Screening to prevent kernicterus

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: 2

Bazian Ltd.

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Abbreviations List

AAP	American Academy of Pediatrics
ABE	Acute bilirubin encephalopathy
AgPT	Aggressive phototherapy
AUC	Area under curve
ConPT	Conventional phototherapy
CI	Confidence interval
DAT	Direct Antiglobulin Test
ELBW	Extremely low birthweight
E-ROR	Early rate of rise
E-TcB	Early transcutaneous bilirubin
ET	Exchange transfusion
G6PD	Glucose-6-phosphate dehydrogenase
IVIG	Intravenous immunoglobulin
LBW	Low birthweight
LR	Likelihood ratio
NICU	Neonatal intensive care unit
NPV	Negative predictive value
PPV	Positive predictive value
PT	Phototherapy
RR	Relative risk
SD	Standard deviation
SE	Standard error
TcB	Transcutaneous bilirubin
TSB	Total serum bilirubin
WMD	Weighted mean difference

Plain English Summary

The Condition

Kernicterus is a very rare complication that can happen if newborn babies have a high level of a substance called bilirubin in their blood. High levels of bilirubin can cause a common problem called jaundice. Jaundice in babies is often easy to detect due to a yellowing of the skin and the whites of the eyes.

Occasionally babies can develop much higher levels of bilirubin than normal. The high levels circulating in the blood can go into the brain and cause brain damage. This is called bilirubin encephalopathy which can cause the baby to become floppy, lethargic or irritable, or to have seizures. Sometimes the initial symptoms can also include coma and death. If not well treated bilirubin encephalopathy can cause permanent brain damage (kernicterus).

The Treatment

The most common treatment for hyperbilirubinaemia involves special fluorescent light, called phototherapy. This light is absorbed by the baby's skin. This helps break down bilirubin into forms that can more easily pass out of the body. Special charts that map levels of bilirubin against the baby's age help guide the need for treatment.

In some cases extra types of treatment are used as well as phototherapy. These can involve replacing the baby's blood with other blood from donors.

Screening and Previous/ Current UK NSC Recommendations

Screening has been suggested to prevent newborn babies with hyperbilirubinaemia from developing Kernicterus. The most recent review in 2011 recommended against screening due to many uncertainties. This review searched for evidence since 2011. It focussed on the areas in the 2011 review that required further evidence or were unmet.

Findings

This review found:

- no evidence that national screening could identify those at risk of developing kernicterus.
- that there is no established bilirubin threshold associated with development of kernicterus. This means it would be difficult to know what level of bilirubin puts the baby at high risk of kernicterus.
- current medical practice needs to be optimised before screening is recommended. There is limited evidence to understand whether this is currently the case.

Recommendation

The evidence suggests that the recommendation not to screen for Kernicterus should be retained.

Executive Summary

Condition

Kernicterus is a very rare complication of neonatal unconjugated (or indirect) hyperbilirubinaemia. High levels of unconjugated bilirubin are able to cross the blood-brain barrier and this causes neurotoxicity (acute bilirubin encephalopathy). The condition can present with symptoms such as altered mental status, lethargy, irritability, seizures and sometimes coma and death. If not effectively treated, bilirubin encephalopathy can lead to permanent brain damage (kernicterus) with long term neurological problems such as hearing loss and cerebral palsy.[1-3]

The build-up of bilirubin in the blood and tissues called jaundice - characterised by a yellowing of skin and the whites of the eyes - is a common complication developing in an estimated 60% of full-term infants and 80% of preterm infants. [1, 3] Around 5 to 11% of all infants develop severe or significant hyperbilirubinaemia with total serum bilirubin (TSB) levels above the 95th percentile.[1] Levels above the 99th percentile are reported to place infants at increased risk of kernincterus.[1]

The recognised risk factors for development of significant hyperbilirubinaemia are:[2, 3]

- gestational age of <38 weeks
- previous sibling requiring phototherapy for jaundice
- exclusive breastfeeding
- development of jaundice within the first 24 hours

Treatment

Phototherapy is the first-line or gold standard treatment for hyperbilirubinaemia in neonates. NICE recommend using consensus-based treatment tables and graphs that interpret total serum bilirubin (TSB) levels by infant age to determine which infants need phototherapy. The treatment works by converting unconjugated bilirubin into a water-soluble form that the body can excrete, so reducing serum bilirubin levels. Exchange transfusion may be used as an adjunct to phototherapy for infants at higher risk, and intravenous immunoglobulin (IVIG) is an additional treatment that may be used specifically for infants with Rhesus or ABO haemolytic disease.

Screening

Screening has been suggested to prevent newborn babies with hyperbilirubinaemia from developing Kernicterus. While current clinical practice involves diagnostic testing for hyperbilirubinaemia upon visual inspection of jaundice, a screening test would be likely to involve taking a routine bilirubin measurement, by blood or transcutaneous, for all infants.

Previous/ Current UK NSC Review

The current UK NSC recommendation on screening for Kernicterus in all newborns is from 2011. This recommended against screening due to a number of uncertainties. Bazian Ltd were commissioned to undertake this rapid review, which considers whether the volume and direction of the evidence produced since the 2011 external review indicates that the previous

recommendation should be reconsidered. Three main criteria will be considered, with particular focus given to areas the 2011 review identified as uncertain, or supported by insufficient evidence.

Findings

The review found:

- no new evidence that a national screening programme for all newborns could identify those at risk of developing kernicterus. No studies with adequate study selection were found. Studies that were included in the review discussion generally demonstrated poor performance of potential screening tests that were also not generalisable to the UK screening population.
- that, while phototherapy and exchange transfusion are known to be effective at reducing bilirubin levels, there is no established bilirubin threshold associated with development of kernicterus. Thus, change in bilirubin levels does not inform risk. Three trials provided some limited evidence that prophylactic/aggressive phototherapy for preterm, low birthweight infants may reduce risk of childhood neurodevelopmental impairment. However, this does not fully inform how effective the treatment would be for the full-term infants who would be the target of a national screening programme.
- There should be evidence of optimised management of clinical practice prior to the adoption of screening. NICE give clear guidelines for the identification and management of neonatal jaundice. There was limited evidence available to determine whether these guidelines to identify and manage at-risk infants are currently being followed in postnatal care units across the UK.

Recommendation

The evidence suggests that the recommendation not to screen for Kernicterus should be retained.

Introduction

Kernicterus

Kernicterus is a very rare complication of neonatal unconjugated (or indirect) hyperbilirubinaemia. Most unconjugated bilirubin is bound to albumin, but at high levels free, unbound bilirubin is able to cross the blood-brain barrier. This causes neurotoxicity (acute bilirubin encephalopathy) which can present with symptoms such as altered mental status, lethargy, irritability, seizures and sometimes coma and death. If not effectively treated, bilirubin encephalopathy can become chronic leading to permanent brain damage (kernicterus) with long term neurological problems such as hearing loss and cerebral palsy.[1-3]

An estimated 60% of full-term infants and 80% of preterm infants develop jaundice[1, 3] with peak levels of bilirubin at around 72 to 120 hours of age.[1] Around 5 to 11% of all infants develop severe or significant hyperbilirubinaemia with total serum bilirubin (TSB) levels above the 95th percentile according to postnatal age in hours.[1] Levels above the 99th percentile (25 to 30mg/dL) are reported to place infants at increased risk of kernincterus.[1]

The recognised risk factors for development of significant hyperbilirubinaemia are:[2, 3]

- Gestational age of <38 weeks
- Previous sibling requiring phototherapy for jaundice
- Exclusive breastfeeding
- Development of jaundice within the first 24 hours

Other risk factors include haemolytic disease such as maternal blood group incompatibility or glucose-6-phosphate dehydrogenase (G6PD) deficiency, or cephalohematoma or bruising.

NICE clinical guidance on Neonatal Jaundice 2010[3] (currently in the process of update[4]) recommends that babies with the above risk factors for significant hyperbilirubinaemia are identified, and that all babies are visually inspected for signs of jaundice in the first 72 hours of life. When indicated, bilirubin may be measured either transcutaneously (TcB) if available, or by TSB (all TcB levels above 250mmol/l require confirmation by TSB). Hyperbilirubinaemia is then managed according to NICE consensus-based treatment graphs and tables where level is interpreted according to postnatal age.[3]

The clinical identification and management of infants with hyperbilirubinaemia is therefore well established. This review aimed to see whether the evidence suggests that national screening of all infants - by any method - could prevent kernicterus.

Basis for current recommendation

The most recent UK NSC external review of neonatal screening for prevention of kernicterus conducted in 2011 [5] concluded that a national screening programme for prevention of kernicterus could not be recommended due to several key uncertainties:

- Hyperbilirubinaemia is a risk factor for kernicterus. However, there is no clear cut-off bilirubin level that accurately identifies those who will progress to kernicterus, and cases have been observed across a range of bilirubin concentrations.
- NICE[3] recommendations to monitor all newborns for signs of jaundice in the first 72 hours after birth (particularly the first 24 hours), and clear treatment algorithms for

phototherapy and exchange transfusion, were expected to give good coverage of at-risk infants, giving the potential for early treatment and reduction in the number who will develop significant hyperbilirubinaemia.

- There was uncertainty on whether current bilirubin-lowering treatments would prevent kernicterus.
- Pre-discharge risk assessment is not currently recommended by NICE.[3] This was highlighted as an area for further research as significant hyperbilirubinaemia may develop at home within the first week of life.

Following the 2011 review, the UK National Screening Committee concluded that systematic population screening for prevention of kernicterus is not recommended.

Current update review

The current review considers whether the volume and direction of the evidence produced since the 2011 external review indicates that the previous recommendation should be reconsidered. Three main criteria will be considered, with particular focus given to areas the 2011 review identified as uncertain, or supported by insufficient evidence. The main criteria and key questions reviewed are:

Table 1. Key questions for current kernicterus update review

Criterion	Theme	Key Questions (KQ)	# KQ Studies Included
5) There should be a simple, safe, precise and validated screening test.	1) Has our understanding of the epidemiology, natural history and disease marker improved enough to provide us with a sufficiently robust screening test for preventing kernicterus?	a) Is there any new evidence on a serum bilirubin level which is sufficiently predictive of risk of kernicterus?	2 cover TSB but not exclusively
		b) Could alternative methods be valid screening instruments for risk of kerincterus?	4 cover TcB with/without risk factors
10) There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	2) Existing or new treatment available	a) Is there sufficient, good quality evidence that the existing primary treatment (phototherapy) is effective at preventing hyperbilirubinaemia developing into kernicterus?	3 studies
		2b) Is there sufficient, good quality evidence that other treatments (e.g. exchange transfusion, intravenous immunoglobulin) are effective at preventing kernicterus?	0 studies

12) Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.	3) Optimised clinical management	a) Are current clinical guidelines regarding risk factors associated with jaundice being followed?	2 abstracts; 0 fully published studies

A systematic literature search of studies published between January 2011 and March 2015 yielded 1337 references addressing kernicterus. Of these, 501 were assessed as being potentially relevant to the key questions outlined in Table 1. These studies were further filtered at title and abstract level, and 77 were selected for appraisal at full text. Each section below provides additional information on the evidence selection process for the given criterion.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

5. There should be a simple, safe, precise and validated screening test.

Description of the previous UK NSC evidence review conclusion

The previous UK NSC review[5] concluded that there are simple tests available that can measure bilirubin levels with reasonable diagnostic accuracy. However, the key question was whether routine screening of all infants by transcutaneous (TcB) or total serum bilirubin (TSB) measurement could improve on current clinical practice of performing a diagnostic bilirubin measurement following visual inspection of jaundice. Previous studies had suggested that the absence of visible jaundice has a negative predictive value (NPV) of up to 100% for ruling out clinically significant hyperbilirubinaemia. The previous UK NSC review found no new evidence contradicting this finding; therefore suggesting that current clinical practice should be able to identify infants with hyperbilirubinaemia.

