NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive

Clinical guideline

Neonatal jaundice (CG98)**:** Neonatal jaundice

Publication date

May 2010

Surveillance report for GE

August 2014

Key findings

			Potential impact on guidance	
			Yes	**No**
Evidence from Evidence Update			✓	
Evidence identified from literature search			✓	
Feedback from Guideline Development Group Chair			✓	
Anti-discrimination and equalities considerations				✓
Feedback from Triage Panel meeting			✓	
No update	CGUT update	Standard update	Transfer to static list	Change review cycle
	✓			

Surveillance recommendation

GE is asked to consider the proposal to update the following clinical questions in the guideline using the Standing Committee for Updates via the Clinical Guidelines Update Team (CGUT):

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

GE is asked to note that this 'yes to update' proposal will not be consulted on.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG98: Neonatal Jaundice

Recommendation for Guidance Executive

Background information

Guideline issue date: May 2010
4 year review: 2014

NCC: Women's and Children's Health

Triage Panel recommendation

1. Through the 4-year surveillance review of CG98 new evidence (section 2) which may potentially impact guideline recommendations was identified in the following two clinical areas which were considered in turn by the Triage Panel:

a. Management
   - *What is the best modality of giving phototherapy (clinical and cost-effectiveness)?*
   - *What is the correct procedure of giving phototherapy?*

The Triage Panel indicated that the recommendations concerning the modality of phototherapy are out of date in terms of current clinical practice as LEDs are already the dominant form of phototherapy. It was also noted that the guideline currently has a do not use recommendation for fibre optic phototherapy (which is a type of LED). The Triage Panel indicated that these questions should be

updated in the light of current practice. The Triage Panel considered that there were limited health economic implications of updating the recommendation and as such a full health economic model would not be required.

Decision - NICE to update these 2 clinical question using Standing Committee for Updates via the Clinical Guidelines Update Team.

b. Albumin transfusion

What are the other ways of treating hyperbilirubinaemia? Are they effective?

a) Metalloporphyrins

b) Gammaglobulins

c) Drugs (phenobarbitol, clofibrate, cholestyramine)

d) Agar, charcoal

e) Suppositories, other rectal modes of treatment

f) Complementary/alternative medicines (Chinese herbal remedies such as Yin-chen)

The Triage Panel indicated that they felt the clinical efficacy evidence for albumin transfusion is weak and based on small studies. With regards to the use of clofibrate the panel concluded that although the evidence was growing, currently this was not sufficient to change clinical practice in the UK. As such, the group felt it was premature to initiate an update with regards to this aspect of the guideline and that deferring the update to the next surveillance review, to enable consideration of additional evidence in this area, would be more appropriate.

Decision - NICE to defer update of this clinical question.

c. Recognition

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?

The Triage Panel indicated that the use of transcutaneous bilirubinometers (TcB) had been an issue with regards to implementation but their use saves time in clinical practice and avoids the cost associated with blood samples. The panel was aware of a growing evidence base in this area and discussed what specific aspects relating to the use of TcB would enhance clinical practice. The Triage panel felt

that a specific question on the lower age threshold for these devices would be appropriate and could potentially enhance clinical practice. It was noted that currently it is pre term babies between 35 and 37 weeks that are most likely to not be recognised and diagnosed for neonatal jaundice.

Decision - NICE to update this clinical question using Standing Committee for Updates via the Clinical Guidelines Update Team.

Current four year surveillance review

2. The Evidence Update on CG98: Neonatal jaundice (published March 2012) was used as a source of evidence for this surveillance review and considered new evidence since the guideline was published. New evidence that would impact on the guideline recommendations was identified in 1 area (albumin infusion) in the Evidence Update. An additional literature search for systematic reviews and RCTs was carried out between November 2011 (the end of the search period for the Evidence Update) and November 2013 and relevant abstracts were assessed. Clinical feedback on the guideline was obtained from 4 members of the GDG through a questionnaire and 3 felt that the guideline did not require an update at present. One GDG member felt the guideline requires updating as they wish NICE to provide new evidence on the problems with visual assessment of babies with neonatal jaundice.
3. New evidence that may impact on recommendations was identified relating to the following areas within the guideline:

