NICE National Institute for Health and Care Excellence

Surveillance proposal consultation document

2019 surveillance of Jaundice in newborn babies under 28 days NICE guideline CG98

Surveillance proposal

We propose to not update the guideline on Jaundice in newborn babies under 28 days (NICE guideline CG98).

The following table gives an overview of how evidence identified in surveillance might affect each area of the guideline.

Section of the guideline	New evidence identified	Impact
1.1 Information for patients and carers	No	No
1.2 Care for all babies	Yes	No
1.3 Management and treatment of hyperbilirubinaemia	Yes	No
1.4 Measuring and monitoring bilirubin thresholds before and after phototherapy	Yes	No
1.5 Factors that influence the risk or kernicterus	No	No
1.6 Formal assessment for underlying disease	No	No
1.7 Care of babies with prolonged jaundice	No	No
1.8 Intravenous immunoglobulin	No	No
1.9 Exchange transfusion	Yes	No
1.10 Other therapies	Yes	No

Reasons for the proposal to not update the guideline

The new evidence was found to be broadly consistent with the current recommendations.

Recommendations in section 1.2 Care for all babies, were updated in 2016 when new evidence on the use of transcutaneous bilirubinometry (TcB) in preterm infants was identified; the recommendation was not changed. In the 2019 surveillance review, 3 additional systematic reviews also supported the existing recommendation. Some recommendations in section 1.4 Measuring and monitoring bilirubin thresholds before and during phototherapy, were updated in 2016. Only a small amount of poor-quality evidence was identified but, based on expert opinion and consensus, the committee revised and updated the original recommendations for optimal total serum bilirubin levels for starting phototherapy and exchange transfusion. The guideline committee also reviewed the different modalities and procedures for giving phototherapy but was unable to identify best methods and the recommendations were unchanged from the original guideline. The 2019 surveillance review did not identify any new evidence that would impact on the recommendations in this section.

In section, 1.7 Care of babies with prolonged jaundice, topic experts suggested that the guideline should consider recommending thyroid functioning tests (TSH and FT4) in babies with prolonged jaundice. This reflects the 2014 PHE Laboratory Guide to Newborn Screening in the UK for congenital Hypothyroidism which states: 'There are also cases reported of babies with low T4 and normal TSH levels in the initial newborn blood spot screening specimen, who later display an abnormally elevated TSH and are subsequently diagnosed with congenital hypothyroidism. Half of these babies with this abnormal profile were preterm. These babies may not be detected by newborn blood spot screening using TSH only (see Mandel et al., 2000).' Although we have identified no new evidence in this area, we agree that it would be useful for the guideline to recognise the need for thyroid function tests in babies with prolonged jaundice of unknown cause. We propose to revise the wording of recommendation 1.7.1, last bullet point, as follows:

> 'ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed, and if no cause of prolonged jaundice has been identified, carry out diagnostic tests (TSH and FT4) for congenital hypothyroidism.'

For further details and a summary of all evidence identified in surveillance, see appendix A below.

Overview of 2019 surveillance methods

NICE's surveillance team checked whether recommendations in on Jaundice in newborn babies under 28 days (NICE guideline CG98) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews and national policy.
- Consideration of evidence from previous surveillance in 2012 and 2014.

- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether the whole guideline or any sections of the guideline need updating.
- Consulting on the proposal with stakeholders (this document).

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

Evidence considered in surveillance

Search and selection strategy

As only part of the guideline had been updated in 2016, we searched for new evidence related to the whole guideline published between 1 February 2014 and 4 July 2019. The following studies were included:

- 46 randomised controlled trials (RCTs) or systematic reviews plus 2 Cochrane reviews
- 1 study from a total of 4 identified by 1 topic expert
- 37 studies from the previous surveillance review in 2014.

From all sources, we considered 86 studies to be relevant to the guideline. See appendix A below for details of all evidence considered, and references.

Ongoing research

We checked for relevant ongoing research. However, none of the 4 studies identified have the potential to immediately impact recommendations and so will not be tracked but will be considered in the next surveillance review where appropriate.

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We sent questionnaires to 11 topic experts and received 4 responses. Two experts thought the guideline should be updated; the other 2 experts thought an update was not needed. Two topic experts stated that that the guideline should consider a specific recommendation to perform thyroid function testing (TSH and FT4) in prolonged jaundice. They shared concerns that that some babies with congenital hypothyroidism are missed and if there are clinical concerns then the relevant diagnostic tests (TSH and FT4) should always be performed. There were no other comments from topic experts

Views of stakeholders

Stakeholders are consulted on all surveillance reviews except if the whole guideline will be updated and replaced. Because this surveillance proposal is to not update the guideline, we are consulting with stakeholders.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

Overall surveillance proposal

After considering all evidence and other intelligence and the impact on current recommendations, we propose that no update is necessary. However, topic experts advised from topic experts that prolonged jaundice may indicate congenital hyperthyroidism and the 2014 PHE Laboratory Guide to Newborn Screening in the UK for congenital Hypothyroidism states: 'There are also cases reported of babies with low T4 and normal TSH levels in the initial newborn blood spot screening specimen, who later display an abnormally elevated TSH and are subsequently diagnosed with congenital hypothyroidism. Half of these babies with this abnormal profile were preterm. These babies may not be detected by newborn blood spot screening using TSH only (see Mandel et al., 2000).' Therefore, recommendation 1.7.1 will be refreshed to advise that healthcare professionals consider thyroid function tests in babies with prolonged jaundice of unknown cause.

Appendix A: Summary of evidence from surveillance

2019 surveillance of Jaundice in newborn babies under 28 days (2010) NICE guideline CG98

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in the abstracts of the published papers. Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline. Evidence from previous surveillance and from an evidence update for this topic was also considered. Evidence updates were produced by NICE to highlight new evidence relating to published NICE guidelines.

The NICE guideline on neonatal jaundice (NICE clinical guideline CG98) was reviewed in May 2014 as part of NICE's routine surveillance programme, and following that, the guideline was updated in 2016.Full details are available in the Full guideline addendum. The review questions considered for the update were as follows:

1) What is the best modality of giving phototherapy (clinical and cost-effectiveness)?

2) What is the correct procedure when administering phototherapy?

3) What is the accuracy of various tests (clinical history and examination, urine/stool examination, icterometer and transcutaneous bilirubin levels) in recognising neonatal jaundice or hyperbilirubinaemia?

4) What are the optimal total serum bilirubin (TSB) thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia?

Information for parents or carers

Recommendations in this section of the guideline

Threshold table

Consensus-based bilirubin thresholds for management of babies 38 weeks or more gestational age with hyperbilirubinaemia

Age (hours)	Bilirubin measurement (micromol/litre)	
0	>100	>100
6	>125	>150
12	>150	>200

18	>175	>250
24	>200	>300
30	>212	>350
36	>225	>400
42	>237	>450
48	>250	>450
54	>262	>450
60	>275	>450
66	>287	>450
72	>300	>450
78	>312	450
84	325	>450
90	>337	>450
96+	>350	>450
Action	Start phototherapy	Perform an exchange transfusion unless the bilirubin level falls below threshold while the treatment is being prepared

1.1.1 Offer parents or carers information about neonatal jaundice that is tailored to their needs and expressed concerns. This information should be provided through verbal discussion backed up by written information. Care should be taken to avoid causing unnecessary anxiety to parents or carers. Information should include:

- factors that influence the development of significant hyperbilirubinaemia
- how to check the baby for jaundice
- what to do if they suspect jaundice
- the importance of recognising jaundice in the first 24 hours and of seeking urgent medical advice
- the importance of checking the baby's nappies for dark urine or pale chalky stools
- the fact that neonatal jaundice is common, and reassurance that it is usually transient and harmless
- reassurance that breastfeeding can usually continue.

Surveillance proposal

No new information was identified at 2012 evidence update, 2014 and 2019 surveillance reviews.

1.2 Care for all babies

Recommendations in this section of the guideline

1.2.1 Identify babies as being more likely to develop significant hyperbilirubinaemia if they have any of the following factors:

- gestational age under 38 weeks
- a previous sibling with neonatal jaundice requiring phototherapy
- mother's intention to breastfeed exclusively
- visible jaundice in the first 24 hours of life.

1.2.2 Ensure that adequate support is offered to all women who intend to breastfeed exclusively. See the NICE guideline on postnatal care for information on breastfeeding support.

1.2.3 In all babies:

- check whether there are factors associated with an increased likelihood of developing significant hyperbilirubinaemia soon after birth
- examine the baby for jaundice at every opportunity especially in the first 72 hours.