Hyperbilirubinaemia can cause kernicterus, and so bilirubin levels may provide an appropriate marker for risk of kernicterus development. However, the review concluded that without better understanding of the relationship between bilirubin level and kernicterus development, the tests reviewed (TSB or TcB measure, with or without visual inspection) may not be appropriate for use as whole population screening tests.

Current UK NSC key question

This review aimed to identify whether there is new evidence of a suitable national screen test and cut-off level that could accurately predict those infants at risk of kernicterus. The review firstly considered evidence relating to taking a TSB measurement for all infants – this being the gold standard bilirubin measure. Secondly we considered any alternative screen method, such as taking a routine TcB or incorporating existing elements of clinical practice, like visual inspection for jaundice.

Description of the evidence

Overall, 73 studies were identified as potentially relevant during title and abstract sifting and 43 were further assessed at full text.

No studies compared screening of completely non-selected infant populations (i.e. representative of national screening) by any method and compared this with current NICE[3] recommended practice (where bilirubin is measured as indicated by visual jaundice and/or index of suspicion from risk factors, and treatment then commenced according to threshold).

No studies assessed whether any screen-test/threshold level in non-selected populations is predictive of outcomes of acute bilirubin encephalopathy (ABE) or kernicterus.

In the absence of studies examining a screen test to predict kernicterus, we aimed to identify prospective studies that looked at the predictive accuracy of a screen test for outcomes that may put the infant at risk of kernicterus – that is, that predicted significant hyperbilirubinaemia or need for bilirubin-reducing treatment.

None of the studies had examined completely non-selected infants, and therefore we identified studies that were in the least selective populations.

All potentially relevant studies had included infants ≥35 weeks gestational age and within the normal birthweight range. Other common exclusions were infants needing admission to a neonatal intensive care unit (NICU), or who were born with obvious congenital abnormalities (see tables for specific exclusions in the included studies). We allowed these exclusions as being acceptable for the purposes of national screening, as infants with these complications would be identified to be high risk and be managed clinically.

We also allowed studies that had excluded infants requiring phototherapy before discharge, and were specifically looking at screen tests to predict post-discharge significant hyperbilirubinaemia. Infants who develop jaundice within the first 24 hours are already clinically recognised to be at increased risk of significant hyperbilirubinaemia. However, bilirubin levels can peak at 72 to 120 hours of age. The issue of whether universal pre-discharge screening (particularly by TcB measure, alone or combined with risk assessment) could reduce risk of jaundice-related morbidity is a question that has been raised by NICE.[3] Therefore this is a pertinent issue to consider here.

In summary we considered studies that included infants ≥35 weeks gestational age and allowed for exclusions of admission to NICU, obvious congenital abnormalities, or development of jaundice/need for phototherapy before hospital discharge.

We did not include studies that gave further exclusions of groups that may be at increased risk of jaundice or significant hyperbilirubinaemia. For example, the exclusion of infants with maternal blood group incompatibility or with a positive Coombs'/Direct Antiglobulin Test (DAT), with cephalohematoma or bruising, or found to have G6PD deficiency. National screening may be the method by which some of these infants could be identified to be at risk of kernicterus.

However, by comparison we excluded studies that focused exclusively on high risk populations, such as preterm infants or those with pathological causes of jaundice. This is because screen cut-offs in these select groups of infants could not inform national screening of all infants.

We also excluded cohorts or case-control studies that focused on individuals suspected to have developed significant hyperbilirubinaemia (e.g. infants visibly jaundiced or with signs of ABE) and compared their examination, test findings or characteristics with control infants. In such

cases the findings may be considered to be diagnostic, rather than factors that may be used to screen currently healthy infants for risk of neurotoxicity.

We excluded studies that examined the accuracy of umbilical cord bilirubin to predict significant hyperbilirubinaemia as this is specifically not recommended by NICE.[3]

We also excluded studies examining hearing screening tests which may indicate infants or children who have developed kernicterus.

Included studies

Three cohort studies and one systematic review with meta-analysis met our inclusion criteria. Jackson et al. (2015)[6] and Bhutani et al. (2013)[7] were both US studies investigating prediction of phototherapy need in line with American Academy of Pediatrics guidelines[8]. Jackson et al. (2015)[6] (Appendix 1) was a single centre cohort (n=516) assessing the predictive accuracy of an early TcB measure (E-TcB) within 6 hours of birth (results summarised in table 2). Bhutani et al. (2013)[7] (Appendix 2) was a multicentre cohort (n=1157) aiming to identify the most accurate pre-discharge risk model, combining TcB and/or TSB measures with or without additional clinical risk factors, for predicting post-discharge phototherapy need (results summarised in table 3).

Yu et al. (2014)[9] (Appendix 3) was a systematic review with meta-analysis aiming to examine the accuracy of pre-discharge TcB or TSB normogram percentiles for predicting post-discharge significant hyperbilirubinaemia. It included 14 cohorts, 5 of which have been published since 2011 and were therefore also identified by this review search.[10-14] As these studies were covered by the review, the primary articles were not extracted additionally. The summarised accuracy data for pre-discharge TcB or TSB is presented in table 4.

Yu et al. (2014)[15] (Appendix 4) was an additional cohort by the same authors aiming to validate the accuracy of a TcB normogram developed at a single centre (Yu et al. 2011,[14] included in the Yu systematic review[9]) in a multicentre Chinese population (n=9174). This additional post-review study is presented in table 5.

Data on TcB, TSB and other clinical characteristics was prospectively collected in all of the included cohorts. However, none of the included studies appear to have used a select cut-off to further manage a high or low index of suspicion, for example. Outcomes of phototherapy or significant hyperbilirubinaemia have been examined, with the predictive ability of the early measures retrospectively assessed.

Results

Table 2: Accuracy of early TcB cut-offs for predicting phototherapy need

Study	Population	Screen test	E-TcB cut-off (mg/dL)	Sensitivity*	Specificity*	PPV	NPV	Positive LR	Negative LR
Jackson et al. (2015)[6] (Appendix 1) Single centre cohort, US (2011 to 2012)	N=516 Gestational age ≥35 weeks; birthweight ≥2100g; stable cardiorespiratory status and no major abnormalities	E-TcB within 6 hours of birth to predict subsequent phototherapy[+] during current or subsequent admission (required by 15/516, 2.9%)	≥0.3	1.0	0.25	0.04	0.96	0.04	0
			≥0.8	0.87	0.45	0.04	0.99	0.05	0.01
			≥0.9	0.73	0.50	0.04	0.98	0.04	0.02
			≥1.0	0.73	0.53	0.04	0.99	0.05	0.01
			≥1.1	0.73	0.57	0.05	0.99	0.05	0.01
			≥1.2	0.60	0.59	0.04	0.98	0.04	0.02
			≥2.0	0.40	0.82	0.06	0.98	0.07	0.02

*Overall AUC of E-TcB for subsequent phototherapy need: 0.66. [+] Also examined predictive accuracy of E-TcB for subsequent TCB >95th percentile; full results in Appendix 1.

Abbreviations: E-TcB, early transcutaneous bilirubin; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio

Table 3: Accuracy of clinical prediction models for post-discharge phototherapy need

Study	Population	Screen test	Model	Clinical risk factor(s) in predictive model	AUC	+/-SE	95% CI
Bhutani et al. (2013)[7] (Appendix 2) Multicentre cohort (6 centres), US	N=1157 (analysis based on 982, 85% with full data) Gestational age ≥35 weeks; not admitted to NICU; no sepsis or use of antibiotics.	TcB and TSB taken before discharge (24-48 hours). Clinical risk factors recorded during birth hospitalisation. Prediction of phototherapy after discharge (≥60 hours; required by 34/982, 3.5%).	A	TSB/TcB alone	0.84	0.03	0.79 to 0.90
			B	Combined clinical risk factors* alone	0.86	0.04	0.79 to 0.93
			C	Combined clinical risk factors* and TSB/TcB (unadjusted for age)	0.93	0.02	0.88 to 0.97
			D	Age-adjusted (hours) TSB/TcB	0.87	0.03	0.82 to 0.93
			E	Combined clinical risk factors and TSB/TcB (age-adjusted)	0.95	0.02	0.92 to 0.98
			F	Gestational age (weeks) alone	0.76	0.04	0.68 to 0.84
			G	Age-adjusted TSB/TcB and gestational age	0.95	0.03	0.93 to 0.97

* Clinical risk factors: gestational age <39 weeks, mother of Asian race, ABO incompatibility, positive DAT, cephalohematoma, bruising, exclusive breastfeeding, extensive jaundice

Abbreviations: AUC, area under curve; SE standard error; CI, confidence interval

Table 4: Accuracy of pre-discharge TcB and TSB normogram percentiles for predicting post-discharge significant hyperbilirubinaemia

Study	Population	Screen test	Pre-discharge TcB/TSB percentile	Summary sensitivity (95% CI)	Summary specificity (95% CI)	Summary positive LR (95% CI)	Summary AUC (SE)
Yu et al. (2014)[9] (Appendix 3) Systematic review and meta-analysis Search 1980 to 2013.	14 cohorts. <u>TcB normograms</u> 7 studies: 3 India, 1 China, 1 Israel, 1 Italy, 1 USA. N=322 to 11,456 <u>TSB normograms</u> 7 studies: 4 USA, 1 Italy, 1 India, 1 Turkey. N=156 to 2840 Gestational age ≥35 weeks; no NICU admission; no phototherapy before discharge	Hour-specific TcB or TSB normograms before discharge. In 12/14 studies the normogram was developed at a single centre; 9/14 developed and validated the normogram using their own population race ethnicity/data. Prediction of post-discharge significant hyperbilirubinaemia. Defined using AAP guidelines[8] in 9/14 studies.	TcB >95th percentile	26.9 (24.0 to 29.9)	95.8 (95.5 to 96.1)	8.46 (7.25 to 9.88)	0.925 (0.044)
			TSB >95th percentile	45.5 (39.8 to 51.2)	95.9 (95.2 to 96.5)	11.46 (8.68 to 15.09)	0.931 (0.042)
			TcB >75th percentile	74.3 (71.5 to 76.9)	77.5 (76.9 to 78.0)	3.61 (3.07 to 4.25)	0.864 (0.015)
			TSB >75th percentile	82.8 (80.0 to 85.3)	65.3 (64.5 to 66.1)	3.34 (2.00 to 5.57)	0.875 (0.041)
			TcB >40th percentile	96.1 (94.4 to 97.3)	45.7 (44.4 to 46.9)	1.67 (1.40 to 1.90)	0.512 (0.087)
			TSB >40th percentile	94.8 (92.9 to 96.3)	38.8 (37.9 to 39.6)	1.76 (1.21 to 2.55)	0.591 (0.063)

Abbreviations: AUC, area under curve; LR, likelihood ratio

Table 5: Post-review study of accuracy of pre-discharge TcB normogram percentiles for predicting post-discharge significant hyperbilirubinaemia

Study	Population	Screen test	Pre-discharge TcB	Sensitivity*	Specificity*	PPV	NPV
Yu et al. (2014)[15] (Appendix 4) Multicentre cohort (8 centres), China (2010 to 2011)	N=9174 Gestational age ≥35 weeks; birthweight ≥2000g; no NICU admission; no phototherapy before discharge	TcB normogram before discharge. (Validation of normogram previously developed by the same authors at a single centre.) Prediction of post-discharge significant hyperbilirubinaemia (>95th percentile on AAP normograms[8]: 972/9174, 10.6%).	>95th percentile	28.3	97.8	60.7	92.0
			>75th percentile	79.8	81.9	34.4	97.2
			>40th percentile	100	49.2	18.9	100

*Overall AUC of pre-discharge TcB for predicting post-discharge significant hyperbilirubinaemia: 0.875.