Clinical area 1: Management		
Q98-05-ii Phototherapy- Recommendations 1.4.9-1.4.12 **ii) What is the best modality of giving phototherapy (clinical and cost-effectiveness)?** **a) Conventional phototherapy (single, double or multiple phototherapy)** **b) Sunlight** **c) Fibreoptic phototherapy (biliblankets, bilibeds and other products)** **Research Recommendation**: **What is the clinical and cost-effectiveness of: LED (light emitting diode) phototherapy compared to conventional phototherapy in term and preterm babies with significant hyperbilirubinaemia?**		
Evidence summary	**GDG/clinical perspective**	**Impact**

<u>Evidence identified from Evidence Update</u> 3 RCTS were identified that examined various types of phototherapy in neonatal infants (gestational age ≥ 35-37 weeks) with hyperbilirubinaemia. One indicated that there was no difference in LED versus compact fluorescent tube therapy on all outcomes [1]. The second found no difference in total serum bilirubin (TSB) after 8 hours, 16, and 24 hours, mean length of hospital stay or in rate of decline in TSB between double or triple light sources[2]. The third RCT indicated that there was no difference in mean decrease in bilirubin level after 24 hours between single or double phototherapy[3]. <u>Evidence identified from literature search</u> Six studies (2 systematic reviews and 4 RCTs) were identified that have investigated the effectiveness of LEDs phototherapy as compared to conventional phototherapy. A Cochrane systematic review which identified 6 RCTs evaluated the effect of LEDs phototherapy as compared to conventional phototherapy (compact fluorescent tubes, halogen spotlight) in decreasing TSB levels and duration of treatment in neonates (term and pre-term) with unconjugated hyperbilirubinaemia[4]. The duration of phototherapy (630 neonates), rate of decline of TSB (511 neonates), treatment failure and adverse events were comparable in LED and conventional phototherapy groups. Likewise a systematic review which included 511 neonates in the meta-analysis found that LED and other phototherapy devices appeared to be equally effective in reducing TSB in term or late preterm neonate[5]. Two RCTs also found no difference in the outcomes of duration of phototherapy, bilirubin levels (rate of decline or maximal level) or the frequency of skin eruptions for pre-term neonates undergoing phototherapy for hyperbilirubinemia when comparing LED with conventional phototherapy devices[6, 7] . Two RCTs comparing phototherapy for neonates with hyperbilirubinemia	Clinical feedback indicated that clinicians feel that LED phototherapy in practice is more effective method than the older light source types. It was noted that during development of the guideline however there was limited evidence available to be able to recommend this option. The use of multiple light therapy may also need to be reconsidered if single source LED lights are more effective.	The new evidence suggests that LED phototherapy is efficacious in reducing levels of TSB at rates that are similar to phototherapy with conventional (compact fluorescent lamp or halogen) light sources. LED phototherapy has potentially less frequent side effects, less energy consumption, longer life span of equipment, and lower costs and may therefore potentially be a more cost effective approach than current conventional phototherapy. The guideline indicated that there was existing evidence that there is no difference between LED and conventional phototherapy. However it was noted that LED phototherapy maybe easier to use in clinical setting by reducing the need for additional fluids. Hence the research recommendation requested RCTs with the outcome of effectiveness in terms of the mean decrease in bilirubin levels and the mean duration of phototherapy. In addition extra outcomes were requested in terms of adverse effects, parental bonding and parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. It is unclear from only an assessment of the abstracts if the 'extra' outcomes have also been reported. Due to word limitations abstracts tend to only report on the primary outcomes. There may now be sufficient evidence to determine if LED phototherapy should be specifically recommended Multiple phototherapy is currently recommended for infants who do not respond to single