1.2.4 Parents, carers and healthcare professionals should all look for jaundice (visual inspection) in babies. [2016]

1.2.5 When looking for jaundice (visual inspection):

- check the naked baby in bright and preferably natural light
- examine the sclerae and gums and press lightly on the skin to check for signs of jaundice in 'blanched' skin. [2016]

1.2.6 Do not rely on visual inspection alone to estimate the bilirubin level in a baby with suspected jaundice. [2016]

1.2.7 Do not measure bilirubin levels routinely in babies who are not visibly jaundiced. [2010]

1.2.8 Do not use any of the following to predict significant hyperbilirubinaemia:

- umbilical cord blood bilirubin level

- end-tidal carbon monoxide (ETCOc) measurement
- umbilical cord blood direct antiglobulin test (DAT) (Coombs' test). [2010]

Additional care

1.2.9 Ensure babies with factors associated with an increased likelihood of developing significant hyperbilirubinaemia receive an additional visual inspection by a healthcare professional during the first 48 hours of life. [2010]

1.2.11 In all babies with suspected or obvious jaundice in the first 24 hours of life, continue to measure the serum bilirubin level every 6 hours until the level is both:

- below the treatment threshold
- stable below the treatment threshold
- stable and/or falling. [2010]

1.2.12 Arrange a referral to ensure that an urgent medical review is conducted (as soon as possible and within 6 hours) for babies with suspected or obvious jaundice in the first 24 hours of life to exclude pathological causes of jaundice. [2010]

1.2.13 Interpret bilirubin levels according to the baby's postnatal age in hours and manage hyperbilirubinaemia according to the threshold table and the treatment threshold graphs. [2010]

Care for babies more than 24 hours old

1.2.14 Measure and record the bilirubin level urgently (within 6 hours) in all babies more than 24 hours old with suspected or obvious jaundice. [2010]

How to measure the bilirubin level

1.2.15 Use serum bilirubin measurement for babies:

- in the first 24 hours of life or
- who have a gestational age of less than 35 weeks. [2016]

1.2.16 In babies who have a gestational age of 35 weeks or more and who are over 24 hours old:

- use a transcutaneous bilirubinometer to measure the bilirubin level
- if a transcutaneous bilirubinometer is not available, measure the serum bilirubin
- if a transcutaneous bilirubinometer measurement indicates a bilirubin level greater than 250 micromol/litre, measure the serum bilirubin to check the result
- use serum bilirubin measurement if bilirubin levels are at or above the relevant treatment thresholds for their age, and for all subsequent measurements. [2016]

1.2.17 Do not use an icterometer to measure bilirubin levels in babies. [2016]

Surveillance proposal

This section of the guideline should not be updated.

Care for all babies

Previous surveillance summary

Recommendations in this section (1.2 Care for all babies) were updated in 2016 and full details are available in the Full guideline addendum. Evidence from 1 study (1) identified during the 2012 surveillance process and 1 study (2) identified during the 2014 surveillance review were considered during the 2016 update.

2019 surveillance summary

Bilirubin assays

Transcutaneous bilirubin nomograms

Three systematic reviews (3–5) were identified that assessed the accuracy of transcutaneous bilirubin (TcB) nomograms to identify neonatal hyperbilirubinaemia.

One systematic review (3) found no differences between the predictive abilities of the total serum bilirubin (TSB) and TcB nomograms (the pooled area under curve was 0.819 versus 0.817 for TSB and TcB respectively n=14 studies).

Two other systematic reviews (4,5) assessed the correlation between TcB and TSB to identify hyperbilirubinaemia. One systematic review (4) found a moderate correlation between TcB and TSB measurements during phototherapy. The pooled estimates of correlation coefficients (r) during phototherapy were: covered sites 0.71 (95% CI 0.64 to 0.77, 11 studies), uncovered sites 0.65 (95% CI 0.55 to 0.74, 8 studies), forehead 0.70 (95% CI 0.64 to 0.75, 12 studies) and sternum 0.64 (95% CI 0.43 to 0.77, 5 studies). The correlation coefficient improved slightly in the post phototherapy phase (r=0.72, 95% CI 0.64 to 0.78, 4 studies). The other systematic review (5) indicated that the TcB measurement was comparable with TSB in preterm infants with hyperbilirubinaemia. The pooled estimates of correlation for combination of both sternal and forehead site measurement for TcB and TSB was r=0.82 (95% CI 0.78 to 0.85).

Smartphone camera

An RCT (6) was identified that investigated the efficacy of a digital image produced by a smartphone camera as a screening tool for neonatal hyperbilirubinaemia. A total of 64 infants with gestational age >35 weeks were included. Images of the glabella were obtained with directly applied pressure, with a dermatoscope, or a dermatoscope equipped with a Wratten filter. The red, green and blue colour intensities of each image were compared with bilirubin

levels. The findings indicated that a smartphone equipped with a consistent light source in the form of a dermatoscope may be an effective screening tool for neonatal hyperbilirubinaemia. The dermatoscope-acquired intensities of the green and blue channels were significantly correlated with bilirubin measurements (Pearson's r=0.59 and 0.48, respectively).

Intelligence gathering

A topic expert highlighted 4 studies for consideration which were assessed; one was included (Munkholm et al., 2018) and 3 excluded as they did not meet this surveillance review's inclusion criteria.

Impact statement

Transcutaneous bilirubin nomograms

This section was updated in 2016 following the 2014 surveillance review where new evidence on the use of TcB in preterm infants was identified. The original recommendation on TcB was in those >35 weeks gestational age (and greater than 24 hours of age) and therefore the primary aim of updating this question was to assess whether the existing recommendation should be extended to preterm babies (<35 weeks) or not. Following extensive review of evidence committee decided against extending the recommendation to those <35 weeks gestation. This was mainly because there was very wide range of mean differences in bilirubin when comparing TcB against TSB was seen across the included studies. Furthermore, the range of accuracy/mean difference in bilirubin observed for the different devices measuring TcB were not clinically acceptable for diagnosing jaundice in preterm infants.

Evidence from 3 systematic reviews in the current surveillance review found no differences between the predictive abilities of the TSB and TcB nomogram for hyperbilirubinaemia in preterm babies. Therefore, no impact on current recommendations is anticipated.

New evidence is unlikely to change guideline recommendations.

1.3 Management and treatment of hyperbilirubinaemia

Information for parents or carers on treatment

1.3.1 Offer parents or carers information about treatment for hyperbilirubinaemia, including:

- anticipated duration of treatment
- reassurance that breastfeeding, nappy-changing and cuddles can usually continue. [2010]

1.3.2 Encourage mothers of breastfed babies with jaundice to breastfeed frequently, and to wake the baby for feeds if necessary. [2010]

1.3.3 Provide lactation/feeding support to breastfeeding mothers whose baby is visibly jaundiced. [2010]

How to manage hyperbilirubinaemia

1.3.4 Use the bilirubin level to determine the management of hyperbilirubinaemia in all babies (see threshold table and the treatment threshold graphs). [2010]

1.3.5 Do not use the albumin/bilirubin ratio when making decisions about the management of hyperbilirubinaemia. [2010]

1.3.6 Do not subtract conjugated bilirubin from total serum bilirubin when making decisions about the management of hyperbilirubinaemia (see threshold table and the treatment threshold graphs). [2010]

Surveillance proposal

This section of the guideline should not be updated.

Management and treatment of hyperbilirubinaemia

Previous surveillance summary

No relevant evidence was identified.

2019 surveillance summary

Bilirubin/albumin ratios

An RCT (7) assessed the use of bilirubin/albumin ratios (B/A ratio) as well as TSB threshold to guide to management of hyperbilirubinaemia in 615 preterm infants (≤32 weeks). The findings indicated that additional use of bilirubin/albumin ratio did not improve the rates of death and/or severe neurodevelopmental impairment and neurodevelopmental outcome.

Intelligence gathering

There was no new intelligence from the 2019 surveillance process of relevance to this section of the guideline.

Impact statement

The identified evidence indicates that the use of bilirubin/albumin ratio in the management of hyperbilirubinaemia may not be effective in improving neonatal outcomes in preterm babies which is in line with the current recommendation (1.3.5 'Do not use the albumin/bilirubin ratio when making decisions about the management of hyperbilirubinaemia').

New evidence is unlikely to change guideline recommendations.