Abbreviations: EPPV, positive predictive value; NPV, negative predictive value

Prediction of overall phototherapy need

The cohort by Jackson et al. (2015)[6] is the least exclusive study and considers the outcome of phototherapy need at any point, either during birth hospitalisation or subsequently after discharge for healthy term/late preterm neonates. However, the study does not demonstrate a reliable early TcB cut-off threshold with a good balance between sensitivity and specificity for predicting which infants will go onto need phototherapy. The PPV at all TcB thresholds examined between 0.3 and 2.0mg/dL was very low at 4 to 6%. The sensitivity above a threshold of 0.3mg/dL was 100% but with very poor specificity of 25%. Meanwhile the upper threshold of 2.0mg/dL gave 82% specificity but only 40% sensitivity.

The overall AUC of 0.66 demonstrates that TcB measurement within 6 hours of birth is a poor screen test for discriminating which healthy term/late preterm neonates will go onto need phototherapy.

However, the main purpose of a national screening programme would be to prevent the long-term sequelae of kernicterus. Therefore a key limitation from this perspective is that need for phototherapy does not inform an infant's risk of developing ABE or kerincterus. The range of TSB levels of infants who required phototherapy is not known. Neither are their subsequent outcomes known, such as whether any reached the threshold for exchange transfusion. Phototherapy need was also based on American Academy of Paediatricians (AAP) normograms which may differ from the UK consensus-based treatment thresholds recommended by NICE[3].

Further limitations are that this was a single centre study with a relatively small sample size of 516, only 15 of whom (2.9%) required phototherapy. The predictive accuracy of E-TcB in this small, predominantly Hispanic (83%) US population may not be representative of what would be found with study of national populations, particularly of different ethnicity or from other countries where prevalence of jaundice or hyperbilirubinaemia and its risk factors may differ.

Prediction of post-discharge phototherapy or significant hyperbilirubinaemia

The remaining study looked at prediction of significant hyperbilirubinaemia or phototherapy need after hospital discharge in healthy term/late preterm neonates.

The multicentre US cohort by Bhutani et al. (2013)[7] examined the performance of different clinical risk models for predicting phototherapy need at 60 or more hours after birth. This study demonstrates very good accuracy for predictive models that take into account pre-discharge age-adjusted TcB or TcB combined with either: clinical risk factors for jaundice (model E); or with gestational age alone as the most predictive of these risk factors (model G) (both AUC 0.95).

However, this study does not give the accuracy of a single cut-off threshold of TcB or TSB at a set time after birth for predicting infants at high or low risk. There is also a lack of clarity on whether a non-invasive TcB measure would be as reliable as TSB (both measures were taken concurrently in this study). Furthermore, combining assessment of TcB/TSB levels with interpretation of clinical risk factors (gestational age, ethnicity, ABO incompatibility, cephalohematoma, bruising, exclusive breastfeeding, and extent of jaundice) places these predictive models more in-line with clinical management, rather than with a simple national screen test. Using TcB/TSB levels alone gave less accurate predictive ability (0.84 to 0.87).

Similar to Jackson et al. (2015)[6], this study has examined need for phototherapy, which does not inform the infant's risk of the key outcomes of ABE or kernicterus. It has also only looked at prediction of those who need phototherapy after hospital discharge. Though this is a key issue, ensuring identification of infants who may be at risk during birth hospitalisation is still important. In Bhutani et al. (2013)[7] 3.5% of the cohort needed phototherapy 60 or more hours after birth and were the focus of the analysis. However, 4.2% needed phototherapy before hospital discharge. These models do not inform identification of these infants, who may be more likely to have pathological causes of hyperbilirubinaemia and may be at increased risk of kernicterus.

Therefore, though the study identifies the optimal clinical identification of healthy infants who may be at risk of significant hyperbilirubinaemia after discharge, it has limited applicability to inform a national screening programme to prevent kernicterus.

Additional limitations to applicability include that, despite being a multicentre cohort, the ethnic composition differs to the UK (55% Hispanic, 25% non-White), and AAP[8] treatment thresholds may differ from those used in the UK.

The Yu et al. (2014)[9] systematic review and subsequent study aimed to look at the predictive accuracy of different percentile thresholds on TcB or TSB normograms to identify those at risk of post-discharge significant hyperbilirubinaemia. Overall these studies found the best performance for TcB or TSB levels above the 95th percentile, with TSB levels having slightly better accuracy than TcB. There was a good likelihood that infants with pre-discharge levels above this percentile would have significant hyperbilirubinaemia after discharge (pooled positive LR 8.5 for TcB and 11.5 for TSB). Specificity at the 95th percentile was very high: pooled specificity 96% in the review[9], and 98% in the additional cohort by Yu et al (2014)[15]. This single study also reported a PPV of 60.7% at this threshold.

However, sensitivity at the 95th percentile was very poor: a pooled value of 46% for TSB and for TcB, 27% in the review[9] and 28% in Yu et al. (2014).[15] This suggests that around half of infants who would go on to have significant hyperbilirubinaemia after hospital discharge would be missed if TSB was used. Three-quarters of at-risk infants would be missed if the non-invasive TcB measure was used instead. Lowering the TSB or TcB threshold to the 75th percentile gave a more even balance between sensitivity and specificity. However with all reported values ranging between 65 and 83%, this would not be a reliable enough test on which to base future management decisions. The 40th percentile changed the balance to a high sensitivity but very poor specificity.

Overall the summarised test performance data suggests that routinely taking pre-discharge TcB or TSB and interpreting normogram percentiles would not reliably discriminate between healthy infants who would or would not develop significant hyperbilirubinaemia after hospital discharge.

There are further important limitations to the evidence provided by this systematic review and subsequent study. The outcome of post-discharge significant hyperbilirubinaemia was variably defined by the included studies. Most defined this by AAP guideline[8] thresholds, three used other normograms, and 2 used set cut-off TSB levels. Therefore it is not possible to give a definite interpretation of the outcome that was examined, and this may not be directly comparable to the consensus-based normograms that are used in the UK. And again, significant hyperbilirubinaemia by any of these definitions does not indicate the management that these infants may require, or what their risk may be of developing ABE or kerincterus.

Additionally, the pre-discharge normograms used to interpret TcB or TSB levels may not be generalisable to the UK population. None of these studies was conducted in the UK, and the majority of normograms had been developed at a single centre, therefore using data specific to the characteristics of that single population. The Yu et al. (2014)[15] subsequent study demonstrated how the performance of these normograms can vary even within the same country: the initial normogram was developed at a single Chinese centre where it had an overall AUC of 0.920,[14] but in the multicentre Chinese population it was lower at 0.875. Not all of the normograms used in these studies have been validated for wider use.

The variable inclusion and exclusion criteria for the population studied may further affect the generalisability of these findings. Yu et al. (2014)[9] stated that they searched for studies in healthy term/late term infants who were not admitted to NICU and who did not have phototherapy before discharge. Five of these 14 studies were published since January 2011 and were therefore identified by this evidence review search and reviewed at full text. Three of the studies (two of the same single centre population in India[10, 11] and the previous Yu et al. study[14]) had also excluded those who had a positive DAT test. The remaining two studies were conducted in five centres in Italy.[12, 13] These studies reported that pre-discharge testing was performed "if clinically jaundiced and/or before discharge". In two of the three centres it was said that pre-discharge testing was performed only if the infant was jaundiced. This is a selective criterion, rather than non-selective screening of healthy infants.

The remaining pre-2011 studies may also have had additional inclusion or exclusion criteria aside from the eligibility criteria set by the review.

Yu et al. (2014)[9] also report that while the majority of studies had interpreted only TSB/TcB levels, five of the 14 studies had also taken into account clinical risk factors (e.g. gestational age, breastfeeding, previous sibling with jaundice).

Overall, both the variable inclusion criteria and clinical risk factors considered by studies calls into question the overall accuracy of the Yu et al. (2014)[9] pooled performance data for pre-discharge TcB/TSB normograms. The applicability of these findings to all term/late term infants is uncertain.

Like Bhutani et al. (2013)[7], the cohorts considered by Yu et al.[9, 15] have aimed to predict which healthy infants may be at risk of significant hyperbilirubinaemia after hospital discharge. However, in excluding infants requiring phototherapy during the birth hospitalisation, such screening would not cover the identification of those who may be at highest risk of bilirubin neurotoxicity. Similarly, excluding infants requiring NICU admission would likely have excluded any infants who required exchange transfusion, and so had the highest risk bilirubin levels.

Therefore this could not inform a national screening programme to give coverage of all infants for the prevention of kernicterus.

NICE specifically recommended that further research was needed to compare the effectiveness of universal timed pre-discharge TcB testing (combined with risk assessment), with standard care. While these studies have considered pre-discharge TcB testing, there are many areas lacking clarity, including the specific timing of the test and how the risk factors were interpreted. Also none of these are comparative studies. All infants received the same pre-discharge assessment and no comparison was made to a control group receiving standard care.

Summary: Criterion 5 not met.

This evidence review does not identify a simple, safe, precise and validated test that could be used in a national screening programme to identify infants at risk of developing kernicterus. No studies have compared non-selective population-based screening of all infants – by any method – with currently recommended clinical practice (where bilirubin is selectively tested as indicated by visual jaundice combined with recognition of clinical risk factors). Neither have any studies examined the performance of any screening test for prediction of the key outcomes of ABE or kernicterus.

Consequently, identification of significant hyperbilirubinaemia (requiring treatment) was used as a proxy outcome for infants who may be at risk. One cohort demonstrated that an early TcB measure within six hours of birth had very poor PPV (only 4 to 6%) for predicting subsequent phototherapy need. Additional cohorts demonstrated that pre-discharge TcB or TSB normogram percentiles have an inadequate balance between sensitivity and specificity to be used as a reliable screening test to discriminate between infants who would and would not develop significant hyperbilirubinaemia after hospital discharge. There were many additional limitations to the reviewed studies which limit applicability to the UK infant population. This includes data based on local populations with different demographics, and variable consideration or exclusion of infants with different risk factors or pathological causes of jaundice.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

Description of the previous UK NSC evidence review conclusion

The previous UK NSC review[5] concluded that bilirubin-lowering treatments are available, and that phototherapy has been demonstrated to reduce the need for invasive exchange transfusion. However, the cut-offs for treatment are based on consensus and it is not clear whether these thresholds prevent the development of kernicterus.

Current recommended treatments

Phototherapy is the first-line or gold standard treatment for hyperbilirubinaemia in neonates. It works by converting unconjugated bilirubin into a water-soluble form that the body can excrete, so reducing serum bilirubin levels.[16] The previous NICE guideline on neonatal jaundice[3] covered a large body of evidence indicating that phototherapy is effective at lowering and preventing rise of bilirubin levels, and can reduce the need for exchange transfusion.