by 'special blue fluorescent' or by LED were identified[8,9]. One RCT in otherwise healthy infants aged between 1 -5 days and the other in preterm neonates (gestational age of 33.5 + 1.2 weeks) produced conflicting results. In full term neonates the 6 special blue fluorescent tubes phototherapy resulted in an increased median rate of plasma bilirubin decline compared to LEDs however the duration of phototherapy was comparable between the types of phototherapy. Whereas in the preterm neonates there was no difference in TBS rate of reduction, treatment duration, treatment failure rates in the LED and fluorescent groups. However, there were more cases of mild hyperthermia in the fluorescent group.		phototherapy, and in those with very high or rapidly rising TSB. The new evidence provides limited evidence that three light sources are not better than two, which is unlikely to affect NICE CG98.
Q98-05-iv What is the correct procedure of giving phototherapy?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence identified from Evidence Update</u> A RCT of infants (gestational age ≥ 33 weeks) receiving phototherapy, to compare supine positioning with alternation between supine and prone positioning every 3 hours[10]. No significant difference was seen in reduction in TSB from baseline at 12 hours or at 24 hours. A RCT of phototherapy with or without white slings (curtains) hung from the sides of phototherapy equipment in otherwise healthy infants (gestational age ≥ 37 weeks)[11]. The duration of phototherapy did not differ between groups and there was no difference in TSB levels were seen between groups (8 hour TSB, TSB at end of phototherapy, rate of TSB fall, absolute TSB fall, or percentage TSB fall). <u>Evidence identified from literature search</u> A RCT to determine a "saturation point" (i.e., an irradiation level above which there is no further decrease in TSB) in 151 infants (gestational age > 33 weeks) with uncomplicated hyperbilirubinaemia investigated 4 distances from the LED phototherapy device to the mattress[12]. A linear relation was seen between light irradiance (20 to 55 muW/cm2/nm and	No clinical feedback provided	There are currently no specific recommendations relating to light intensity and distance of phototherapy device from the infant receiving phototherapy in the guideline. The new evidence that utilises LED phototherapy may impact guidance if this type of phototherapy is additionally recommended in any update of the guideline. The GDG indicated that whilst the use of white curtains as an adjunct to phototherapy can aid serum bilirubin reduction it was not recommended as their use compromises the ability to observe the baby. Hence the new evidence identified is unlikely to impact on the current recommendations. In the UK supine positioning only is advised to help to prevent sudden infant death syndrome, which is in line with recommendations in NICE CG98. The results of 2 studies suggest no clinical effect of alternating position in phototherapy, so

TSB reduction at 24 hours with no evidence of a saturation point. A second RCT which compared the efficacy of phototherapy between conventional blue light tubes (30 muW/cm2/nm) and LED equipment (30 muW/cm2/nm or 40 muW/ cm2/nm) in neonates (165 neonates gestational age >35 weeks) with non-haemolytic hyperbilirubinaemia[13] . The LED phototherapy at 40muW/cm2/nm significantly reduced phototherapy duration. A RCT showed that single phototherapy with reflecting curtains was as effective as double phototherapy in term neonates with hyperbilirubinaemia at reducing TSB after 4 hours and 10 hours of phototherapy and on reducing the duration of phototherapy[14]. Likewise a RCT which examined the effect of white plastic cover around the phototherapy unit on hyperbilirubinaemia in full term neonates indicated that TBS declined significantly more if the phototherapy unit was covered compared to non-covered during the first 48 hours of treatment and resulted in a reduced duration of jaundice and hospitalization for the neonates[15]. A RCT examining whether changing the position of the infant from supine or alternating between supine and prone found no effect in management of hyperbilirubinaemia with phototherapy in terms of duration of therapy of rate of fall of bilirubin in late preterm and term neonates[16].		this evidence is unlikely to affect NICE CG98.
Q98-08 What are the other ways of treating hyperbilirubinaemia? Are they effective? Recommendation 1.10 **a) Metalloporphyrins** **b) Gammaglobulins** **c) Drugs (phenobarbitol, clofibrate, cholestyramine)** **d) Agar, charcoal** **e) Suppositories, other rectal modes of treatment** **f) Complementary/alternative medicines (Chinese herbal remedies such as Yin-chen)** **Research recommendation: What is the effectiveness, cost-effectiveness and safety of clofibrate alongside phototherapy versus phototherapy alone for non-haemolytic significant hyperbilirubinaemia?**		