1.4 Measuring and monitoring bilirubin thresholds before and during phototherapy

Recommendations in this section of the guideline

Before starting phototherapy

1.4.1 In babies who are clinically well, have a gestational age of 38 weeks or more and are more than 24 hours old, and who have a bilirubin level that is below the phototherapy threshold but within 50 micromol/litre of the threshold (see the threshold table and the treatment threshold graphs), repeat bilirubin measurement as follows:

- within 18 hours for babies with risk factors for neonatal jaundice (those with a sibling who had neonatal jaundice that needed phototherapy or a mother who intends to exclusively breastfeed)
- within 24 hours for babies without risk factors. [new 2016]

1.4.2 In babies who are clinically well, have a gestational age of 38 weeks or more and are more than 24 hours old, and who have a bilirubin level that is below the phototherapy threshold by more than 50 micromol/litre (see threshold table and the treatment threshold graphs), do not routinely repeat bilirubin measurement. [new 2016]

1.4.3 Do not use phototherapy in babies whose bilirubin does not exceed the phototherapy threshold levels in the threshold table and the treatment threshold graphs). [2010]

During phototherapy

1.4.5 During phototherapy:

- repeat serum bilirubin measurement 4–6 hours after initiating phototherapy
- repeat serum bilirubin measurement every 6–12 hours when the serum bilirubin level is stable or falling. [2010]

Stopping phototherapy

- 1.4.5 Stop phototherapy once serum bilirubin has fallen to a level at least 50 micromol/litre below the phototherapy threshold (see threshold table and the treatment threshold graphs) [2010]

1.4.6 Check for rebound of significant hyperbilirubinaemia with a repeat serum bilirubin measurement 12–18 hours after stopping phototherapy. Babies do not necessarily have to remain in hospital for this to be done. [2010]

Type of phototherapy to use

1.4.7 Do not use sunlight as treatment for hyperbilirubinaemia. [2010]

- 1.4.8 Use phototherapy* to treat significant hyperbilirubinaemia (see threshold table and the treatment threshold graphs) in babies. [new 2016]

1.4.9 Consider intensified phototherapy** to treat significant hyperbilirubinaemia in babies if any of the following apply [new 2016]:

- the serum bilirubin level is rising rapidly (more than 8.5 micromol/litre per hour)
- the serum bilirubin is at a level within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours or more since birth (see threshold table and the treatment threshold graphs)
- the bilirubin level fails to respond to initial phototherapy (that is, the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting phototherapy). [2010]

1.4.10 If the serum bilirubin level falls during intensified phototherapy to a level 50 micromol/litre below the threshold for which exchange transfusion is indicated reduce the intensity of phototherapy. [2010]

Information for parents or carers on phototherapy

1.4.11 Offer parents or carers verbal and written information on phototherapy including all of the following:

- why phototherapy is being considered
- why phototherapy may be needed to treat significant hyperbilirubinaemia
- the possible adverse effects of phototherapy
- the need for eye protection and routine eye care
- reassurance that short breaks for feeding, nappy changing and cuddles will be encouraged
- what might happen if phototherapy fails
- rebound jaundice
- potential long-term adverse effects of phototherapy

- potential impact on breastfeeding and how to minimise this. [2010]

General care of the baby during phototherapy

1.4.12 During phototherapy:

- place the baby in a supine position unless other clinical conditions prevent this
- ensure treatment is applied to the maximum area of skin
- monitor the baby's temperature and ensure the baby is kept in an environment that will minimise energy expenditure (thermoneutral environment)
- monitor hydration by daily weighing of the baby and assessing wet nappies
- support parents and carers and encourage them to interact with the baby. [2010]

1.4.13 Give the baby eye protection and routine eye care during phototherapy. [2010]

1.4.14 Use tinted headboxes as an alternative to eye protection in babies with a gestational age of 37 weeks or more undergoing phototherapy. [2010]

Monitoring the baby during phototherapy

1.4.15 During phototherapy:

- using clinical judgement, encourage short breaks (of up to 30 minutes) for breastfeeding, nappy changing and cuddles
- continue lactation/feeding support
- do not give additional fluids to babies who are breastfed.

Maternal expressed milk is the additional feed of choice if available, and when additional feeds are indicated. [2016]

Phototherapy equipment

1.4.17 Ensure all phototherapy equipment is maintained and used according to the manufacturers' guidelines. [2010]

1.4.18 Use incubators or bassinets according to clinical need and availability. [2010]

1.4.19 Do not use white curtains routinely with phototherapy as they may impair observation of the baby. [2010]

* Phototherapy given using an artificial light source with an appropriate spectrum and irradiance. This can be delivered using light-emitting diode (LED), fibreoptic or fluorescent lamps, tubes or bulbs.

** Phototherapy that is given with an increased level of irradiance with an appropriate spectrum. Phototherapy can be intensified by adding another light source or increasing the irradiance of the initial light source used.

Surveillance proposal

These recommendations should not be updated.

Measuring and monitoring bilirubin thresholds before and during phototherapy

Previous surveillance summary

Recommendations in this section (1.4 Measuring and monitoring bilirubin thresholds before and during phototherapy) were considered for update in 2016 and full details are available in the Full guideline addendum. The review questions for the update were:

- What are the optimal total serum bilirubin (TSB) thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia? What is the best modality of giving phototherapy (clinical and cost-effectiveness)?
- What is the best modality of giving phototherapy (clinical and cost-effectiveness)?

Evidence from 6 studies (8–12) identified during the 2012 surveillance process and 13 studies (13–19)(20–25) identified during the 2014 surveillance review were considered during the 2016 update.

2019 surveillance summary

Type of phototherapy to use

We identified 10 RCTs of light-emitting diode (LED) phototherapy treatment for neonatal hyperbilirubinaemia (see Table 1).

Conventional phototherapy versus LED

One RCT (26) found that LED phototherapy is more effective than a conventional phototherapy to reduce TSB levels (mean decrease (micromol/litre/hour) LED: 5.3±2.91 conventional: 3.76±2.39). Two other RCTs (27,28) also found that TSB decrease was higher after 24 hours treatment following LED and intensive phototherapy compared with conventional phototherapy, while 1 RCT (29) found that double LED is more effective than the single LED to decrease TSB.

LED versus fluorescent tubes

One RCT (30) found that LED with heterogeneous irradiance was as effective as fluorescent tubes phototherapy with homogeneous irradiance (TSB decline after 24 hours: LED: 0.16±0.09 mg/dl/hour; fluorescent light 0.16±0.08 mg/dl/hour p=0.87). One other RCT (31) found that LED treatment was superior to fluorescent tubes (success rate [avoidance of exchange transfusion] LED: 87% fluorescent tubes: 64%).

Evidence from 1 RCT (32) indicated that mean duration of treatment of phototherapy with LED light was significantly shorter compared with fluorescent lights (36.83±2.09 hours versus 45.66±2.52 hours).

Broad-spectrum light phototherapy versus a blue light LED

One RCT (33) found that duration of phototherapy is reduced with a broad-spectrum light (BSL) phototherapy compared with a blue LED phototherapy for the treatment of hyperbilirubinaemia in late preterm and term infants (duration of phototherapy BSL:15.8±4.9 hours LED: 20.6±6.0 hours). Evidence from 1 RCT (29) indicated that the intensive phototherapy (double light versus single light) may improve the efficacy of phototherapy.

Turquoise, green light versus blue light LED

Two RCTs (34,35) found turquoise, green light and blue light LED had equally reduced hyperbilirubinaemia in neonates.

Prophylactic versus therapeutic phototherapy

Evidence from 1 RCT (36) that assessed the efficacy of prophylactic versus therapeutic phototherapy in 50 very low birthweight babies indicated that prophylactic phototherapy had no effect in improving the rate of exchange transfusion.

Procedure of giving phototherapy

We identified 10 RCTs or systematic reviews examining different methods of giving phototherapy treatment for neonatal hyperbilirubinaemia (see Table 2).

Intermittent phototherapy versus continuous phototherapy

Three RCTs assessed the efficacy of intermittent phototherapy compared with continuous phototherapy in improving hyperbilirubinaemia. In 1 RCT (37), decrease in serum bilirubin was similar in intermittent phototherapy group and continuous phototherapy group after 36 hours, whereas in other 2 RCTs (38,39) decrease in TSB was higher in the intermittent group.

Discontinuation of phototherapy

One RCT (40) indicated that there was no significant post-phototherapy bilirubin rebound in 2 groups of neonates, with 2 levels of bilirubin 11 mg/dl level compared with 13 mg/dl, at discontinuation of phototherapy.