NICE recommend using consensus-based treatment tables and graphs to interpret TSB level by infant age to see when phototherapy is indicated. In the current 2010 guideline[3] NICE recommend conventional phototherapy from a single blue light source (not fibreoptic) as a first-line treatment. If TSB is rapidly rising or is close to the consensus-based threshold for exchange transfusion, then multiple PT using more than one light source (either two or more conventional, or combined with fibreoptic) is recommended.[1]

[1] NICE guidance on Neonatal Jaundice is currently in the process of update. The draft guideline currently out for consultation does not now specify ConPT using a single blue light source and recommends that phototherapy (using an artificial light source with an appropriate spectrum and irradiance) may be delivered using light-emitting diode (LED), fibreoptic or fluorescent lamps, tubes or

Term infants (≥37 weeks) are clinically recognised to be at increased risk of kernicterus if their TSB is >340µmol/l, is rapidly rising at a rate of >8.5µmol/l per hour, or if they have signs of ABE.[3]

Exchange transfusion (double volume) is the recommended treatment if the infant is at higher risk based on TSB levels or clinical signs of ABE. In their evidence review NICE[3] concluded that double volume exchange transfusion when carried out by experienced health professionals is a relatively safe and effective procedure for babies at risk of kernicterus from severe hyperbilirubinaemia.

Intravenous immunoglobulin (IVIG) is the main additional treatment that may sometimes be used in the treatment of hyperbilirubinaemia. It is given as an adjunct to PT if the infant has Rhesus or ABO haemolytic disease.

NICE[3] specifically advise against the use of any of the following to treat hyperbilirubinaemia: agar, albumin, barbiturates, charcoal, cholestyramine, clofibrate, D-penicillamine, glycerin, manna, metalloporphyrins, riboflavin, traditional Chinese medicine, acupuncture, homeopathy.

Current UK NSC key question

It is well established that the currently available and recommended treatments reduce serum bilirubin levels. This review aimed to see whether there was specific evidence that any bilirubin-lowering treatment could prevent the development of ABE or kernicterus. We aimed to look for good quality evidence that any form of phototherapy as the gold standard treatment reduces risk of these outcomes. We also looked at evidence for exchange transfusion, as this is the treatment used for higher-risk babies, or evidence for any other treatment that may be used in management of hyperbilirubinaemia, such as IVIG.

Description of the evidence

Overall a total of 32 therapeutic studies were considered possibly relevant to this question, including 7 systematic reviews, 19 RCTs and 6 cohort studies, all of which were accessed at full text. Studies with participant size of less than 40 had been excluded.

Only three of these studies examined any potentially relevant outcomes of encephalopathy, kernicterus, or neurodevelopmental outcomes such as cerebral palsy or hearing impairment. These studies are covered by this review question.

The remaining studies did not examine any of these outcomes and so were excluded. The outcomes most commonly evaluated by these excluded studies were effects on bilirubin levels and duration of phototherapy or hospitalisation. It is already known that the recommended treatments reduce bilirubin levels. However, as there is no established bilirubin threshold associated with development of kernicterus, and kernicterus has been observed across a range of levels, change in bilirubin levels does not inform whether treatment reduces risk of kernicterus. Some studies had also reported adverse effects, complications or mortality, but none of the effects covered included those related to ABE or kernicterus. The majority of excluded studies had examined phototherapy, either different forms (e.g. LED vs. conventional), or additional management alongside phototherapy (e.g. positioning, use of cover, or use of clofibrate or phenobarbital). Three of the excluded studies had examined exchange transfusion

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bulbs. Rather than multiple, “intensified” PT is now recommended for higher risk infants. That is, increasing irradiance either by adding another light source or by increasing the irradiance of the initial light source.

(one of two-stage single vs. one-stage double volume, one comparing different intravenous routes of administration, and one investigating prior administration of albumin).

The three studies reporting on kernicterus-related outcomes – two Cochrane systematic reviews[16, 18] and one secondary analysis of a randomised controlled trial[19] – are covered below. However, these studies provided very limited evidence relevant to national population-based screening.

Results

The Cochrane systematic review by Gholitabar et al. (2012)[16] (Appendix 5) had the most relevance to national screening. This placed no restrictions on the eligible infant population, including studies in both preterm and term infants who could potentially be identified through a national screening programme. It aimed to identify randomised and quasi randomised controlled trials investigating the effects of clofibrate (any dose) in combination with phototherapy, compared with phototherapy alone. It is thought that clofibrate may reduce bilirubin levels by activating glucuronyl transferase so enhancing conjugation and excretion of bilirubin. Bilirubin encephalopathy was one of the primary outcomes that the review aimed to examine. However, none of the 12 identified trials (n=739) provided data for this outcome. Therefore this study provides no further evidence of relevance to this review. Meta-analysis did suggest that the addition of clofibrate significantly reduced bilirubin levels and duration of PT, (see Appendix 5 for results) but of note the treatment is not recommended by NICE, either in the current[3] or draft updated guidance.[17]

The second Cochrane review by Okwundu et al. (2013)[18] (Appendix 6) investigated giving prophylactic PT for preterm (<37 weeks) or low birthweight (LBW) infants (<2500 g) – prophylactic meaning before TSB has reached a pre-specified threshold. The primary outcomes investigated by the review included clinical or pathological kernicterus and neurodevelopmental outcomes at one year of age.

None of the 9 included studies (n=3449) examined the outcomes of kernicterus, but three reported on neurodevelopmental impairment. Two of these studies (n=1017) found that prophylactic PT had no effect on the outcome of cerebral palsy at 12 to 18 months (pooled RR 0.96, 95% CI 0.50 to 1.85). One of these two studies (n=922) also found it had no effect on sensorineural hearing loss at 6 years (RR 0.31, 95% CI 0.07 to 1.50). The third 2008 study (n=1974) did find an effect of prophylactic PT on neurodevelopmental impairment. This was also the third study identified by this evidence review.

Tyson et al. (2012)[19] (Appendix 7) is a secondary analysis of the multicentre US RCT originally reported in 2008[20] and investigating the effects of aggressive compared with conventional PT on preterm, extremely low birthweight (ELBW) infants (n=1974). In this secondary publication Tyson et al. (2012)[19] had specifically performed a subgroup analysis to examine the effects on the smallest and sickest infants (mechanically ventilated). However, the original primary results of this trial were also reported, and are covered here.

The primary outcome was the composite of death or neurodevelopmental impairment examined at 18 to 22 months after term. Neurodevelopmental impairment was defined as blindness, severe hearing loss, moderate or severe cerebral palsy, or a score <70 on the Mental or Psychomoter Development index of the Bayley Scales of Infant Development II. Aggressive PT

had no effect on this composite outcome compared with conventional PT.[19, 20] However, when these two outcomes were examined separately, aggressive PT had no effect on risk of death (RR 1.05, 95% CI 0.90 to 1.22), but did significantly reduce risk of neurodevelopmental impairment (RR 0.86, 95% CI 0.74 to 0.99). In post hoc analyses aggressive PT also significantly reduced the risk of profound impairment, defined as Mental or Psychomoter Development index ≤50 or level 5 on the Palisano et al. criteria for gross motor function (RR 0.68, 95% CI 0.52 to 0.89).[19, 20]

However, both the Tyson/Morris RCTs[19, 20] and the two additional RCTs covered in the Okwundu et al. (2013)[18] review provide evidence of limited applicability to this review question. Though they have examined outcomes of relevance, the studied populations are preterm, low birthweight infants. Preterm infants are already clinically recognised to be at risk of hyperbilirubinaemia. A national screening programme would likely cover infants of term age, as have the studies reviewed for criterion 5. Therefore the treatment of preterm infants – particularly prophylactic or early/aggressive phototherapy – may not be directly comparable to the treatment that may be considered for infants identified to be at risk through a screening programme.

Likewise caution must be taken before extrapolating the effects of phototherapy in these trials – one trial finding it reduced risk of neurodevelopmental impairment at 18-22 months, two others finding no effect on cerebral palsy or hearing impairment – to a healthy term population should they be screened and receive similar treatment.

There are further limitations to the strength of this evidence, even for the applicable preterm/LBW population. None of the trials examined kernicterus as an outcome. Though the neurodevelopmental outcomes examined may be the result of this, it cannot be known with certainty that these outcomes were caused by bilirubin encephalopathy.

Of note, the study by Morris et al. (2008)[20] affirms the recognised uncertainty about whether a particular bilirubin concentration, or particular clinical circumstances, puts an infant at increased risk of neurotoxicity, as highlighted in the previous UK NSC evidence review[5]. They found no significant difference in the mean TSB level during the first 14 days of life among infants who had subsequent neurodevelopment impairment (5.4mg/dL ±1.6) compared with unimpaired survivors (5.4mg/dL ±1.5) (p=0.45). There was also no difference in the mean peak infant TSB between impaired (8.6mg/dL ±2.3) and unimpaired (8.3mg/dL ±2.3) survivors (p=0.02). With the considerable overlap in peak values between the groups, Morris et al. (2008)[20] concluded that this provides little evidence to support a specific bilirubin threshold causing neurodevelopment impairment.

Kernicterus and associated neurodevelopment impairment are very rare outcomes. This may be the reason why many studies considered for this question did not report on these outcomes, particularly when in lower risk populations than the very premature, LBW infants examined by these three studies. If trials do examine the effect of an intervention and comparator on risk of kernicterus, then there is a chance that these risk figures may be unreliable in any case due to the rarity of the outcome. Therefore it may be difficult to provide firm evidence of whether a treatment prevents kernicterus without study of a very large sample of infants.

Summary: Criterion 10 not met.

It is well established that the currently recommended treatments of phototherapy and exchange transfusion are effective at reducing bilirubin levels. However, as there is no established bilirubin threshold associated with development of kerincterus, and kernicterus has been observed across a range of concentrations, change in bilirubin levels does not inform risk of kerincterus. This evidence review identified only three trials (two covered by a systematic review) that have examined the effects of a treatment on kernicterus or related neurodevelopmental outcomes. These trials were all of prophylactic/aggressive phototherapy in preterm, low birthweight infants. These trials provide some limited evidence that this treatment may reduce risk of neurodevelopmental impairment in this population. However, these treatments or treatment effects cannot be generalised to the term infant population who may be identified as having hyperbilirubinaemia through a national screening programme.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

Previous UK NSC evidence review conclusion and current question

The previous UK NSC review[5] concluded that, though NICE[3] has produced recommendations on the management of neonatal jaundice, adherence to these recommendations has not been studied.

NICE[3] recommends that all newborns are visually monitored for signs of jaundice in the first 72 hours after birth (particularly the first 24 hours). Those with gestational age of <38 weeks, who develop jaundice within the first 24 hours, with a previous sibling with jaundice, and who are exclusively breastfed, are recognised to be at particular risk of significant hyperbilirubinaemia. When indicated bilirubin can be measured either by TcB or TSB (all TcB levels above 250mmol/l require confirmation by TSB), with subsequent management guided by NICE consensus-based treatment tables and graphs.

Following NICE[3] guideline recommendations would therefore be expected to give good coverage of the infant population, allowing early identification and treatment of those with jaundice and a reduction in the number who will develop significant hyperbilirubinaemia.

However, the previous review[5] noted that variations in clinical practice have been reported in other countries and were observed in the UK before the current guidance was introduced.

The current review therefore aimed to see whether there is new evidence that NICE[3] guideline recommendations to identify infants at risk for jaundice or significant hyperbilirubinaemia are being followed in clinical practice.

