate recommendations (see recommendations 1.4.1 and 1.4.2).

The committee noted that clinicians followed the final 2 columns of the threshold table (when to 'start phototherapy' and 'perform an exchange transfusion unless the bilirubin level falls below threshold while the treatment is being prepared') which are reproduced by the threshold charts used in practice. The committee therefore proposed to make no changes to the actual treatment thresholds within the gestational age-based charts for starting phototherapy or exchange transfusion given there seemed to be no issues implementing these.

Previous surveillance of this guideline

The 2020 surveillance review did not identify any evidence in relation to TSB thresholds for starting phototherapy and exchange transfusion in neonatal hyperbilirubinaemia from a literature search for randomised controlled trials and systematic reviews published between 1 February 2014 and 4 July 2019. Neither topic experts nor stakeholders provided any evidence or highlighted any concerns with variability between assays from different manufacturers in reported bilirubin measurement.

Other relevant NICE guidance

Statement 3 of NICE's quality standard on jaundice in newborn babies under 28 days states that babies with hyperbilirubinaemia are started on treatment in accordance with standardised threshold tables or charts. Standardised threshold tables or charts are defined as those that help healthcare professionals to implement treatment thresholds for phototherapy and exchange transfusion in accordance with NICE's guideline on jaundice in newborn babies. These include treatment threshold graphs for NICE's guideline on jaundice in newborn babies. All tables or charts should take into account serum bilirubin level, gestational age and postnatal age. Information on variability between assays from different manufacturers in reported bilirubin measurement and the need for healthcare professionals to consult their local pathology laboratory when interpreting threshold tables or charts will be added to this quality statement.

Information that triggered the exceptional review

Letter from Synnovis and Guy's and St Thomas' NHS foundation trust

The letter from Synnovis and Guy's and St Thomas' NHS foundation trust questioned the accuracy of the TSB values within the NICE guideline's bilirubin thresholds table for management of babies 38 weeks or more gestational age with hyperbilirubinaemia. They noted that values were consensus-based, informed by a particular method of measuring bilirubin in the Bhutani et al. study (Roche Cobas analyser method), the method for which has changed over time. The original algorithm has also been updated and extended. This is outlined in a study by Bahr et al. 2021, which reports on a retrospective analysis of first TSB measurements of newborns from 15 years of universal bilirubin screening data at 20 hospitals (n=397,395 TSB values for primary analysis). Hour-specific TSB values were compiled into a nomogram by percentile. General agreement was reported with the Bhutani et al. nomogram for TSB values in the first 60 hours, but higher 75th and 95th percentile values in the 2021 version. In a sub-group analysis, some significant differences were found in TSB values: higher TSB values in newborns ≥35 weeks to <37 weeks gestational age compared with newborns ≥37 weeks (which is to be expected), lower TSB values in newborns of Black ethnicity and higher values in newborns of Asian ethnicity when compared with newborns of white ethnicity (see the equalities section for further discussion).

The letter says that the dependence of the algorithm on the bilirubin assay used was not considered during development of the NICE guideline and that 'if there is no primary agreed reference standard then biochemical assays tend to be subject to relative standardisation to achieve consistency across an assay supplied by any particular manufacturer.'

The letter reported that assays other than Roche (Cobas) for measuring bilirubin are now in common use. Importantly, these assays are not equivalent, and can therefore lead to variations in the reported bilirubin level for an individual baby that can have clinical consequences. Information was shared on the clinical consequences arising from a recent change in the analytical platforms used by Synnovis laboratories at Guy's and St Thomas' hospitals from Roche (Cobas) to a different manufacturer: 'in effect this changed the assay from 1 that read on the lower part of [the] spectrum to one that read 20% higher on average, but which was supposedly within acceptable standards for assay acceptance'. Reference was made to information reported in a study by Lyon et al. 2015 on the clinical impact of implementing the Roche bilirubin total Gen.3 method on neonate phototherapy.

This study found that replacement of 1 assay (the BILTS method) with 1 by Roche (the Gen.3 bilirubin method) was expected to result in a 7% decrease in newborns with TSB values meeting phototherapy thresholds. The authors said that it wasn't possible to establish whether the BILTS assay was associated with 'over-treatment' or the Gen.3 assay 'under-treatment'; but that, importantly, 'while standardisation of bilirubin assays remains elusive, nomograms based on bilirubin methods will remain susceptible to method-biases and patient care decisions will remain subject to this uncertainty'.