Additional fluids

One Cochrane systematic review (41) and 1 RCT (42) assessed the efficacy of oral or intravenous fluid supplementation adjunct to phototherapy on accelerating the decline of serum bilirubin in neonates with hyperbilirubinemia. The systematic review (41) indicated that the addition of IV fluid supplementation to phototherapy improved the total serum bilirubin compared with phototherapy alone at 4 hours following the treatment (MD −34.00 micromol/litre 95% CI −52.29 to −15.71 n=67, study=1). The change in serum bilirubin was similar between the IV fluid and oral fluid supplementation groups. The RCT (42) indicated

that decline in serum bilirubin was greater in the IV group when compared with the oral group (IV group:15.5%, 95% CI 11.7 to 19.4%, Oral group: 9.1%, 95% CI 7.3 to 10.9%).

Phototherapy with and without chest shielding

Two systematic reviews (43,44) on chest shielding in preterm babies receiving phototherapy were identified. Both systematic reviews included 2 studies and one systematic review indicated that use of chest shield was associated with a lower frequency of patent ductus arteriosus (OR=0.47, 95% CI 0.23 to 0.96) (43) while the other found no difference (44).

Reflective materials

Evidence from 1 systematic review (45) and 1 RCT (46) indicated that using white curtains and reflective materials around phototherapy machines decreased the mean serum bilirubin and duration of the phototherapy.

Intelligence gathering

There was no new intelligence from the 2019 surveillance process of relevance to this section of the guideline.

Impact statement

Type of phototherapy to use

This section was updated in 2016. The committee discussed that the actual spectrum of light and levels of irradiance are directly related to the rate of decrease of serum bilirubin, not just the overall modality of light sources used (e.g. fluorescent, LED or fiberoptic) as each of these modality of light sources has a different spectrum and could be set to varying degrees of irradiance. Therefore, simply comparing the overall modality of light sources without comparing the actual spectrum and irradiance used would not give a clear picture of the efficacy. The committee felt that current evidence is unclear to suggest any differences on these outcomes simply by the modality of light sources. Therefore, the guideline committee could not specify which specific modality is the best.

Evidence from 10 RCTs in the current surveillance review indicated that phototherapy treatment with LED light seems more effective than conventional phototherapy (shorter treatment length, lower exchange transfusion rate, higher TSB decrease). Further evidence from 6 RCTs indicated that LED phototherapy and intensive treatment may be superior to fluorescent tube light in reducing the length of treatment and increasing the success rate. Turquoise, green light and blue light LED had equally reduced hyperbilirubinaemia in neonates and broad-spectrum light appeared more effective than a blue light LED phototherapy. These findings are based on the assessment of the abstracts only and actual spectrum and degrees of irradiance were not reported. There are currently no recommendations to specify the type of phototherapy to use in the guideline. Although, the new evidence supports previous findings suggesting effectiveness of LED, the studies are heterogeneous and insufficient to recommend LED compared with conventional phototherapy.

New evidence is unlikely to change guideline recommendations.

Procedure of giving phototherapy

Conflicting results from 3 RCTs does not allow a conclusion about whether one procedure of giving phototherapy is superior to another.

One RCT indicated that occurrence of bilirubin rebound was similar when two threshold levels for discontinuation of phototherapy were examined. No further evidence was identified, and this small single study's finding has no impact on current recommendation on discontinuation of phototherapy based on the threshold table.

The guideline recommends that good clinical practice should ensure that babies are kept hydrated while undergoing phototherapy and maternal expressed milk is the additional feed of choice if available when additional feeds are indicated. The guideline also recommends 'do not' give additional fluid or feeds routinely for hydration. Evidence from 1small study (n=67) a in a systematic review and 1 other RCT indicated that the addition of IV fluid supplementation to phototherapy may decrease total serum bilirubin better than the phototherapy alone. The new evidence is from one small study and insufficient to change the current guideline recommendations.

Evidence from 2 systematic reviews was conflicting for the effect of shielding on the ductus arteriosus. The findings were based on 3 small studies (in the 2 systematic reviews) with limited clinical outcomes reported. As such, the evidence is insufficient to impact on the guideline.

Evidence from 1 systematic review and 1 RCT supports the use of reflective curtains and materials around phototherapy machines. However, the original guideline development committee did not want to recommend the use of curtains around phototherapy machines as their use compromises the ability to observe the baby. Hence the identified new evidence is unlikely to impact the current recommendations.

New evidence is unlikely to change guideline recommendations.

Table 1-Type of phototherapy to use (data extracted from abstracts)

(RCT = randomised controlled trial, SR = systematic review, TSB = total serum bilirubin)

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
Conventional phototherapy versus light-emitting diode (LED)				
Gutta et al., 2019 (26) RCT	166 babies, ≥35 weeks gestation	LED vs Conventional phototherapy	TSB decrease	Improved with intervention TSB decrease (micromol/litres/hour mean±SD) LED: 5.3±2.91

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
				Conventional: 3.76±2.39, p<0.001
El-Farrash et al., 2019 (27) RCT	120 babies, ≥35 weeks gestation	Blue LED vs Conventional phototherapy vs Intensive phototherapy	TSB decrease Follow up 24 hours	Improved with intervention TSB. Decreased in all 3 groups with significantly lower levels following intensive and LED phototherapy compared with conventional phototherapy (p<0.05 for both)
Zhang et al., 2016 (28) RCT	144 babies	Intensive phototherapy vs Conventional phototherapy	TSB level Reduction in serum bilirubin level Follow up 12 hours	Improved with intervention TSB level. Significantly lower in intensive group compared with conventional phototherapy (p<0.05) Reduction in serum bilirubin level. Significantly lower in intensive group compared with conventional phototherapy (p<0.05)
LED versus fluorescent tubes				
Brandao et al., 2015 (30) RCT	74 babies, ≥35 weeks gestation	Blue LED (17-bulb) vs Fluorescent tubes (7-bulb daylight device)	TSB decrease Hypothermia (<36°) Follow up 24 hours	Improved with intervention TSB decrease (mg/dl/hour ±SD) LED: 0.16±0.09 Day light device 0.16±0.08 Hypothermia LED: 23% Day light device: 9%, p=0.02
Sherbiny et al., 2016 (31) RCT	200 babies ≥35 weeks gestation	LED vs Fluorescent tubes	Avoidance of exchange transfusion Side effects: hyperthermia, dehydration, skin rash	Improved with intervention Avoidance of exchange transfusion LED: 87%, fluorescent tubes: 64% p=0.003 Hyperthermia LED: 0%, fluorescent tubes: 12% p=0.03 Dehydration LED: 2%, fluorescent tubes: 8% p=0.26 Skin rash LED: 1%, fluorescent tubes: 39% p=0.002
Tufail, et al., 2019 (32) RCT	460 babies, mean gestational age 32 weeks	Phototherapy LED vs Phototherapy with fluorescent lights	Duration of treatment Follow up at end of treatment	Improved with intervention Mean duration of treatment (hours ±SD) LED: 36.83±2.09 Fluorescent lights: 45.66±2.52, p=0.0001
Broad-spectrum light (BSL) phototherapy versus a blue light LED				
Pratesi et al., 2015 (33) RCT	40 babies, 35-41 weeks gestation	Blue LED vs Broad-spectrum light	Duration of phototherapy Follow up, end of treatment	Improved with intervention Duration of phototherapy (hours ±SD) Blue LED: 20.6±6.0 Broad-spectrum light: 15.8±4.9, p=0.009
Donneborg et al., 2018 (29) RCT	83 babies, ≥33 weeks gestation	Double LED vs Single LED	% TSB decrease Follow up 12 and 24 hours	% TSB decrease, 12 hours Double LED: 39% (95% CI 37 to 42) Single LED: 30% (95% CI 27 to 32), p<0.001 % TSB decrease, 24 hours Double LED: 58% (95% CI 56 to 61) Single LED: 47% (95% CI 44 to 50), p<0.001

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
Turquoise, green light versus blue light LED				
Ebbesen et al., 2016 (34) RCT	91 babies, ≥33 weeks gestation	Blue LED vs Turquoise LED	Median TSB decline Follow up 24 hours	No significant difference between intervention and comparator Median TSB decline Blue LED: 33.1% (95% CI 27.1 to 36.8) Turquoise LED: 35.3% (95% CI 32.5 to 37.3)
Kuboi et al., 2019 (35) RCT	34 babies	Blue LED vs Green LED	Mean TSB decline Follow up 24 hours	No significant difference between intervention and comparator Mean TSB decline (mg/dl ±SD) Blue LED: from 16.2±1.3 to 14.5±1.7 Green LED: from 15.3±1.5 to 13.9±1.5

Table 2 Procedure of giving phototherapy (data extracted from abstracts)

(RCT = randomised controlled trial, SR = systematic review, TSB = total serum bilirubin)