Description of the evidence

For this question we aimed to identify audits, reviews or qualitative studies examining adherence to NICE guideline recommendations[3] for the identification and management of neonatal jaundice. Twenty-one potentially relevant publications were identified. After exclusion of studies conducted outside of the UK, no fully published studies were identified that relate to implementation of NICE guidance. Two studies, Ravindran et al. (2012)[21] and Ramachandran et al. (2011)[22] both assess adherence to or implementation of NICE guidance at single UK centres,

but neither study is fully published and both are available as abstracts only. Both have been described briefly below but are not included as part of the review due to the full studies not been published as yet.

Ravindran et al. (2012)[21] is an audit that reviews the medical notes of a random sample of 48 newborns with jaundice managed on the postnatal unit during an 8 month period. It reports that there was poor identification of the risk factor of whether the baby's previous sibling had jaundice requiring treatment (15% - presumably the proportion of jaundiced infants who had this recorded). There was said to be 90% compliance with the recommendation to take a TSB for infants presenting with jaundice in the first 24 hours. Of those who developed jaundice after 24 hours, TcB was taken for 83%. No further results are reported on identification of other risk factors.

Ramachandran et al. (2011)[22] was a before-after study design comparing the 9 weeks before and after implementation of NICE guideline at the hospital (September 2010). The main focus of this study was to look at changes following recommendation to use TcB where available, rather than TSB as previously. In the 9 weeks before it reported that 5% of all infants (32/586) had TSB testing and 12 received phototherapy. After implementation of NICE guidance 8% of all infants (53/651) had TcB estimations, 6 had TSB measurement and 2 received phototherapy. No further data is reported, other than that all junior doctors and nurse practitioners, and 80% of midwifes, felt the TcB measure was safe, easy to use, reduced workload and resulted in earlier discharge.

Summary: Criterion 12 not met.

This review did not identify any fully published studies in the literature. Therefore, it is not able to answer whether identification and management of infants with neonatal jaundice, as recommended by NICE, is currently being optimised in clinical practice.

Conclusions

Implications for policy

This evidence review assesses neonatal screening for kernicterus against select UK National Screening Committee (UK NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This topic was last assessed by an external evidence review in 2011[5] which concluded that a national screening programme for prevention of kernicterus could not be recommended due to several key uncertainties. Hyperbilirubinaemia is the known risk factor, but there is no established bilirubin threshold level that accurately identifies those who will progress to kernicterus, and cases have been observed across a range of bilirubin concentrations. There are also well established treatments (phototherapy and exchange transfusion) that reduce bilirubin levels, but there was a lack of direct evidence that these treatments prevented kernicterus.

NICE provides guidance on the identification and management of neonatal jaundice[3] (currently in the process of update[4]). This outlines the risk factors for development of significant hyperbilirubinaemia, and recommends that all babies are visually inspected for signs of jaundice in the first 72 hours of life (particularly the first 24 hours). Further management is then guided

by consensus-based treatment thresholds. It may be expected that following these guidelines could give good coverage of at-risk infants, allowing the potential for early treatment and reduction in the number who will develop significant hyperbilirubinaemia.

This review addressed key questions to see whether there is new evidence that national screening of all infants for hyperbilirubinaemia could prevent kernicterus.

The identified body of evidence neither alters the conclusions of the 2011 evidence review, nor supports overturning previous UK NSC recommendations regarding a UK newborn screening programme for prevention of kernicterus. A summary of key findings for the three assessed criteria is provided below:

- **Simple, safe, precise and validated screening test –** There is no new evidence that a national screening programme for all newborns could identify those at risk of developing kernicterus. No studies have compared non-selective population-based screening of all infants – by any method – with currently recommended clinical practice to identify infants at risk. Neither have any studies examined the performance of any screening test for prediction of the key outcomes of acute bilirubin encephalopathy or kernicterus. Studies were subsequently selected that examined screen tests in the least selective populations to predict development of significant hyperbilirubinaemia (requiring treatment). One cohort demonstrated that an early TcB measure within six hours of birth had very poor PPV (only 4 to 6%) for predicting subsequent phototherapy need. Other cohorts demonstrated a very poor balance between sensitivity and specificity of pre-discharge TSB or TcB measurement to predict subsequent post-discharge significant hyperbilirubinaemia. The local study populations on which these results were based may also not be generalisable to the UK population.
- **Effective treatment available –** It is known that the currently recommended treatments of phototherapy and exchange transfusion are effective at reducing bilirubin levels. However, as there is no established bilirubin threshold associated with development of kerincterus, change in bilirubin levels does not inform risk. Three trials were identified (two covered by a systematic review) that provided some limited evidence that prophylactic/aggressive phototherapy for preterm, low birthweight infants may reduce risk of childhood neurodevelopmental impairment. However, both this treatment and its effects cannot be generalised to the term infant population who may be identified to have hyperbilirubinaemia through a national screening programme.
- **Optimised management in clinical practice –** NICE gives clear guidelines for the identification and management of neonatal jaundice. No full publications were identified that have reviewed the uptake or implementation of NICE guidance.

Implications for research

Given the limited evidence identified for each key question, additional high quality studies in the following areas are needed in order to resolve uncertainties regarding national newborn screening for prevention of kernicterus:

- Studies comparing screening of non-selected infant populations (i.e. reflecting a national, population-based approach), for example through use of a routine newborn TSB or TcB measure, with current clinical practice of identification of risk factors and

visual inspection for jaundice. Studies would ideally need to compare whether this practice has an influence on the incidence of kernicterus or related outcomes.

- Further study into whether there is a bilirubin threshold level, assessed using either TSB or TcB, and taken at a particular time after birth, that is predictive of development of kernicterus.
- Further study into whether the recommended treatments prevent development of kernicterus.
- Audit into whether NICE guidelines to identify infants at risk of significant hyperbilirubinaemia, and subsequently manage according to consensus-based treatment table and graphs, are being followed.

Methodology

The draft update report was prepared by Bazian Ltd., and then adapted in discussion with the National Screening Committee. Each criterion was summarised as 'met', 'partially met' or 'not met' by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were assessed to determine the quality of the identified evidence, including study design and methodology, risk of bias, directness and applicability of the evidence. Factors that were determined to be pertinent to the quality of the body of evidence identified for each criterion are outlined in the results section as well as the comment section of the Appendix tables.

For Criterion 5, quality assessment focused on four main domains: patient selection, the index test, the reference standard, and flow and timing of index test and reference standard. Each domain was assessed for risk of bias, and the first three domains were assessed for applicability to a potential UK screening programme population. Details of these assessments can be found in the comment section of the Appendix tables.

Search strategy

Search/sifting results

Databases and sites searched	Dates searched	Number of hits
Guideline sites	No date limits	9
EMBASE.com	01/01/2011 - 17/03/2015	648
PubMed	01/01/2011 - 16/03/2015	805
Cochrane Database Syst Rev (Wiley)	01/01/2011 - 17/03/2015	11
CENTRAL	01/01/2011 - 17/03/2015	88
DARE	01/01/2011 - 17/03/2015	5

HTA	01/01/2011 - 17/03/2015	1
NHS EED	01/01/2011 - 17/03/2015	2
Total number of hits		**1569**
Total number after de-duplication		**1337**
Total number after first appraisal		**501**

Record of searches strategies

PubMed

1. kernicterus[MeSH Terms] OR hyperbilirubinemia, neonatal[MeSH Terms]
2. kernicterus[Title/Abstract] OR "bilirubin encephalopathy"[Title/Abstract]
3. (hyperbilirubin*[Title/Abstract] AND (neonat*[Title/Abstract] OR newborn[Title/Abstract]))
4. 1 or 2 or 3
5. Filters: From 2011/01/01 to 2015/12/31, English

EMBASE.com

1. 'kernicterus'/de or 'neonatal hyperbilirubinemia'/de
2. kernicterus:ab,ti or 'bilirubin encephalopathy':ab,ti
3. (hyperbilirubin*:ab,ti and (neonat*:ab,ti or newborn:ab,ti))
4. 1 or 2 or 3
5. 4 and [2011-2015]/py and [english]/lim

Cochrane Library (Wiley)

#1 MeSH descriptor: [Kernicterus] this term only
#2 MeSH descriptor: [Hyperbilirubinemia, Neonatal] this term only
#3 kernicterus:ti,ab,kw
#4 "bilirubin encephalopathy":ti,ab,kw
#5 hyperbilirubin*:ti,ab,kw
#6 (neonat* or newborn):ti,ab,kw
#7 #5 and #6
#8 #1 or #2 or #3 or #4 or #7 Publication Year from 2011 to 2015

Appendices

Appendix number	1
Relevant criteria	5
Publication details	Jackson GL, Saumur M, Chandwani V, et al. Evaluation of Early Transcutaneous Bilirubinometry to Predict Subsequent Hyperbilirubinemia in Neonates Admitted to a Well-Baby Nursery. American Journal of Perinatology. 2015.[6]
Study details	Prospective cohort Single centre, US (Newborn Nursery at Parkland Memorial Hospital, June 2011 to May 2012)

<table>
<tr><td>Study objectives</td><td>To determine whether an early transcutaneous bilirubin measurement taken within 6 hours of birth (E-TcB), or whether the early rate of rise in TcB (E-ROR), predicted those at increased risk of subsequent hyperbilirubinaemia, with or without need for phototherapy (PT).</td></tr>
<tr><td>Inclusions</td><td>Infants admitted to the Newborn Nursery with requirement: gestational age ≥35 weeks; birthweight ≥2100g; stable cardiorespiratory status and no major abnormalities.</td></tr>
<tr><td>Exclusions</td><td>Infants not admitted to the Newborn Nursery, or attending another hospital for follow-up/further treatment.</td></tr>
<tr><td>Population</td><td>N=516.

Mean birthweight 3401g (+/- 468), gestational age 39 weeks (+/-1.4), 53% male, 83% Hispanic, 78% predominantly breastfed.</td></tr>
<tr><td>Intervention/test</td><td>Early TcB obtained within 6 hours of birth (taken using the JM-103 system).

Median time E-TcB obtained 3.8 hours (range 1.1 to 6 hours)

TSB not routinely obtained unless TcB values were of concern (not specified) or the infant had visual jaundice.</td></tr>
<tr><td>Comparator</td><td>NA</td></tr>
<tr><td>Results/outcomes</td><td>Outcomes:

• TcB at 18 to 36, and at 42 to 66 hours of age
• Need for phototherapy during birth hospitalisation or subsequent re-admission (according to American Academy of Pediatrics [APP] guidelines)

PT was given to 15 (2.9%) and not required by 501 (97.1%)

7/12 needing PT with information available had ABO incompatibility (3 with a positive DAT).

PT was started at mean 54.6 +/- 46.0 hours (median 41, range 4.5 to 164.5 hours). 6/15 were <36 hours when PT started, 2 were <12 hours.