Evidence summary	GDG/clinical perspective	Impact
<u>Evidence identified from Evidence Update</u> An RCT evaluated albumin infusion given before exchange transfusion in 50 babies (gestational age > 37 weeks) with non-haemolytic hyperbilirubinaemia who had not responded to 'intensive' phototherapy was identified[17]. TSB was significantly lower in the albumin group compared with the control group at both 6 hours and at 12 hours. Duration of phototherapy was significantly shorter in the albumin group. No infant in the albumin group needed a second exchange transfusion but four infants in the control group did. This study of 50 infants is small, but exchange transfusions for severe hyperbilirubinaemia in otherwise healthy near-term or term babies are rare (around 25 cases per year in the UK). <u>Evidence identified from literature search</u> **Albumin transfusion**. A RCT which evaluated the role of 5% albumin infusion before exchange transfusion to reducing post-exchange unconjugated serum bilirubin levels in 42 low birth weight (1000g-2499g>=32 weeks gestational age) neonates with intensive phototherapy failure was identified[18]. 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. No albumin transfusion-related complications were observed. **Clofibrate** Two systematic reviews were identified that evaluated the effect of clofibrate with phototherapy versus phototherapy alone for unconjugated hyperbilirubinaemia in neonates[19].The Cochrane systematic review which include 15 studies (two on preterm neonates and 13 on term neonates) indicated that for preterm neonates, clofibrate significantly lowered bilirubin levels at 48hrs, and for term neonates significantly lower bilirubin levels at both 24 and 48 hours of treatment. For both	No clinical feedback provided	Two small RCTS provide evidence that albumin infusion maybe potentially beneficial in neonates with hyperbilirubinaemia. It was noted with the EU that because the potential population for a UK study is so small, conducting a larger study would be difficult. However, the definition of 'intensive' phototherapy used in these trials may not represent the high irradiance of multiple phototherapy used in the UK, so fewer such babies in the UK might progress to needing exchange transfusion. NICE CG98 lists albumin priming before exchange transfusion as a 'do not use' intervention. However, within the guideline only one small study from 1976 addressed the use of albumin before exchange transfusion and the GDG therefore stated that albumin priming could not be recommended because of an 'absence of evidence'. The evidence from the 2 RCTs identified indicates that the recommendation could be considered for update **Clofibrate** The meta-analysis of good quality RCTs within CG98 indicated that a single dose of clofibrate led to statistically significant reductions in mean serum bilirubin levels and duration of phototherapy compared with phototherapy alone. However, as all the studies were carried out in one country the GDG felt that the results were not generalisable to UK clinical practice. Hence the current recommendation states 'do not use' clofibrate to treat hyperbilirubinaemia. The new evidence

ages of neonates the duration of phototherapy was significantly reduced by the adjunctive addition of clofibrate group to phototherapy. However, the review concluded that there was insufficient data from different countries on the use of clofibrate in combination with phototherapy for hyperbilirubinaemia to make recommendations for practice. The second systematic review which included 13 studies (867 infants) also found that a single oral administration of clofibrate was associated with decreased need of phototherapy, shortened duration of phototherapy and reduced peak TSB[20]. Two RCTs which evaluated a single dose of clofibrate as an adjunctive to phototherapy in term neonates with hyperbilirubinemia were identified[21] . The first RCT conducted on 52 new-borns with pathologic unconjugated hyperbilirubinemia found that clofibrate adjunctive therapy resulted in a reduction in serum bilirubin at 24 hours and 48 hours after treatment. The second RCT conducted on 60 healthy term neonates found that clofibrate adjunctive therapy resulted in reduced mean TSB after 12, 24, 48hrs of treatment, reduced mean of hospital stay days and duration of phototherapy[22]. In addition 1 RCT was identified that compared, the efficacy of clofibrate to phenobarbital in 60 full-term neonates with non-haemolytic jaundice as adjunctive treatment to phototherapy[23]. The mean TSB in phenobarbital group was significantly lower at 24hrs, and after 72 hours of significantly more neonates were discharged with TBS of <10 mg. **Suppositories, other rectal modes of treatment** A systematic review of 3 RCTs found no effect on serum bilirubin and the need for phototherapy by the induction of meconium evacuation on neonatal hyperbilirubinemia in term infants[24]. **Other treatments** Two RCTs that have investigated the efficacy of using prebiotic/probiotics or probiotics alone as a supplementation on the course of hyperbilirubinemia and duration of phototherapy in very low		identified indicates the same clinical benefit but is not from a diverse range of countries. **Suppositories, other rectal modes of treatment** Evidence on the use of rectal laxative is in in line with the current 'do not use' recommendation. **Other treatments** There was evidence from 2 small RCTs that massage may be beneficial for babies receiving phototherapy. The evidence base for this adjunctive approach is limited and at present may be insufficient to guide clinical practice. There is conflicting evidence on the effectiveness of pre and probiotics and it is unlikely that this evidence alone would result in recommendations for this approach at this stage.