The impact at Guy's and St Thomas' hospitals of the change in the analytical platforms was a serious incident due to a 'marked increase' in the number of newborns requiring phototherapy and assessment for exchange transfusion. They reported that 'an emergency solution was introduced by comparing Roche and Abbott methods to introduce a 20% reduction factor in results reported to restore the status quo ante'. They said that 'such factors, though clinically necessary, pose difficulties for laboratory accreditation through the UK accreditation body.

The letter said that they undertook a survey of the literature (methods not provided) which 'identified a small number of papers that had noted this potential issue within manufacturers'. A study by Thomas et al. 2022 was referenced. This study was undertaken due to a clinical incident in which a newborn baby in Australia was 'transferred to a tertiary hospital for treatment of severe hyperbilirubinemia but on arrival was reclassified into a lower risk category due to a 20% difference in TSB between laboratories'. The study assessed interlaboratory variability of TSB values in newborns (11 samples across a range of total bilirubin concentrations) on 7 commercial platforms at 4 accredited medical laboratories. They found a 24% to 30% difference in results for individual samples which would, in some of the cases, lead to different clinical interventions. The differences were found to be 'largely due to a lack of standardisation of calibrator values' and the authors concluded that 'this has implications for healthcare resource use and possibly for the neurodevelopment of infants'.

Synnovis and Guy's and St Thomas' NHS foundation trust have requested that the original algorithm for management of neonatal bilirubinaemia in the NICE guideline is reviewed and (if necessary) updated. They also said that a review of the evidence should consider the effect that analytical methods and platforms may have on clinical decision making across UK neonatal units.

SBAR report

NICE subsequently received a SBAR report which said that difference in laboratories methods for measuring TSB are now 'significant enough that at high levels it is impacting on the treatment and management of neonates with hyperbilirubinaemia. This is particularly relevant if there are 2 different manufacturer analysers within a network, as 1 assay may meet the bilirubin threshold for treatment and another assay may not.' They provided an example of where variability in both the calibration standard and in the different methods used to measure bilirubin led to discrepancies in the care of 5 individual babies. It mentions 'individual hospital's own reported incidents' reporting serious untoward incidents in more than 1 hospital/network because of this.

The SBAR recommended that:

- NICE's guideline is reviewed, taking into consideration differences in current method performance for bilirubin measurements
- there is discussion between the Royal College of Pathology quality assurance in pathology committee (QPAC) and the Medicines and Healthcare products Regulatory Agency (MHRA) about the analytical differences between methods and manufacturers of bilirubin assays and the impact that this is having on patient treatment and management.

Equalities

The retrospective analysis of first TSB measurements in newborns, which resulted in a revised hour-specific serum bilirubin nomogram for neonates ≥35 weeks gestational age, reported that TSB values were statistically significantly lower in newborns of Black ethnicity and higher in newborns of Asian ethnicity (Bahr et al.). However the authors concluded that the differences in TSB values were not large enough to indicate a need for nomograms based on ethnic group. Therefore, while those undertaking the update of this topic area should be aware of potential differences in TSB values between newborns from different ethnic groups, these differences do not appear to be of clinical significance.

An equalities and health inequalities assessment was completed during this surveillance review. See appendix A for details.

Overall decision

The original recommendations in the NICE guideline for TSB treatment thresholds were based on 1 method of measuring bilirubin. NICE received 2 external communications providing evidence that the method of measuring bilirubin has changed over time, and other assays for measuring bilirubin are now in common use. The issue is that these assays are not equivalent, and this can lead to variations of up to 20% in the reported bilirubin level for an individual baby, which in turn can have clinical consequences, particularly if there are 2 different manufacturer analysers within a clinical network, as 1 assay may meet the bilirubin threshold for treatment and another assay may not. We have therefore decided that an update of the NICE guideline should take place, which will include a review of the evidence on the optimal TSB thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia, taking into account the effect that analytical methods and platforms may have on clinical decision making across UK neonatal units and how this impacts on the TSB threshold table values and recommendations within the NICE guideline. In the interim, because of the serious incidents that have occurred due to variability between different assays in reported TSB measurement, we have amended the NICE guideline to ensure that users are aware of this issue.

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