No differences from those not needing PT in gender (p=0.13), delivery mode (p=0.38) or feeing method (p=1.0)

Comparative characteristics of those needing PT and not needing PT :
<table>
<tr><td></td><td>Needing PT
Mean +/- SD
Median (range)</td><td>Not needing PT
Mean +/- SD
Median (range)</td><td>p</td></tr>
<tr><td>E-TcB (mg/dL)</td><td>1.0 +/- 0.9</td><td>2.2 +/- 1.7</td><td>0.003</td></tr>
</table>
</td></tr>
</table>

	0.9 (0 to 4.8)	1.6 (0.3 to 5.7)	
TcB at 18 to 36* hours (mg/dL)	5.1 +/- 1.9 5.2 (0 to 13.6)	7.8 +/- 2.8 7.7 (3.0 to 12.3)	0.0001
E-ROR* (mg/dL per hour)	0.18 +/- 0.07 0.18 (-0.03 to 0.42)	0.27 +/- 0.13 0.30 (0.07 to 0.44)	0.0005

*Based on n=365 and n=8 respectively (TcB not used after the start of phototherapy)

Accuracy of different E-TCB (mg/dL) cut-offs for predicting the outcome of PT vs. no PT

E-TcB	Sensitivity	Specificity	PPV	NPV	+LR	-LR	p
≥0.3	1.0	0.25	0.04	0.96	0.04	0	0.03
≥0.8	0.87	0.45	0.04	0.99	0.05	0.01	0.02
≥0.9	0.73	0.50	0.04	0.98	0.04	0.02	0.11
≥1.0	0.73	0.53	0.04	0.99	0.05	0.01	0.06
≥1.1	0.73	0.57	0.05	0.99	0.05	0.01	0.03
≥1.2	0.60	0.59	0.04	0.98	0.04	0.02	0.18
≥2.0	0.40	0.82	0.06	0.98	0.07	0.02	0.04

Accuracy of different indices for predicting TcB >95th percentile:

Sensitivity	Specificity	PPV	NPV	+LR	-LR	p
E-TcB ≥0.9mg/dL for predicting TcB at 18 to 36 hours						
0.94	0.53	0.15	0.99	0.18	0.01	<0.00001
E-TcB ≥0.9mg/dL for predicting TcB at 42 to 66 hours						
0.70	0.57	0.02	0.92	0.26	0.08	0.002
E-ROR ≥0.18mg/dL per hour for predicting TcB at 42 to 66 hours						
0.83	0.49	0.18	0.95	0.22	0.05	0.001
TcB ≥6mg/dL at 18 to 36 hours for predicting TcB at 42 to 66 hours						
0.79	0.80	0.35	0.97	0.55	0.04	<0.00001

Comparison AUC for different screening modes:

E-TcB for PT need: 0.66

E-TcB for TcB >95th percentile at 18 to 36 hours: 0.83

E-TcB for TcB >95th percentile at 42 to 66 hours: 0.62

E-ROR for TcB >95th percentile at 42 to 66 hours: 0.79

TcB at 18 to 36 hours for TcB >95th percentile at 42 to 66 hours: 0.86

	Significant differences in characteristics: E-ROR was significantly higher in infants predominantly breastfed than not (mean 0.19 +/- 0.01 vs. 0.16 +/-0.02 mg/dL per hour, p=0.0007) TcB >95th percentile at 42 to 66 hours compared to those <95th percentile had breastfeeding predominance (p=0.02), lower gestational age (p=0.048), lower birthweight (p=0.004).

Comments

Single centre study. Relatively small sample size with few needing PT (15/516) with data on all characteristics (e.g. ABO incompatibility) and subsequent TcB measures not available for all.

Only examines the outcomes of PT and subsequent TcB at 18 to 66 hours. Doesn't give data on prediction for TSB, treatments of different severity (e.g. more intense PT or need for ET), or examine outcome of ABE or kernicterus.

Uncertain clinical significance of subsequent TcB >95th percentile.

US AAP[8] treatment protocols may differ from UK

Further limitations as below:

Question	**Assessment (Y, N, unclear)**	**Risk of Bias (low, high, unclear)**	**Supporting info**
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Unclear	Unclear	Described as a convenience sample during the study period June 2011 to May 2012. Unclear whether inclusive of everyone.
Case-control design avoided?	Y	Low	Not a case control study.
Inappropriate exclusions avoided?	Y	Low	Aside from excluding preterm, low birthweight and those with abnormalities or unstable cardiorespiratory status, no additional exclusions
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Unclear	E-TcB recorded without knowledge of subsequent PT need. Note though, unclear whether any interpretation of E-TcB was made at the time (e.g. identified as high or low risk)

Threshold pre-specified?	N	High	No threshold was pre-specified, unclear whether E-TcB levels were used to manage with a high index of suspicion, but were not the basis for PT decisions
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	N	High	Need for PT or subsequent TcB does not inform the infant's risk of ABE or kernicterus risk
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	Unclear whether E-TcB levels were reviewed when subsequent measures were taken or PT was given, but decision to start PT was based on AAP guidelines. Outcome of interest was not measured.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Unclear	Unclear	Unclear applicability: continuum of change in TcB levels with hours after birth. Outcome of ABE or kernicterus was not the diagnosis assessed.
Did all participants receive same reference standard?	Y	Low	All infants received the same TcB measures and decisions to treat based on AAP guidelines. Note though that the outcome of interest was not examined.
All patients included in analysis?	N	High	All infants included for main analysis of treatment need, but not for subsequent TcB levels as they were not routinely taken for all, particularly those needing treatment.
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	US population of healthy late preterm/term neonates, but predominantly Hispanic. Prevalence of jaundice/hyperbilirubinaemia and risk factors for it may differ.
Applicable to UK screening test of interest?	Unclear	Unclear	Uncertain what screen test may be considered in the UK.
Target condition measured by reference test applicable to UK screening condition of interest?	N	High	Outcome of ABE or kernicterus has not been examined.

Appendix number	2

Relevant criteria	5
Publication details	Bhutani VK, Stark AR, Lazzeroni LC, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. The Journal of pediatrics. 2013;162(3):477-82.e1.[7]
Study details	Prospective cohort study 6 centres, US.
Study objectives	To identify the most effective pre-discharge assessment for risk of subsequent hyperbilirubinaemia. Specifically to identify whether the use of TSB combined with clinical risk factors more accurately identified infants who receive PT than either method alone.
Inclusions	Infants ≥35 weeks' gestation admitted to the newborn nursery.
Exclusions	Infants transferred to NICU for any reason; receiving parenteral antibiotics for sepsis or proven sepsis for ≥48 hours; or who were unable to attend follow-up at the study centre.
Population	N=1157. Reported maternal race: 76.6% White, 8.6% Black, 5.8% Asian, remainder other. Reported ethnicity: 55.2% Hispanic or Latino, 35% non-Hispanic. Mean birthweight 3310 +/- 667g Median discharge age: 56 hours (range 14 to 780) Reported risk factors: • Bruised at birth: 75 (6.5%) • Cephalohematoma: 98 (8.5%) • Positive DAT (18/766 tested): 18 (2.3%) • Sibling with jaundice: 217 (18.7%) • Sibling received PT: 92 (8%) • Exclusive breastfeeding: 424 (36.6%) • Mixed feeding: 592 (51.2%) • G6PD deficiency: tested in 4 infants (no further information) Final sample n=1144 (3 transferred to NICU, 10 consent withdrawn) 84/1144 (7.3%) lost to subsequent follow-up (none receiving PT before

<table>
<tr><td></td><td>discharge)

Analysis based on final sample of 982 (85%) with complete data.</td></tr>
<tr><td>Intervention/test</td><td>TcB measured at age 24 +/- 6 hours and before discharge using the BiliChek device

TcB was generally taken concurrently with routine TSB measure (all TcB ≥12mg/dL verified by TSB) and pre-discharge TSB was taken at 18 to 60 hours and plotted on a previously developed normogram (Bhutani).

Outpatient TcB measured at age 3-5 and 7-14 days.

Clinical risk factors for jaundice recorded during birth hospitalisation</td></tr>
<tr><td>Comparator</td><td>NA</td></tr>
<tr><td>Results/outcomes</td><td>Phototherapy given at age ≥60 hours (according to AAP guidelines[8])

• PT given to 75/982 (7.6%) – 41 (4.2%) treated during birth hospitalisation, 34 (3.5%) treated after discharge

• Characteristics: 45% 35 to 37 weeks gestation; 32% bruising or cephalohematoma

• Treatment based on physician’s interpretation of treatment AAP normograms[8]: all treated had bilirubin >75th percentile; 10 had TSB ≥20mg/dL, none had levels ≥25mg/dL; 7/75 (9%) treated were 1-2mg/dL below treatment threshold.

• None received exchange transfusion

Clinical risk factors to predict PT use

Evaluated for 982 infants, 34 of whom received post-discharge PT (excluding those: receiving PT <60 hours of age; no TSB within 24-48 hours; no gestational age recorded).

Clinical risk factors found to have significant association with PT use were selected for use in predictive models: gestational age <39 weeks; ABO incompatibility; positive DAT; mother of Asian race; bruising; cephalohematoma; exclusive breastfeeding; more extensive jaundice.

TSB/TcB values are the last measure taken in the 24-48 hour window.

Select clinical risk factors as predictors for post-discharge PT use (n=982)
<table>
<tr><td>Model</td><td>Clinical risk factor(s)</td><td>AUC</td><td>+/- SE</td><td>95% CI</td></tr>
<tr><td>A</td><td>TSB/TcB alone</td><td>0.84</td><td>0.03</td><td>0.79 to 0.90</td></tr>
<tr><td>B</td><td>Combined clinical risk factors alone</td><td>0.86</td><td>0.04</td><td>0.79 to 0.93</td></tr>
<tr><td>C</td><td>Combined clinical risk factors and</td><td>0.93</td><td>0.02</td><td>0.88 to 0.97</td></tr>
</table></td></tr>
</table>

	TSB/TcB (unadjusted for age)			
D	Age-adjusted (hours) TSB/TcB	0.87	0.03	0.82 to 0.93
E	Combined clinical risk factors and TSB/TcB (age-adjusted)	0.95	0.02	0.92 to 0.98
F	Gestational age (weeks) alone	0.76	0.04	0.68 to 0.84
G	Age-adjusted TSB/TcB and gestational age	0.95	0.03	0.93 to 0.97

Comments

Only AUC for overall predictive models provided, no cut-off thresholds identified.

Set in the context of universal screening where TSB are routinely collected. Risk model uses either TcB/TSB measure with lack of clarity to whether TcB alone would be sufficient.

Doesn't examine outcome of ABE or kernicterus.

Only examines the outcomes of post-discharge PT (≥60 hours gestation). The models do not inform the accuracy to detect infants who may be at risk of early significant hyperbilirubinaemia or ABE/kernicterus risk (e.g. those with haemolytic disease causes).

US AAP[8] treatment protocols may differ from UK.

Further limitations as below:

Question	**Assessment (Y, N, unclear)**	**Risk of Bias (low, high, unclear)**	**Supporting info**
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Unclear	Unclear	Unclear whether inclusive of everyone in the newborn nurseries during the study period (dates not reported).
Case-control design avoided?	Y	Low	Not a case control study.
Inappropriate exclusions avoided?	Y	Low	Aside from excluding preterm, those admitted to NICU or with infection, no additional exclusions
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	N	High	Pre-discharge TSB/TcB and risk factors were prospectively recorded on medical records, but predictive risk models were subsequently developed after examination of the outcome.
Threshold pre-specified?	N	High	No threshold was pre-specified, and decisions to treat or manage with a high index of suspicion have not been based on

			risk models which were subsequently developed.
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	N	High	Need for PT does not inform the infant's risk of ABE or kernicterus
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	Uncertain applicability: PT need was based on AAP thresholds and unclear whether any interpretation was made of pre-discharge risk factors. Outcome of interest was not measured as the reference standard.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Unclear	Unclear	Uncertain applicability: Pre-discharge TcB/TSB and risk factors was separated from post-discharge diagnostic TSB at initiation of PT. Outcome of ABE or kernicterus not measured.
Did all participants receive same reference standard?	Y	Low	All infants received the same TSB, though the outcome of interest was not examined.
All patients included in analysis?	N	Unclear	85% of cohort with data available for follow-up.
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	US population of healthy late preterm/term neonates, but a quarter non-white and half Hispanic or Latino. Prevalence of jaundice/hyperbilirubinaemia and risk factors for it may differ.
Applicable to UK screening test of interest?	Unclear	Unclear	Uncertain what screen test may be considered in the UK.
Target condition measured by reference test applicable to UK screening condition of interest?	N	High	Outcome of ABE or kernicterus has not been examined.