Authors (Year) Study type	population	Intervention and Comparator	Outcome and Follow up	Result
Intermittent phototherapy versus continuous phototherapy				
Taheritafti and Taheritafti 2019 (37) RCT	60 term babies	Intermittent phototherapy, on for 18 hours and off for 8 hours vs Continuous phototherapy for 24 hours	Duration of phototherapy	No significant difference between intervention and comparator Duration of phototherapy (hours±SD) Continuous: 45.26±16.39 Intermittent: 46±11.82 Rate of serum bilirubin cessation was similar after 36 hours
Sachdeva et al., 2015 (38) RCT	75 babies, ≥35 weeks gestation	Continuous phototherapy vs Intermittent phototherapy	Decrease in TSB Follow up phototherapy was continued until TSB<13 mg/dl	Improved with intervention Decrease in TSB Decrease was significantly higher in intermittent phototherapy p=0.002
Khaliq, et al., 2016 (39) RCT	258 babies	Intermittent phototherapy vs Continuous phototherapy	Decrease in TSB	No significant difference between intervention and comparator Decrease in TSB (mg/dl ±SD) Intermittent: 4.78 mg/dl±1.20 Continuous: 4.63 mg/dl±1.18
Discontinuation of phototherapy				
Niknafas et al., 2014 (40) RCT	115 babies	Group A: phototherapy discontinued at bilirubin level 11 mg/dl vs Group B: phototherapy discontinued at bilirubin level 13 mg/dl	Significant rebound Follow up 24 hours	No significant difference between intervention and comparator Significant rebound Group A: N=9 (69%) Group B: n=3 (21%) Logistic regression analysis showed that intravenous serum therapy was the only risk factor significantly associated with rebound (p=0.005).
Additional fluids				

Authors (Year) Study type	population	Intervention and Comparator	Outcome and Follow up	Result
Lai, et al., 2017 (41) Cochrane SR, 6 studies	494 term babies	IV fluid supplementation vs No IV fluid supplementation	Serum bilirubin level Need for exchange transfusion Follow up 4 and 8hours	Improved with intervention Serum bilirubin level, 4 hours (1 study, 67 babies) Mean Difference −34.00 micromol/litres (95% CI −52.29 to −15.71) Exchange transfusion (6 studies, 462 babies) Risk Ratio 0.39 (95% CI 0.21 to 0.71) Risk Difference −0.01 (95% CI −0.04 to 0.02)
Lai, et al., 2017 (41) Cochrane SR, 6 studies	494 term babies	IV fluid supplementation vs Oral fluid supplementation (1 study)	Serum bilirubin level Need for exchange transfusion Follow up 4 and 8hours	Not significant difference between intervention and comparator Serum bilirubin level 4 hours (54 babies) Mean Difference 11.00 micromol/litre (95% CI −21.58 to 43.58) Exchange transfusion Risk Ratio 1.60 (95% CI 0.60 to 4.27) Risk Difference 0.11 (95% CI −0.12 to 0.34)
Goyal et al., 2018 (42) RCT	101 term and nearly term babies with severe hyperbiliru binaemia	IV fluid supplementation vs Oral fluid supplementation vs No supplementation	Decline in serum bilirubin Follow up 8hours	Improved with intervention Decline in serum bilirubin IV: 15.5% (95% CI 11.7 to 19.4) Oral: 9.1% (95% CI 7.3 to 10.9) Control: 8.0% (95% CI 6.2 to 9.7), p<0.001 Duration of phototherapy and proportion of neonates needing exchange transfusion were comparable in the 3 study groups
Phototherapy with and without chest shielding				
Mannan and Amin., 2017 (43) SR, 2 small studies		Phototherapy with chest shielding vs Phototherapy with no chest shielding	Haemodynamically patent ductus arteriosus	Improved with intervention Haemodynamically patent ductus arteriosus (1 RCT, 74 babies) Odds Ratio 0.47 (95% CI 0.23 to 0.96)
Bhola et al., 2015 (44) SR (Cochrane), 2 small studies		Phototherapy with chest shielding vs Phototherapy with no chest shielding	Haemodynamically patent ductus arteriosus Patent ductus arteriosus detect by murmur	Not significant difference between intervention and comparator Haemodynamically patent ductus arteriosus Risk Ratio 0.23 (95% CI 0.05 to 1.01) Risk Difference −0.18 (95% CI −0.34 to −0.03) Number Needed to Treat 5 (95% CI 3 to 33) Improved with intervention Patent ductus arteriosus detect by murmur (1 RCT, 74 babies) Risk Ratio 0.50 (95% CI 0.29 to 0.88) Risk Difference −0.30 (95% CI −0.52 to −0.08) Number Needed to Treat 3 (95% CI 2 to 12)
Reflective materials				
Lee Wan Fei, 2019 (45) SR		Use of reflective materials around phototherapy units: white 100% cotton cloths (one study),	Duration of phototherapy Mean decrease TSB Follow up 4 hours	Improved with intervention Duration of phototherapy (3 studies) Effect size: 0.82, p=0.04 Mean decrease TSB (micromol/litre) 11.39 (95% CI 2.26 to 20.52), p=0.01

Authors (Year) Study type	population	Intervention and Comparator	Outcome and Follow up	Result
		white plastic covers (2 studies), under pads (one study), and silver fabric cloth (one study) vs No reflective material		
Lahiri et al., 2016 (46) RCT	102 term babies	Curtains during phototherapy vs No curtains during phototherapy.	Mean TSB Mean duration of phototherapy Follow up 4, 12, and 24 hours	Improved with intervention Mean TSB (mg/dl ±SD) Curtains 4 hours: 17.42±1.04 12 hours:14.52±1.05 24 hours: 11.33±1.11 No curtains 4 hours: 18.02±1.13 12 hours: 17.6±1.09 24 hours: 16.65±1.11 Mean duration of phototherapy (hours ±SD) Curtains: 28.87±4.11 No curtains: 51.14±18.62, p<0.01

1.5 Factors that influence the risk of kernicterus

Recommendations in this section of the guideline

1.5.1 Identify babies with hyperbilirubinaemia as being at increased risk of developing kernicterus if they have any of the following:

- a serum bilirubin level greater than 340 micromol/litre in babies with a gestational age of 37 weeks or more
- a rapidly rising bilirubin level of greater than 8.5 micromol/litre per hour
- clinical features of acute bilirubin encephalopathy. [2010]

Surveillance proposal

This recommendation should not be updated.

Factors that influence the risk of kernicterus

Previous surveillance summary

No studies relevant to this section of the guideline were identified in the 2012 evidence update. One RCT (47) was identified in 2014 surveillance review; this indicated that anaesthesia during caesarean section may be a risk factor for hyperbilirubinaemia.

2019 surveillance summary

No relevant evidence was identified.

Intelligence gathering

There was no new intelligence from the 2019 surveillance process of relevance to this section of the guideline.

Impact statement

The original guideline did not consider delivery type to be a consistent factor associated with an increased risk of hyperbilirubinaemia and we did not find any new evidence in the current surveillance review concerning this, therefore no impact on current recommendations is anticipated.

New evidence is unlikely to change guideline recommendations.

1.6 Formal assessment for underlying disease

Recommendations in this section of the guideline

1.6.1 In addition to a full clinical examination by a suitably trained healthcare professional, carry out all of the following tests in babies with significant hyperbilirubinaemia as part of an assessment for underlying disease (see threshold table and the treatment threshold graphs):

- serum bilirubin (for baseline level to assess response to treatment)
- blood packed cell volume
- blood group (mother and baby)
- DAT (Coombs' test). Interpret the result taking account of the strength of reaction, and whether mother received prophylactic anti-D immunoglobulin during pregnancy. [2010]

1.6.2 When assessing the baby for underlying disease, consider whether the following tests are clinically indicated:

- full blood count and examination of blood film
- blood glucose-6-phosphate dehydrogenase levels, taking account of ethnic origin
- microbiological cultures of blood, urine and/or cerebrospinal fluid (if infection is suspected). [2010]

Surveillance proposal

These recommendations should not be updated.

1.7 Care of babies with prolonged jaundice

Recommendations in this section of the guideline

1.7.1 In babies with a gestational age of 37 weeks or more with jaundice lasting more than 14 days, and in babies with a gestational age of less than 37 weeks and jaundice lasting more than 21 days:

- look for pale chalky stools and/or dark urine that stains the nappy
- measure the conjugated bilirubin
- carry out a full blood count
- carry out a blood group determination (mother and baby) and DAT (Coombs' test). Interpret the result taking account of the strength of reaction, and whether mother received prophylactic anti-D immunoglobulin during pregnancy
- carry out a urine culture
- ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed. [2010]

1.7.2 Follow expert advice about care for babies with a conjugated bilirubin level greater than 25 micromol/litre because this may indicate serious liver disease. [2010]

Surveillance proposal

These recommendations should not be updated.