birth weight neonates (gestational age of <=32 weeks and birth weight of <=1500 g). The RCTs gave conflicting results with a combination of prebiotics and probiotics been ineffective compared to placebo on bilirubin levels or duration of phototherapy but probiotics alone significantly reducing duration of phototherapy and feeding intolerance[25,26]. Two RCTs have examined the effect of massage as an adjunctive treatment to phototherapy in term neonates with hyperbilirubinemia compared to no massage. Both RCTS indicate that massage can reduce bilirubin levels (TBS or mean bilirubin) either during early phototherapy (first 24hr) or over the initial 5 day period. However, massage therapy did not show any benefit with regards to weight gain in the neonates[27,28].		
Clinical area 2: Recognition		
98-02 What is the best method of recognising hyperbilirubinaemia? Recommendations 1.2.14-1.2.15 **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?**		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence identified from literature search A systematic review to assess the reliability of transcutaneous bilirubin (TcB) devices in preterm infants identified 22 studies[29]. It was noted that results from transcutaneous bilirubinometers in neonates with 32 weeks' gestation were similar to the overall preterm population. A comparison of the 2 most common TcB devices, the JM103 and BiliCheck, found that these devices were comparable at the forehead site, although the JM103 device exhibited better correlation at the sternum, and overall the JM-103 device exhibited better precision than the BiliCheck. The authors concluded that the TcB devices used in the studies could reliably estimate bilirubin levels in preterm infants and could be used in clinical practice to reduce blood sampling.	GDG feedback indicated that there may be sufficient evidence available now to make recommendations relating to transcutaneous bilirubin measurements in premature neonates. However it was noted that caution needs to be applied for recommending a particular manufacturer/model due to potential costs.	Within CG98 it was noted that there were no published studies directly comparing the BiliChek and the JM-103. Hence the GDG was unable to recommend a particular device over another and recommended the use of ' transcutaneous bilirubinometer' only when a case of jaundice is suspected via visual inspection in babies with a gestational age of 35 weeks or more and postnatal age of more than 24 hours. However it was noted that measurement over the sternum was more acceptable to parents and babies and sternal measurement avoided the problem of failing to obtain a reading associated with forehead methods. The new systematic review indicates that there

		may now be sufficient evidence to allow recommendations on specific transcutaneous bilirubinometers to be made and that this approach may also be effective in younger preterm neonates.

On-going Research

b. None identified.

Anti-discrimination and equalities considerations

c. None identified

Implications for other NICE programmes

d. This guideline relates to a Quality Standard on Neonatal jaundice (QS57) published March 2014.

e. Quality statement 2 may be affected by the proposed areas for update.

Conclusion

f. Through the review of CG98 new evidence which may potentially impact guideline recommendations was identified in the following areas and discussed at the Triage Panel meeting:

- Management
  - What is the best modality of giving phototherapy (clinical and cost-effectiveness)?
  - What is the correct procedure of giving phototherapy?
  - What are the other ways of treating hyperbilirubinaemia? Are they effective?
    - Metalloporphyrins
    - Gammaglobulins

- Drugs (phenobarbitol, clofibrate, cholestyramine)
- Agar, charcoal
- Suppositories, other rectal modes of treatment
- Complementary/alternative medicines (Chinese herbal remedies such as Yin-chen)

- Recognition
    - 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?

g. For all other areas of the guideline no evidence was identified which would impact on recommendations.

Surveillance recommendation

h. GE is asked to consider the proposal to update the following clinical questions in the guideline using the Standing Committee for Updates via the Clinical Guidelines Update Team:
    - What is the best modality of giving phototherapy (clinical and cost-effectiveness)?
    - What is the correct procedure of giving phototherapy?
    - 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?

i. GE is asked to note that this 'yes to update' proposal will not be consulted on.