Appendix number	3
Relevant criteria	5

Publication details	Yu ZB, Han SP, Chen C. Bilirubin nomograms for identification of neonatal hyperbilirubinemia in healthy term and late-preterm infants: a systematic review and meta-analysis. World journal of pediatrics: WJP. 2014;10(3):211-8.[9]
Study details	Systematic review and meta-analysis
Study objectives	To review previously published studies and compare the TcB normogram with the TSB normogram to see whether the former as a non-invasive, non-time-consuming procedure, has the same predictive value for significant hyperbilirubinaemia
Inclusions	Any study that developed and evaluated an hour-specific bilirubin nomogram (TcB or TSB) to identify significant hyperbilirubinemia in healthy term and late-preterm infants (gestational age ≥35 weeks). Eligible studies were required to: • Classify risk of hyperbilirubinemia according to percentile values of TSB or TcB divided into four risk zones: high, high-intermediate, low-intermediate, low risk zone • Evaluate the predictive ability of TcB/TSB nomograms to identify significant hyperbilirubinemia • Construct receiver operating characteristic (ROC) curves and allow area under the curve (AUC) of diagnostic accuracy could be calculated Search: Medline, EMBASE, the Chinese Biomedical Literature Database, the Chinese National Knowledge Infrastructure database, and the Cochrane Library; January 1980 to July 2013.
Exclusions	Eligible studies were required to exclude newborns admitted to NICU or who required phototherapy before discharge. Additional exclusions: • TcB/TSB nomograms were constructed but predictive abilities were not evaluated • AUC of diagnostic accuracy of the TcB/TSB nomograms could not be calculated • if the same institution reported two or more studies for the same population, the large study was included
Intervention/test	Risk percentile on pre-discharge TcB/TSB nomograms to predict post-discharge significant hyperbilirubinaemia
Comparator	NA
Included studies/population	14 studies met eligibility criteria: <u>TcB normograms</u> • 7 studies: 3 from India, 1 China, 1 Israel, 1 Italy, 1 USA*

	• Study sample size range: 322 to 11,456 • All but one study was single centre (Italy 5 centres), and involved development and/or validation of TcB normograms using JM-103 (3 studies) or BiliCheck (4 studies). • The normograms were developed using their own race/ethnicity data in 5/7 studies; 2 used those previously developed by another study group • Method of diagnosis of post-discharge significant hyperbilirubinaemia: AAP 2004 guidelines[8] (5 studies); TSB >13mg/dL (1 study); >95th percentile on previously developed Bhutani normogram (1 study) *including 3 studies published 2011 onwards,[10, 13, 14] all identified by current review search <u>TSB normograms</u> • 7 studies: 4 USA, 1 Italy, 1 India, 1 Turkey* • Study sample size range: 156 to 2840 • All but one single centre (Italy 5 centres), and involving development and/or validation of TSB normograms. • Normograms were developed using their own race/ethnicity data in 4 studies; 3 used the Bhutani normogram • Method of diagnosis of post-discharge significant hyperbilirubinaemia: AAP guidelines (2004[8] in 3 studies, 1994 in 1); TSB >20mg/dL (1 study); >95th percentile on Bhutani normogram (1 study); >95th percentile on their own normogram (1 study) *including 2 studies published 2011 onwards,[11, 12] all identified by current review search Overall 11 studies assessed to be of medium methodological quality, 3 studies low quality.
Results/outcomes	<u>TcB normograms</u> AUC range in 7 studies: 0.720 to 0.971; pooled AUC 0.817 <u>TSB normograms</u> AUC range in 7 studies: 0.731 to 0.931; pooled AUC 0.819 Predictive results pooled using random effects model: Summary of accuracy of pre-discharge TcB normogram percentiles for predicting subsequent significant hyperbilirubinaemia

Pre-discharge TcB	Studies in MA (n)	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	AUC (SE)
>95th percentile	4/7	26.9 (24.0 to 29.9)	95.8 (95.5 to 96.1)	8.46 (7.25 to 9.88)	0.925 (0.044)
>75th percentile	7/7	74.3 (71.5 to 76.9)	77.5 (76.9 to 78.0)	3.61 (3.07 to 4.25)	0.864 (0.015)
>40th percentile	3/7	96.1 (94.4 to 97.3)	45.7 (44.4 to 46.9)	1.67 (1.40 to 1.90)	0.512 (0.087)

Summary of accuracy of pre-discharge TSB normogram percentiles for predicting subsequent significant hyperbilirubinaemia

Pre-discharge TSB	Studies in MA (n)	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	AUC (SE)
>95th percentile	4/7	45.5 (39.8 to 51.2)	95.9 (95.2 to 96.5)	11.46 (8.68 to 15.09)	0.931 (0.042)
>75th percentile	6/7	82.8 (80.0 to 85.3)	65.3 (64.5 to 66.1)	3.34 (2.00 to 5.57)	0.875 (0.041)
>40th percentile	5/7	94.8 (92.9 to 96.3)	38.8 (37.9 to 39.6)	1.76 (1.21 to 2.55)	0.591 (0.063)

Comments

TcB and TSB normograms predominantly developed from single centre populations in non-UK countries. Uncertain applicability to UK population.

Despite review inclusion criteria, included studies may be variable in inclusion and exclusion criteria populations (e.g. reviewed studies post-2011, 3 also excluded infants with positive DAT test; 2 tested infants “if clinically jaundiced and/or before discharge”). Therefore variable exclusion of disease causes of hyperbilirubinaemia and unclear applicability to all term/late term infants.

The majority of the studies based risk on TcB/TSB values, but 5 considered additional clinical risk factors (e.g. gestational age, breastfeeding, previous sibling with jaundice).

Overall unclear applicability to all term/late term infants.

Unclear timing of post-discharge TSB outcome.

Examines outcome of significant hyperbilirubinaemia; definition of this was not consistent across all included studies limiting meta-analysis.

Doesn’t examine how this outcome relates to treatment initiated, ABE or kernicterus.

Further limitations as below:

Question	**Assessment (Y, N,**	**Risk of Bias (low, high,**	**Supporting info**

	unclear)	unclear)	
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	NA	NA	Systematic review.
Case-control design avoided?	Y	Low	Did not include case control studies.
Inappropriate exclusions avoided?	Unclear	Unclear	Review inclusion criteria were appropriate in only excluding preterm infants, those admitted to NICU and needing PT before discharge. However, included studies are likely to vary in their population inclusion/exclusion criteria on which normograms were developed.
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Unclear	Pre-discharge TcB/TSB recorded without knowledge of subsequent post-discharge significant hyperbilirubinaemia, but unclear whether any interpretation of these values was made at the time (e.g. identified as high or low risk)
Threshold pre-specified?	N	High	No threshold was pre-specified, unclear whether pre-discharge TcB/TSB normograms were used to manage with a high/low index of suspicion.
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	N	High	Definitions of subsequent significant hyperbilirubinaemia varied between included studies and also does not inform the infant's risk of ABE or kernicterus
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	Unclear whether any interpretation of pre-discharge TcB/TSB risk percentile was made, but outcome of significant hyperbilirubinaemia was variably defined. Outcome of interest was not measured.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Unclear	Unclear	Uncertain applicability: Pre-discharge TcB/TSB was separated from post-discharge outcome assessment but interval was not specified and likely to vary between studies. Outcome of ABE or kernicterus not measured.

Did all participants receive same reference standard?	N	High	Significant hyperbilirubinaemia was variably defined in included studies. Outcome of interest was not examined.
All patients included in analysis?	N	High	All studies could not be included in pooled analysis because of variability in predictive thresholds and outcomes assessed. Unclear drop-out in individual included studies.
Applicability			
Applicable to UK screening population of interest?	Unclear	High	Mostly healthy late preterm/term neonates, but the normograms were developed from different ethnic populations, mostly single centre, and with variable additional inclusion/exclusion criteria.
Applicable to UK screening test of interest?	Unclear	Unclear	Uncertain what screen test may be considered in the UK.
Target condition measured by reference test applicable to UK screening condition of interest?	N	High	Outcome of ABE or kernicterus has not been examined.

Appendix number	4
Relevant criteria	5
Publication details	Yu Z, Han S, Wu J, et al. Validation of transcutaneous bilirubin nomogram for identifying neonatal hyperbilirubinemia in healthy Chinese term and late-preterm infants: a multicenter study. Jornal de pediatria. 2014;90(3):273-8.[15]
Study details	Prospective cohort study 8 centres, China (August 2010 to December 2011)
Study objectives	To prospectively validate a previously constructed TcB normogram* to identify severe hyperbilirubinaemia in healthy Chinese term and late preterm infants. *TcB normogram previously developed by the same authors in a 2011 study,[14] included in the Yu et al. (2014)[9] review (Appendix 4).

Inclusions	Infants gestational age ≥35 weeks and birthweight ≥2000g
Exclusions	Infants admitted to NICU and requiring PT before discharge (treatment decisions based on AAP guidelines[8]).
Population	N=9174. Mean gestational age 38.6 +/- 2.9 weeks. Mean birthweight 2875 +/- 412g (5.6% small for gestational age) Exclusive breastfeeding: 34.5% (3165) ABO incompatibility diagnosed in 1.6% (147)
Intervention/test	Pre-discharge TcB measured using the JM-103 device (all measures confirmed by TSB) A total 6 TcB measures taken per infant during hospitalisation at time intervals of 12 +/- 2 hours.
Comparator	NA
Results/outcomes	Follow-up evaluation offered at 24 to 96 hours after discharge Outcome: Post-discharge significant hyperbilirubinaemia defined as TSB >95th percentile according to AAP[8] normograms. • Significant hyperbilirubinaemia in 972 (10.6%) • Pre-discharge TcB: ○ > 95th percentile: 275 ▪ 28.3% of those significant hyperbilirubinaemia ▪ 60.7% of all with pre-discharge TcB >95th ○ 76th to 95th percentile: 501 ▪ 51.5% of significant hyperbilirubinaemia ▪ 27.8% of all with TcB in 76th to 95th percentile ○ 40th to 75th percentile: 196 ▪ 20.2% of significant hyperbilirubinaemia ▪ 6.8% of all with TcB in 40th to 75th percentile ○ 0 <40th percentile: 0 *Pre-discharge TcB to predict significant post-discharge hyperbilirubinaemia* Pre-discharge TcB | Post-discharge TSB | Predictive characteristics

		>95th percentile					
Percentile	Number n=9174	Yes N=972	No n=8202	Sensitivity %	Specificity %	PPV %	NPV %
>95th	453	275	178	28.3	97.8	60.7	92.0
>75th	2258	776	1482	79.8	81.9	34.4	97.2
>40th	5137	972	4165	100	49.2	18.9	100

AUC for pre-discharge TcB for predicting significant post-discharge hyperbilirubinaemia: 0.875.

Comments

TcB normogram to predict subsequent significant hyperbilirubinaemia was developed by the authors in a previous study, which was from a single Chinese centre. This multicentre Chinese study demonstrated lower AUC (0.875) of the normogram than the previous study population (0.920). Uncertain applicability to the UK population.