Care of babies with prolonged jaundice

Previous surveillance summary

No relevant evidence was identified.

2019 surveillance summary

No relevant evidence was identified.

Intelligence gathering

A topic expert suggested that the guideline should consider a specific recommendation to perform thyroid function testing (TSH and FT4) in prolonged jaundice so that a rare cause of prolonged jaundice, can be ruled out. The topic expert stated that with using metabolic screening alone, some babies with congenital hypothyroidism will be missed. A second topic expert agreed that this is a concern. This concern reflects the 2014 PHE Laboratory Guide to Newborn Screening in the UK for congenital Hypothyroidism which states: 'There are also cases reported of babies with low T4 and normal TSH levels in the initial newborn blood spot screening specimen, who later display an abnormally elevated TSH and are subsequently diagnosed with congenital hypothyroidism. Half of these babies with this abnormal profile were preterm. These babies may not be detected by newborn blood spot screening using TSH only (see Mandel et al., 2000).'

No evidence was identified but an additional external expert submitted a comment on the threshold table, asking whether the threshold for management of hyperbilirubinaemia remains the same beyond the 14 days and what is the threshold if the jaundice recurs.

Impact statement

The importance of hypothyroidism as a cause of neonatal jaundice was specified in the guideline and currently recommends that in babies with prolonged jaundice lasting more than 21 days, health care professionals should ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed (rec 1.7.1). Two topic experts advised that guideline should also consider recommending thyroid functioning tests (TSH and FT4) in prolonged jaundice. Although no new relevant evidence was identified, recommendation 1.7.1 will be refreshed to address this issue.

New evidence is unlikely to change guideline recommendations.

1.8 Intravenous immunoglobulin

Recommendations in this section of the guideline

1.8.1 Use intravenous immunoglobulin (IVIG) (500 mg/kg over 4 hours) as an adjunct to continuous intensified phototherapy in cases of rhesus haemolytic disease or ABO haemolytic disease when the serum bilirubin continues to rise by more than 8.5 micromol/litre per hour. [2010].

1.8.2 Offer parents or carers information on IVIG including:

- why IVIG is being considered
- why IVIG may be needed to treat significant hyperbilirubinaemia
- the possible adverse effects of IVIG
- when it will be possible for parents or carers to see and hold the baby. [2010]

Surveillance proposal

These recommendations should not be updated.

Previous surveillance summary

In the 2014 surveillance review the result from 1 systematic review (48) of 14 studies (n=942 infants) on intravenous immunoglobin for treatment of haemolytic disease in neonates indicated that intravenous immunoglobin reduced the need for exchange transfusion.

2019 surveillance summary

No relevant evidence was identified.

Intelligence gathering

There was no new intelligence from the 2019 surveillance process of relevance to this section of the guideline.

Impact statement

In a previous surveillance review, evidence from 1 systematic review was consistent with the current guideline recommendation to offer intravenous immunoglobulin as an adjunct to continuous multiple phototherapy in cases of rhesus haemolytic disease. But no further evidence was identified in the current surveillance review and no impact on current recommendations is anticipated.

New evidence is unlikely to change guideline recommendations.

1.9 Exchange transfusion

Recommendations in this section of the guideline

1.9.1 Offer parents or carers information on exchange transfusion including:

- the fact that exchange transfusion requires that the baby be admitted to an intensive care bed
- why an exchange transfusion is being considered
- why an exchange transfusion may be needed to treat significant hyperbilirubinaemia
- the possible adverse effects of exchange transfusions
- when it will be possible for parents or carers to see and hold the baby after the exchange transfusion. [2010]

1.9.2 Use a double-volume exchange transfusion to treat babies:

- whose serum bilirubin level indicates its necessity (see the threshold table and the treatment threshold graphs) and/or
- with clinical features and signs of acute bilirubin encephalopathy. [2010]

1.9.3 During exchange transfusion do not:

- stop continuous intensified phototherapy
- perform a single-volume exchange
- use albumin priming
- routinely administer intravenous calcium. [2010]

1.9.4 Following exchange transfusion:

- maintain continuous intensified phototherapy
- measure serum bilirubin level within 2 hours and manage according to the threshold table and the treatment threshold graphs. [2010]

Surveillance proposal

These recommendations should not be updated.

Albumin transfusion

Previous surveillance summary

In the 2012 surveillance review, 1 small RCT (49) with 50 term babies indicated that when compared with control group, albumin infusion shortened the duration of phototherapy and decreased TSB at 6 hours and at 12 hours. In the 2014 surveillance review, a small RCT (50) with 42 low birthweight babies (1000g-2499g) indicated that pre-exchange 5% albumin transfusion significantly reduced the post-exchange unconjugated bilirubin levels at 6 hours and 12 hours, reduced the requirement for repeat exchange transfusions, reduced the duration of phototherapy required and mean duration of hospital stay.

2019 surveillance summary

Evidence from 1 RCT (51) indicated that priming with 1g/kg of 20% albumin before exchange transfusion (n=50 term and late preterm neonates with hyperbilirubinaemia), was not superior to infusion of 0.9% saline in reducing post-exchange transfusion phototherapy duration or lowering the amount of bilirubin mass removed.

Intelligence gathering

There was no new intelligence from the 2019 surveillance process of relevance to this section of the guideline.

Impact statement

NICE Guideline CG98 recommends against albumin priming before exchange transfusion. Findings from 2 small RCTs in 2012 evidence update and 2014 surveillance review provided evidence that albumin infusion may be potentially beneficial to neonates with hyperbilirubinaemia. In contrast, evidence from 1 RCT in the current review indicated that albumin before exchange transfusion was not superior to infusion of saline in removing the amount of bilirubin mass and supports the current recommendation. The current evidence identified is insufficient to change current guideline recommendations. This area will be revisited at subsequent surveillance review time points. New evidence is unlikely to change guideline recommendations.

1.10 Other therapies

Recommendations in this section of the guideline

1.10.1 Do not use any of the following to treat hyperbilirubinaemia:

- agar
- albumin

- barbiturates
- charcoal
- cholestyramine
- clofibrate
- D-penicillamine
- glycerin
- manna
- metalloporphyrins
- riboflavin
- traditional Chinese medicine
- acupuncture
- homeopathy. [2010]

Surveillance proposal

These recommendations should not be updated.

Other therapies

Previous surveillance summary

Laxatives

A systematic review of 3 RCTs (52) found no effect on serum bilirubin and the need for phototherapy by the induction of meconium evacuation on neonatal hyperbilirubinaemia in term infants.

Clofibrate

Two systematic reviews (53)(54) and 3 RCTs (55–57) found that a single oral administration of clofibrate adjunct to phototherapy was associated with decreased need of phototherapy, shortened duration of phototherapy and reduced mean TSB in neonates with hyperbilirubinaemia.

Prebiotic/probiotics

Two RCTs (58,59) investigated the efficacy of using probiotics supplementation in hyperbilirubinaemia but provided conflicting results on decreasing bilirubin levels or duration of phototherapy.

Massage

Two RCTs (60,61) have examined the effect of massage as an adjunctive treatment to phototherapy in term neonates with hyperbilirubinaemia compared with no massage. Both RCTs indicated that massage can reduce bilirubin levels (TSB or mean bilirubin) either during early phototherapy (first 24 hours) or over the initial 5-day period.

2019 surveillance summary

Laxatives (see Table 3)

Three RCTs (62–64) evaluated the effect of laxatives in addition to phototherapy in improving hyperbilirubinaemia. In 2 RCTs (62,64) phototherapy plus Billinaster oral drops (manna) and significantly decreased the total serum bilirubin level when compared with phototherapy alone. In 1 RCT phototherapy plus glycerin suppositories no different from phototherapy alone in reducing total serum bilirubin but did reduce the total hours of phototherapy (72±49 hours in intervention versus 61±53 hours in phototherapy alone) (63).

Probiotics (see Table 4)

Four RCTs and 1 systematic review evaluated adjunctive effect of probiotics on hyperbilirubinaemia treatment. Evidence from 2 RCTs (67,68) and 1 systematic review (69) indicated that combination of probiotics and phototherapy decreased the serum bilirubin levels in neonates with hyperbilirubinaemia when compared with the phototherapy alone. However, evidence from 2 other RCTs (70,71) showed that probiotic in addition to phototherapy had no significant effect on reducing total serum bilirubin level.