Mark Baker – Centre Director
Sarah Willett – Associate Director
Katy Harrison– Technical Analyst

Centre for Clinical Practice

August 2014

Appendix- Decision Matrix

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
RECOGNITION			
98-01 **What are the factors associated with an increased risk of hyperbilirubinaemia? Rec 1.2.1** Which factors affect the relationship between neonatal hyperbilirubinaemia and kernicterus or other adverse outcomes (neurodevelopmental, auditory)?			
None identified	None	A RCT indicated that anaesthesia during caesarean section may be a risk factor for hyperbilirubinaemia however it did not increase the need for interventions such as phototherapy and no comparison to normal delivery was made[30].	New evidence is unlikely to impact on guideline recommendations. The RCT identified made no comparison to normal delivery and the original guideline did not consider delivery type to be a good consistent factor associated with an increased risk of hyperbilirubinaemia it is unlikely that this evidence would impact on the recommendations.
98-02 **What is the best method of recognising hyperbilirubinaemia?** 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?			
A RCT investigated whether transcutaneous bilirubinometry reduced the need to test for total serum bilirubin (TSB) compared with visual evaluation of neonatal jaundice in infants of gestational age of 35 weeks[31]. Transcutaneous bilirubinometry was more effective at identifying neonatal	New evidence is unlikely to impact on guideline recommendations The results of the identified study support current clinical practice and guideline recommendations to not rely only on visual	None identified	No impact

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
jaundice than visual inspection.	assessment of neonatal jaundice.		
DIAGNOSIS			
98-03 **What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia?** What are the elements of a formal assessment in a baby with neonatal hyperbilirubinaemia? Clinical examination Total and split bilirubin Blood tests – blood grouping, G6PD levels, haematocrit, Urine tests Biochemical tests (bilirubin/albumin ratio, other relevant tests) ii) What is the clinical and cost-effectiveness of the tests carried out during formal assessment?			
None identified	None	None identified	No impact
98-04 **How useful are the following tests in predicting neonatal hyperbilirubinaemia?** What is the accuracy of the following tests in predicting neonatal hyperbilirubinaemia? Umbilical cord blood bilirubin levels Timed serum bilirubin levels Transcutaneous bilirubin levels End tidal CO levels Nomograms Risk assessment Coombs' test What is the effectiveness (clinical & cost) of various tests in predicting hyperbilirubinaemia and preventing morbidity/mortality?			
None identified	None	None identified	No impact
MANAGEMENT			
98-05 **Phototherapy** How effective is phototherapy? What is the best modality of giving phototherapy (clinical and cost-effectiveness)? Conventional phototherapy (single, double or multiple phototherapy)			

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
Sunlight Fibreoptic phototherapy (biliblankets, bilibeds and other products) What are the criteria/indications for starting and stopping phototherapy in babies with neonatal hyperbilirubinaemia? What is the correct procedure of giving phototherapy? Focus on the method of feeding/types of feed, incubator/bassinet care, effect of intermittent versus constant method on maternal–infant bonding, parental anxiety **Recommendations – 7.2.4 Additional equipment**			
Phototherapy ii) **Modality** 3 RCTS were identified that examined various types of phototherapy in neonatal infants (gestational age ≥ 35-37 weeks) with hyperbilirubinaemia. One indicated that there was no difference in LED versus compact fluorescent tube therapy on duration of therapy required rate of fall of TSB; 'failure of phototherapy'; exchange transfusions; or rebound in TSB needing phototherapy[1]. The second found no difference in TSB after 8 hours, 16, and 24 hours, mean length of hospital stay or in rate of decline in TSB between double or triple light sources [2].The third RCT indicated that there was no difference in mean decrease in bilirubin level after 24 hours between single or double phototherapy[3].	New evidence is unlikely to impact on guideline recommendations ii) **Modality** NICE CG98 currently recommends 'blue-light' conventional phototherapy. The EU stated that the identified study did not find a difference in effect between light sources, which supports the current recommendation. Multiple phototherapy is recommended for infants who do not respond to single phototherapy and in those with very high or rapidly rising TSB. The new study provides limited evidence that three light sources	**ii)Modality** **see research recommendation at end of table** **iii)Delivery** A RCT showed that single phototherapy with reflecting curtains was as effective as double phototherapy in term neonates with hyperbilirubinaemia at reducing TSB after 4 hours and 10 hours of phototherapy and on reducing the duration of phototherapy[14]. Likewise a RCT which examined the effect of white plastic cover around the phototherapy unit on hyperbilirubinaemia in full term neonates indicated that TBS declined significantly more if the phototherapy unit was covered	New evidence is unlikely to impact on guideline recommendations **Delivery** The GDG indicated that whilst the use of white curtains as an adjunct to phototherapy can aid serum bilirubin reduction it was not recommended as their use compromises the ability to observe the baby. Hence the new evidence identified is unlikely to impact on the current recommendations. There are currently no specific recommendations relating to light intensity and distance of phototherapy device from infant in the current guideline. The study which utilises LEDs may impact guidance if this type of phototherapy is recommended in the future.