Only examines outcome of TSB >95th percentile on AAP normogram[8]. Doesn't examine treatment initiated or outcomes including ABE or kernicterus.

US AAP[8] treatment thresholds may differ from those used in UK.

Further limitations as below:

Question	**Assessment (Y, N, unclear)**	**Risk of Bias (low, high, unclear)**	**Supporting info**
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	Exclusions reported and study dates given, therefore sample is expected to be all eligible within that period.
Case-control design avoided?	Y	Low	Not a case control study.
Inappropriate exclusions avoided?	Y	Low	Aside from excluding preterm, LBW, admitted to NICU or with infection, or phototherapy before discharge, additional exclusions
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Unclear	Pre-discharge TcB recorded without knowledge of subsequent post-discharge significant hyperbilirubinaemia, but unclear whether any interpretation of these values was made at the time (e.g. identified as high or low risk)

Threshold pre-specified?	N	High	No threshold was pre-specified, unclear whether TcB normograms were used to manage with a high/low index of suspicion.
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	N	High	Significant hyperbilirubinaemia does not inform the infant's risk of ABE or kernicterus
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	Unclear whether any interpretation of pre-discharge TcB was made, but significant hyperbilirubinaemia was based on AAP thresholds. Outcome of interest was not measured.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Unclear	Unclear	Uncertain applicability: Pre-discharge TcB was separated from post-discharge TSB normogram, but time interval is unclear. Outcome of ABE or kernicterus not measured.
Did all participants receive same reference standard?	Y	Low	All infants received the same TSB measures, though the outcome of interest was not examined.
All patients included in analysis?	Y	Low	No reported loss to follow-up
Applicability			
Applicable to UK screening population of interest?	Unclear	High	Healthy late preterm/term neonates, but normogram developed from a single centre Chinese population. Accuracy differs in this multicentre Chinese population. Prevalence of jaundice/hyperbilirubinaemia and risk factors for it may differ.
Applicable to UK screening test of interest?	Unclear	Unclear	Uncertain what screen test may be considered in the UK.
Target condition measured by reference test applicable to UK screening condition of interest?	N	High	Outcome of ABE or kernicterus has not been examined.

Appendix number	5

Relevant criteria	10
Publication details	Gholitabar M, McGuire H, Rennie J, et al. Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia. The Cochrane database of systematic reviews. 2012;12:Cd009017[16]
Study details	Systematic review with meta-analysis
Study objectives	To investigate the effectiveness and safety of clofibrate in combination with phototherapy versus phototherapy alone in unconjugated neonatal hyperbilirubinaemia.
Inclusions	Randomised and quasi randomised controlled trials investigating clofibrate (any dose) in combination with phototherapy in preterm or term infants. Control comparison: PT alone, or placebo clofibrate in combination with PT Primary outcomes: • Bilirubin encephalopathy • Change in bilirubin levels • Mean duration of PT • Number of ET needed • Adverse effects of clofibrate • Neonatal morbidity Secondary outcomes included: • Parental anxiety • Staff satisfaction with treatment Search: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and CINAHL to April 2012.
Exclusions	Phototherapy given after relapse of hyperbilirubinaemia following successful phototherapy (rebound jaundice).
Population	12 studies, total n=739, individual study sample size range 40 to 90. 11 studies conducted in Iran, all studies single centre. Short-term outcomes reported for 6/9 studies, 2 studies followed to 18 months, 1 study to 6 years.
Intervention/test	PT plus oral clofibrate
Comparator	PT alone or PT plus placebo
Results/outcomes	Relevant outcomes: • Bilirubin encephalopathy

	○ No studies provided data • Mortality ○ No studies provided data Other outcomes: • Significantly lower bilirubin levels in the clofibrate than control groups: ○ Term neonates: at both 24 hours (WMD -2.14 mg/dL, 95% CI -2.53 to -1.75) and 48 hours (WMD -1.82 mg/dL, 95% CI -2.25 to -1.38) ○ Preterm neonates at 48 hours (WMD -1.37 mg/dL, 95% CI -2.19 to -0.55) • Significantly lower duration of PT in the clofibrate than control groups: ○ Term neonates: WMD -25.40 hours (95% CI - 28.94 to -21.86) ○ Preterm neonates: WMD -23.82 hours (95% CI -30.46 to -17.18)
Comments	Applicable population but no studies have examined ABE or kernicterus. Studies mostly relevant to Iran population, small studies, variability in intervention and control.

Appendix number	6
Relevant criteria	10
Publication details	Okwundu CI, Okoromah CA, Shah PS. Prophylactic phototherapy for preventing jaundice in preterm or low birth weight infants. The Cochrane database of systematic reviews. 2012;1:Cd007966.[18]
Study details	Systematic review with meta-analysis
Study objectives	To investigate the effectiveness and safety of prophylactic phototherapy for preterm (<37 weeks) or low birth weight (LBW) infants (birthweight <2500 g).
Inclusions	Randomised and quasi-randomised controlled trials investigating the effects of prophylactic PT in preterm and/or LBW infants. Prophylactic PT defined as PT initiated before the bilirubin has reached a pre-specified threshold (according to the study criteria) at which therapeutic phototherapy is indicated. Control comparison: either therapeutic use at pre-specified threshold; or no prophylactic PT Primary outcomes: • Clinical kernicterus • Pathological kernicterus • Need for exchange transfusion • Long-term neurodevelopment after one year of age

	Secondary outcomes included: • Highest TSB level in the first 7 days of life • Duration of PT • Duration of hospital stay • Mortality in NICU: kernicterus-related and all-cause Search: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL to March 2011.
Exclusions	No additional beyond not meeting inclusions.
Population	9 studies, total n=3449, individual study sample size range 22 to 1974. 6 studies from USA, 1 Canada, 1 Brazil, 1 India. Short-term outcomes reported for 6/9 studies, 2 studies followed to 18 months, 1 study to 6 years.
Intervention/test	Prophylactic PT (started within 12 hours in 6/9 studies)
Comparator	Control (mostly late commencement PT)

Results/outcomes	Relevant outcomes:
	• Clinical or pathological kerincterus
	  ○ No studies provided data
	• Neurodevelopmental impairment
	  ○ One study (n=1974) assessed the composite outcome of visual or hearing impairment, and moderate or severe cerebral palsy at 18-22 months
	  ○ Prophylactic PT reduced risk (RR 0.85, 95% CI 0.74 to 0.99, risk difference -0.04, 95% CI -0.09 to 0.00)
	  ○ *NB this is the 2008 study by Morris et al.,[20] secondary analysis of which is the study by Tyson et al. (2012)[19] The actual risk figure reported in both of these publications is 0.86*
	• Cerebral palsy
	  ○ Assessed by two studies (n=1017) at 12 and 18 months
	  ○ Prophylactic PT had no effect (RR 0.96, 95% CI 0.50 to 1.85)
	• Sensorineural hearing loss
	  ○ One study (n=922) found no effect of PT at 6 years (RR 0.31, 95% CI 0.07 to 1.50)
	• Exchange transfusion
	  ○ 3 studies (n=2946) using different treatment thresholds. One study found significant reduction in need for ET, the others found no effect.

	○ Pooled effect prophylactic PT reduced ET need (RR 0.22, 95% CI 0.15 to 0.34; significant heterogeneity) Other outcomes: ○ Prophylactic PT reduced peak TSB during the first week of life (mean difference, -2.73, 95% CI -2.89 to -2.57) in 6 studies. ○ Prophylactic PT has no effect on mortality in 4 studies (RR 1.08, 95% CI 0.93 to 1.26)
Comments	Significant limitation to applicability: examines prophylactic PT use in all preterm/LBW infants therefore not relevant to national screening. No study was reported to examine kernicterus but relevant neurodevelopmental outcomes have been assessed. However, not certain that bilirubin encephalopathy was the cause. Also may not be primary outcomes of the trials. Variability between studies in intervention and control used and outcomes assessed.

Appendix number	7
Relevant criteria	10
Publication details	Tyson JE, Pedroza C, Langer J, et al. Does aggressive phototherapy increase mortality while decreasing profound impairment among the smallest and sickest newborns? Journal of perinatology : official journal of the California Perinatal Association. 2012;32(9):677-84.[19]
Study details	Randomised controlled trial Multicentre, US
Study objectives	To assess the effect of aggressive compared with conventional phototherapy on risk of death or neurodevelopmental impairment at 18 to 22 months in extremely low birthweight infants. *Note this is a secondary analysis of the original trial[20] specifically focusing on the effects in subgroups according to ventilator need and birthweight.
Inclusions	Extremely low birthweight (ELBW) infants (birthweight ≤1000g) enrolled at 12 to 36 hours of age
Exclusions	Terminal illness (pH <6.8 or persistent bradycardia and hypoxemia for >2 hours), major congenital anomaly, severe haemolytic disease, and congenital nonbacterial infection.
Population	N=1974 ELBW infants Subgroup analysis by birthweight stratum (501–750g and 751–1000g) and

	mechanical ventilation
Intervention/test	Aggressive phototherapy (AgPT): provided at a TSB value of ≥5mg/dL in the first week and ≥7mg/dL in the second week
Comparator	Conservative phototherapy (ConPT): provided at a TSB value of ≥8mg/dL for infants weighing 501–750g, and ≥10mg/dL for 751–1000g infants
Results/outcomes	Outcomes assessed at 18–22 months after term (note the main overall trial outcomes are reported here, rather than the subgroup analyses): • Primary outcome: composite of death or neurodevelopmental impairment (defined as blindness, severe hearing loss, moderate or severe cerebral palsy, or score <70 on the Mental or Psychomotor Development Index of the Bayley Scales of Infant Development II [score range 50 to 150 with 150 the most advanced]): o AgPT had no effect: 465/902 (52%) vs. ConPT 493/902 (55%): RR 0.94, 95% CI 0.87 to 1.02 • Neurodevelopmental impairment alone: o AgPT significantly reduced risk: 235/902 (26%) vs. ConPT 275/902 (30%): RR 0.86, 95% CI 0.74 to 0.99 • Profound impairment (defined as score ≤50 on either the Mental or Psychomotor Development Index, or a level of 5 for gross motor function on the modified Palisano criteria [score range 0 to 5, 5 indicating need for assistance]) o AgPT significantly reduced risk: 80/895 (9%) vs. ConPT 119/896 (13%): RR 0.68, 95% CI 0.52 to 0.89 • Mortality: o AgPT had no overall effect: 230/946 (24%) vs. ConPT 218/944 (23%): RR 0.92, 95% CI 0.72 to 1.17 (note Morris et al.[20] reported RR 1.05 [95% CI 0.90 to 1.22] for the same proportions) o AgPT did increase risk in subgroup of 501–750g ventilated infants: 153/353 (43%) vs. ConPT 124/343 (36%): RR 1.19, 95% CI 1.01 to 1.39
Comments	Secondary analysis and discussion of the authors' trial with initial publication date 2008[20] Limited applicability to potential screened population being all ELBW (mean gestational age 26 weeks). Not certain that neurodevelopemental impairment was caused by bilirubin encephalopathy.

	Morris et al.[20] reported the mean TSB (+/- SD) during the first 14 days among impaired survivors (5.4mg/dL ±1.6) and unimpaired survivors (5.4mg/dL ±1.5) (p=0.45). Mean peak TSB did differ between impaired (8.6mg/dL ±2.3) and unimpaired (8.3mg/dL ±2.3) (p=0.02). However, with the considerable overlap in peak values between the groups Morris et al.[20] noted that this provides little evidence to support a specific bilirubin threshold causing impairment.

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