Massage plus phototherapy (see Table 5)

Six RCTs (72–77) and 2 systematic reviews (78,79) examined the effect of massage as an adjunctive treatment to phototherapy in term and preterm neonates with hyperbilirubinaemia compared with no massage. Four RCTs (75–77,80) and 2 systematic reviews (78,79) indicated that massage can reduce bilirubin levels (TSB or mean bilirubin) during phototherapy or over the initial 5-day period. However, in 2 of these RCTs (75,80), massage had no effect on reduction of TSB during the early period of phototherapy (first 24 hours). In the other 2 RCTs (72,74), massage therapy had no effect on the reduction of bilirubin in neonates under phototherapy (74).

Zinc supplementation (see Table 6)

Four RCTs (81–84) indicated that oral zinc sulphate 10 mg/day, is not effective in the management of idiopathic neonatal hyperbilirubinaemia. In one RCT, administration of oral zinc sulphate to low birth weight infants significantly reduced TSB level at 24 hours after treatment but there was no difference in its effect (compared with control) at 48 and 72 hours after treatment. The 2 other RCTs included term and preterm babies (≥35 weeks gestation) and indicated that administration of zinc sulphate had not differently affected TSB and duration of phototherapy when compared with a placebo control.

Chinese medicine (see Table 7)

Two systematic reviews (65,66) indicated that Yinzhihuang oral liquid combined with phototherapy may be effective in reducing serum bilirubin in neonates with hyperbilirubinaemia.

Intelligence gathering

There was no new intelligence from the 2019 surveillance process of relevance to this section of the guideline.

Impact statement

Laxatives

The guideline recommends that glycerin and manna should not be used. Three RCTs indicated that phototherapy plus Billinaster oral drops (manna) drop decreased the TSB but glycerin suppositories had limited effectiveness. The limited evidence is insufficient to change recommendations.

New evidence is unlikely to change guideline recommendations.

Clofibrate

The guideline recommends that clofibrate should not be used. No new evidence was identified in this surveillance review and limited evidence from previous reviews might not be generalizable to the UK so there is unlikely to be an impact on the recommendations.

New evidence is unlikely to change guideline recommendations.

Chinese medicine

This guideline recommends that Chinese medicine should not be used. No relevant evidence was identified in previous surveillance reviews. Evidence from 2 systematic reviews in the current review indicated that Yinzhihuang oral liquid combined with phototherapy may be effective in reducing serum bilirubin but studies were conducted in China which may limit generalisability and authors of one review expressed concerns about poor methodological quality of the included studies.

New evidence is unlikely to change guideline recommendations.

Probiotics

The guideline contains no recommendations around the use of probiotics. There is conflicting evidence on the effectiveness of probiotics in treatment of hyperbilirubinemia therefore no impact on the guideline at this time.

New evidence is unlikely to change guideline recommendations.

Massage plus phototherapy

The guideline contains no recommendations around the use of massage. Evidence from 2 small RCTs from previous surveillance reviews and 8 studies (6 RCTs, 2 systematic reviews) from current review on massage plus phototherapy was conflicting. Four studies indicated that massage may be beneficial to babies receiving phototherapy while 2 RCTs indicated that massage had no effect on reduction of TSB at early period of phototherapy and 2 other RCTs indicated that therapy had no effect on reduction of TSB at any time point. Therefore, the evidence base is inconsistent and shows no clear benefit of massage and is insufficient to impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Zinc supplementation

The guideline does not make recommendations around the use of zinc supplementation. There is conflicting evidence on the effectiveness of oral zinc sulphate on management of hyperbilirubinaemia which is insufficient to impact the guideline.

New evidence is unlikely to change guideline recommendations.

Table 3 Other therapies: laxatives (data extracted from abstracts)

(RCT = randomised controlled trial, SR = systematic review, TSB = total serum bilirubin)

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
Laxatives, suppositories				
Fallah et al., 2014 (62) RCT	90 term babies (TPB level of 15-20mg/dl)	Group B: Phototherapy plus Billinaster drop (5 drop/kg Billinaster every 8 hours) vs Group G: Phototherapy plus glycerin suppository (half of glycerine suppository every 12 hours) Vs Phototherapy alone	TSB Follow up 12, 24 and 48 hours	Improved with intervention TSB <14 mg/dl, 48 hours Group B: N=22 (73.3%) Group G: N=26 (86.7%) Control: N=15 (50%) TSB 12 hours (mg/dl, mean ±SD) Group B: 15.97±1.96 Group G: 14.38±2.27 Control: 16.67±1.77 TSB 24 hours (mg/dl, mean ±SD) Group B: 12.57±2.05 Group G: 12.56 ±1.59 Control: 14.36±2.26 TSB 48 hours (mg/dl, mean ±SD) Group B: 9.96±2.95 Group G: 9.34±1.6 Control: 12.27±2.4
Butler-O'Hara et al., 2017 (63)	79 babies	Glycerin suppositories (every	Total hours of phototherapy	No significant difference between intervention and comparator

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
RCT	30 weeks to 34 weeks+6 days gestation	8 hours while under phototherapy) vs Sham treatment		Total hours of phototherapy Suppositories: 72±49 hours Sham: 61±53 hours No differences in peak bilirubin levels, rate of bilirubin decline, or repeat episodes of phototherapy.
Monsef et al., 2019 (64) RCT	150 term babies	Bilineaster drop (purgative manna) plus phototherapy (5 drops per kg of body weight, 3 times a day) vs phototherapy alone	TSB reduction Follow up 48 and 72 hours	Improved with intervention TSB reduction 48 and 72 hours TSB significantly reduced in the intervention group compared with phototherapy alone (p<0.05)

Table 4 Other therapies: probiotics (data extracted from abstracts)

(RCT = randomised controlled trial, SR = systematic review, TSB = total serum bilirubin)

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
Probiotics				
Chen et al., 2017 (69) SR, 13 RCTs	1067 babies	Phototherapy plus probiotics supplementation vs Phototherapy alone	TSB Follow up 3, 5 and 7 days	Improved with intervention TSB at 3 days Mean Difference −18.05 (95% CI 25.51 to −10.58), p<0.00001 TSB at 5 days, Mean Difference −23.49 (95% CI −32.80 to −14.18), p<0.00001, TSB at 7 days Mean Difference −33.01 (95% CI −37.31 to −28.70), p<0.00001
Armanian et al., 2016 (67) RCT	50 babies	Probiotics:Mixture short-chain galacto oligosacarids/long-chain fructo-oligosacarids for 1 week vs Placebo (distilled water)	TSB	Improved with intervention Decrease in TSB level (mg/dl) Probiotic −1.3±1.8, placebo −0.1±3.3 Peak bilirubin level mg/dl Probiotic 8.3±1.7, placebo 10.1±2.2, p=0.003
Suganthi et al., 2016 (68) RCT	181 babies	Phototherapy plus probiotic (Saccharomyces boulardii) for 2 days vs Phototherapy plus placebo	TSB Follow up 3 days	No sig diff between intervention and comparator Mean TSB day 3 Probiotic: 5 mg% Placebo: 6.5 mg%
Torkaman et al., 2017 (71)	92 term babies	Probiotic plus phototherapy. Once a	TSB Follow up 3 days	No sig diff between intervention and comparator

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
RCT		day (half of a capsule of Prokid probiotic) vs Phototherapy plus placebo capsule		Mean TSB level (mg/dl ±SD) Probiotic 17.00±2.49 Placebo 16.42±3.53, p=0.37
Serce et al., 2015 (70) RCT	119 babies ≥35 weeks gestation	S. boulardii 125 mg every 12 hours plus phototherapy vs Placebo plus phototherapy	TSB Follow up 24, 48 and 96 hours	No sig diff between intervention and comparator Serum bilirubin level during phototherapy 24 hours: Probiotic 14.1 (95% CI 12.8 to 15.7) Placebo 13.5 (95% CI 12.4 to 14.9) p=0.085 48 hours: Probiotic; 14.1 (95%CI 12-15.3) Placebo 13.4 (95% CI 12.4-14.5) p=0.41 72 hours Probiotic 13.9 (95% CI 12.2 to 15.6) Placebo 13.5 (95% CI 12.5 to 14.5) p=0.41 96 hours Probiotic 14.7 (95% CI 11.4-15.5) Placebo 13.4 (95% CI 10.7-14.1) p=0.24

Table 5 Other therapies: massage (data extracted from abstracts)

(RCT = randomised controlled trial, SR = systematic review, TSB = total serum bilirubin)