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
iii) Stopping phototherapy A small non-blinded pilot RCT investigated whether phototherapy could safely be stopped earlier by using a higher TSB limit to indicate when to end treatment in infants, (gestational age > 36 weeks)[32]. High threshold group phototherapy stopped when TSB was 17 micromol/l less than the threshold for starting phototherapy or to the low threshold group (n = 27, stopping at 51 micromol/l below phototherapy threshold). The duration of phototherapy and length of hospital stay were significantly shorter in the high-threshold group than in the low-threshold group. **iv) Delivery** A RCT of infants (gestational age ≥ 33 weeks) receiving phototherapy, to compare supine positioning with alternation between supine and prone positioning every 3 hours[10]. No significant difference was seen in reduction in TSB from baseline at 12 hours or at 24 hours.	are not better than two, which is unlikely to affect NICE CG98. iii) Within the limitations of this small, non-blinded, single-centre, single-doctor study, the results suggest that a higher limit of TSB for ceasing phototherapy may be safe and effective. If replicated in a larger study, such evidence may be a consideration for future reviews of NICE CG98. Further data from a definitive study are needed iv) **Delivery** In the UK supine positioning only is advised to help to prevent sudden infant death syndrome, which is in line with recommendations in NICE CG98. The results of this study suggest no clinical effect of alternating position in phototherapy, so this evidence is unlikely to affect NICE CG98. NICE CG98 states 'do not use white curtains routinely'. The	compared to non-covered during the first 48 hours of treatment and resulted in a reduced duration of jaundice and hospitalization for the neonates[15]. A RCT to determine a "saturation point" (i.e., an irradiation level above which there is no further decrease in TSB) in 151 infants (gestational age > 33 weeks) with uncomplicated hyperbilirubinaemia investigated 4 distances from the LED phototherapy device to the mattress[12]. A linear relation was seen between light irradiance (20 to 55 muW/cm2/nm and TSB reduction at 24 hours with no evidence of a saturation point. A second RCT which compared the efficacy of phototherapy between conventional blue light tubes (30 muW/cm2/nm) and LED equipment (30 muW/cm2/nm or 40 muW/ cm2/nm) in neonates	In the UK supine positioning only is advised to help to prevent sudden infant death syndrome, which is in line with recommendations in NICE CG98. The results of 2 studies suggest no clinical effect of alternating position in phototherapy, so this evidence is unlikely to affect NICE CG98.

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
A RCT of phototherapy with or without white slings (curtains) hung from the sides of phototherapy equipment in healthy infants (gestational age ≥ 37 weeks)[11]. The duration of phototherapy did not differ between groups and there was no in TSB levels were seen between groups (8 hour TSB, TSB at end of phototherapy, rate of TSB fall, absolute TSB fall, or percentage TSB fall).	conclusions of this under-powered study are aligned with that recommendation and no change would be anticipated	(165 neonates gestational age >35 weeks) with non-haemolytic hyperbilirubinaemia[13] . The LED phototherapy at 40muW/cm2/nm significantly reduced phototherapy duration. A RCT examining whether changing the position of the infant from supine or alternating between supine and prone found no effect in management of hyperbilirubinaemia with phototherapy in terms of duration of therapy of rate of fall of bilirubin in late preterm and term neonates[16].	
98-06 **Is it beneficial to give additional fluids (cup feeds, fluids) during treatment with phototherapy? Rec 1.4.18** What is the effectiveness of nutritional support and/or rehydration during treatment with phototherapy in babies with neonatal hyperbilirubinaemia? Oral – top milk feeds by bottle/cup/spoon or other liquids (water/juice) b) Parenteral – IVF			
None identified	None identified	1 RCT in full-term neonates (n=84) with severe hyperbilirubinaemia, compared the use of hypotonic or isotonic fluid in addition to phototherapy to prevent blood exchange transfusion was identified [33]. The	New evidence does not impact on guideline recommendations. The guideline indicated that good clinical practice should ensure that babies are kept hydrated while undergoing