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
Massage plus phototherapy				
Rahani et al. 2017 (72) RCT	68 babies	Manna drop (Bilineaster) plus phototherapy (n=24) vs Massage group plus phototherapy(n=23) vs Phototherapy only (n=21)	Mean reduction rate of bilirubin Follow up 24, 48 and 72 hours	No sig diff between intervention and comparator Mean reduction rate of bilirubin/hour 24 hours Massage 0.23±0.17 Bilineaster drop group 0.25±0.18 Control 0.27±0.19 42 hours Bilineaster drop 0.26±0.22 Control 0.4±0.26, Massage 0.22±-0.18 72 hours Massage, 0.9±0.13 Bilineaster 0.7±0.1 Control 0.19±0.17
Ahmadipour et al., 2019 (80) RCT	83 full term babies	Massage therapy plus phototherapy for 4 days vs	Mean bilirubin level Follow up 1 and 4 days	Improved with intervention Mean bilirubin level (mg/dl ±SD) Day 1 Massage plus phototherapy 13.4 ± 0.7

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
		Phototherapy only		Control 14.4 ± 1.5 Day 4 Massage plus phototherapy 7.4 ± 0.56 Phototherapy only 9.0 ± 2.3, p < 0.05
Karbandi et al., 2016 (74) RCT	60 premature in intensive care unit	Massage therapy plus phototherapy for 5 days vs Phototherapy only	Change in TSB Follow up 5 days	No sign diff between intervention and comparator Change in TSB (mg/dl) Massage plus phototherapy=9.7 Control=8.1
Babaei & Vakiliamini 2018 (75) RCT	102 full term	Massage therapy plus phototherapy for 5 days vs Phototherapy only	Mean decease at bilirubin level Follow up 1 and 4 days	Improved with intervention Daily mean decease bilirubin level (mg/dl) Day 1 Massage plus phototherapy 1.14±1.08 Control 1.10±0.865, p=0.336 Day 4 Massage plus phototherapy 0.805±4.08 Control 0.660±2.731, p < 0.005
Dag, & Yayan 2019 (76) RCT	140 babies, 34 weeks gestation in intensive care	Massage plus phototherapy (n=35) vs Tub bath plus phototherapy (n=35) vs Sponge bath plus phototherapy (n=35) vs Phototherapy only (n=35)	Change in bilirubin levels Follow up 12 hours	Improved with intervention Mean bilirubin levels (change from baseline): Massage: 3.82±1.78 Sponge bath: 4.42±1.30 Tub bath: 3.63±1.50 Control:7.62±2.54
Gozen et al., 2019 (77) RCT	44 babies	Massage plus phototherapy vs Phototherapy only	Increase of serum bilirubin level Follow up 48 hours	Improved with intervention Increase of bilirubin levels from baseline to 48 hours (mg/dl ±SD) Massage: 1.96±1.69 Control: 2.80±2.30, p=0.048
Zhang et al., 2019 (78) SR, 6 studies	357 babies	Massage therapy vs No massage therapy	Serum bilirubin level Transcutaneous bilirubin level Follow up 2 and 4 days	2 days Serum bilirubin Mean Difference -0.82 (95% CI 2.16 to 0.52) p=0.23 Transcutaneous bilirubin Mean Difference −0.17 (95%CI −1.34 to 1.00) p=0.77 4 days Serum bilirubin Mean Difference -2.31 (95% CI −2.92 to −1.70) p<0.00001 Transcutaneous bilirubin Mean Difference −1.97 (95% CI −2.55 to −1.39) p<0.00001
Lei et al., 2018 (79) SR, 14 RCTS	1889 babies	Massage plus phototherapy	percutaneous bilirubin	Improved with intervention Percutaneous bilirubin

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
		vs Phototherapy only	Follow up 48, 72, 96 and 168 hours	48 hours Mean Difference −1.21 (95% CI −1.90 t o−0.52) p<0.05 72 hours Mean Difference −2.00 (95% CI −2.68 to −1.32) p<0.05 96 hours Mean Difference −2.00 (95% CI 2.56 to −1.44) p<0.05 168 hours Mean Difference −1.93 (95% CI −2.44, −1.43) p<0.05

Table 6 Other therapies: zinc (data extracted from abstract)

(RCT = randomised controlled trial, SR = systematic review, TSB = total serum bilirubin)

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
Zinc supplementation				
Mohammadzadeh et al 2016 (81) RCT	61 low birthweight neonates	zinc sulphate (10 mg twice per day for 5 days) vs Placebo	TSB Follow up 24 hours	Improved with intervention Baseline mean TSB level (mg/dl) Zinc: 14.73±3.22 Placebo: 14.87±2.65 Mean decline in TSB level (mg/dl) Zinc 2.13, Placebo 2.71, p=0.04
Maamouri et al 2014 (82) RCT	131 term babies	Zinc sulphate (n=57) vs Placebo (n-74)	Mean bilirubin values Follow up 3 and 7 days	No sig diff between intervention and comparator Mean bilirubin values (mg/dl ±SD) 3 days Zinc 12.9±3, Placebo 12.6±2, p=0.473 7 days Zinc 12.4±3, Placebo 12.4±, p=0.989
Hashemian et al., 2017 (83) RCT	70 term babies TSB level≤20 mg/dl	Zinc (10 mg/day, single dose) plus phototherapy and vs Placebo plus phototherapy	Mean durations of phototherapy Follow up 12, 24 and 48 hours	Improved with intervention Mean durations of phototherapy (days) Zinc 2.03±0.174 Control 2.33±-0.478, p=0.002 The mean TSB levels were significantly lower in the zinc group after 12, 24 and 48 hours (p=0.038, 0.005, 0.001, respectively).
Kumar et al., 2014 (84) RCT	80 babies, near term (≥35)	Oral zinc sulphate (10 mg/d) for 7 days vs Placebo	TSB Follow up 7 days	TSB decreased with intervention only at first 24 and 48 hours. No difference at 96 and 144 hours. TSB (mg/dl mean ±SD) 48 hours Zinc 13.9±2.5, Placebo 13.4±1.9 Mean Difference 0.566; 95% CI −0.535 to 1.668, p=0.038 96 hours Zinc 13.1±2.7, Placebo 12.8±2.3

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
				Mean Difference 0.234; 95% CI -1.011 to 1.479, p =0.708) 144 hours Zinc 8.0±2.0, Placebo 8.6±1.2 Mean Difference −0.569, 95% CI −1.382 to 0.242, p=0.166

Table 7 Other therapies: Chinese medicine (data extracted from abstracts)

(RCT = randomised controlled trial, SR = systematic review, TSB = total serum bilirubin)

Authors (Year) Study type	Population	Intervention and Comparator	Outcome and Follow up	Result
Yinzhihuang oral liquid				
Wu, Ruo-Han et al., 2018 (65) SR 17 studies	2561 babies	Yinzhihuang oral liquid plus phototherapy vs Phototherapy alone	TSB	Improved with intervention TSB (micromol/litre) Mean Difference 50.25 (95% CI −64.01 to −36.50) (11 trials)
Zeng, et al., 2017(66) SR, studies not reported	Not reported	Yinzhihuang oral liquid plus phototherapy vs Phototherapy only	TSB Follow up 3 and 6 days	Improved with intervention TSB Standardised Mean Difference 95%CI day 3 (5 studies): −1.63 (95% CI −2.20 to −1.06) day 5 (5 studies): −5.00 (95% CI −7.88 to −2.12)

Areas not currently covered in the guideline

In surveillance, evidence was identified for an area not covered by the guideline.

Delayed cord clamping

Two RCTs (85,86) indicated that delayed cord clamping (2 to 5 minutes) may improve the haematocrit value at birth. However, this delay significantly increased duration of phototherapy significantly in one study (85) and had no effect on bilirubin level in the other study. However, NICE guideline CG190 Intrapartum care for healthy women and babies, makes recommendations for delayed cord clamping in active management of the third stage of labour, setting a time limit of no earlier than 1 minute and no later than 5 minutes after birth. Guideline CG190 is currently being updated and will include further review of the evidence for delayed cord clamping.

Research recommendations

What are the factors that underlie the association between breastfeeding and jaundice?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the comparative effectiveness and cost-effectiveness of universal pre-discharge transcutaneous bilirubin screening alone or combined with a risk assessment in reducing jaundice-related neonatal morbidity and hospital readmission?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the comparative accuracy of the Minolta JM-103 and the BiliChek when compared to serum bilirubin levels in all babies?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

How frequently and for how long can phototherapy be interrupted without adversely effecting clinical outcomes?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

National registries are needed of cases of significant hyperbilirubinaemia, kernicterus and exchange transfusions.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the experience and acceptability of phototherapy from the perspective of parents and healthcare professionals?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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