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		administration of hypotonic fluid was significantly associated with a higher incidence of hyponatremia while isotonic fluid was significantly associated with an increased incidence of hypernatremia. A RCT which compared the genotoxic effect of different approaches to phototherapy (intensive phototherapy conventional phototherapy) in 172 term infants with hyperbilirubinemia[34]. Following intensive phototherapy, DNA damage, sister chromatid exchange frequency and total oxidant status were significantly higher in the peripheral blood lymphocytes of infants that had received the intensive phototherapy than in the conventional group or control.	phototherapy and that maternal expressed milk is the additional feed of choice if available when additional feeds are indicated. The guideline also recommend 'do not' give additional fluid or feeds routinely for hydration. The new evidence indicates that hypotonic or isotonic fluid use maybe detrimental to the neonates electrolyte balance and does not therefore impact on the current recommendations. The guideline reported on 1 study that indicated that phototherapy is associated with DNA damage. The GDG concluded that there was no evidence that this genotoxic effect on DNA at a microscopic level can lead to long-term adverse effects in phototherapy-treated babies. Hence no recommendations were made in this area. It is therefore unlikely that the additional study would impact on the guideline as longer term outcomes would be required.
98-07 **Exchange transfusion** How effective is exchange transfusion? What is the best method (single volume versus double volume exchange)? iii) What are the criteria/indications for carrying out an exchange transfusion?			

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
None identified	None identified	A RCT on 104 neonates with hyperbilirubinaemia needing exchange transfusion was identified that compared a two-stage single-volume exchange transfusion to single-stage double-volume (DVET) exchange transfusion on the post-exchange rebound increase in serum bilirubin level and the subsequent need for repeated exchange transfusions[35]. The two-stage single-volume exchange transfusion was more effective in reducing rebound serum bilirubin level post-exchange and in decreasing the need for repeated exchange transfusions. There was no difference in morbidity and mortality between the two approaches to transfusion. A multicentre RCT on 100 full term neonates with confirmed ABO-Hemolytic Disease of the Newborn evaluated whether prescribing ABO compatible	New evidence is unlikely to impact on guideline recommendations. A single study (n=20) reported no difference between single volume exchange transfusion (SVET) and DVET within the guideline evidence base and was considered to be insufficient evidence to change current clinical practice. The new evidence indicates that a 2 stage SVET is more effective than DVET. NICE CG98 currently lists SVET as a 'do not use' intervention. The addition of one further small study is unlikely to lead to a change in guidance. A RCT indicated that the exact constituents used for transfusion with regards to blood products did not impact on the effectiveness of the therapy. As such this study does not impact on the guideline.

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		packed cell, dried O, and routine O groups influenced the need for further exchange transfusions[36]. The results of the study indicated that only the neonate's level of bilirubin before exchange transfusion was associated with the necessity of second or third exchange transfusion.	
98-08 **What are the other ways of treating hyperbilirubinaemia? Are they effective?** What is the effectiveness of the following interventions in treating neonatal hyperbilirubinaemia/preventing kernicterus? Metalloporphyrins Gammaglobulins Drugs (phenobarbitol, clofibrate, cholestyramine) Agar, charcoal Suppositories, other rectal modes of treatment f) Complementary/alternative medicines (Chinese herbal remedies such as Yin-chen)			
A RCT evaluated albumin infusion given before exchange transfusion in 50 babies (gestational age > 37 weeks) with non-haemolytic hyperbilirubinaemia who had not responded to 'intensive' phototherapy was identified[17]. TSB was significantly lower in the albumin group compared with the control group at both 6 hours and at 12 hours. Duration of	New evidence could potentially impact guideline recommendations. The RCT provides some evidence to support albumin infusion however this is a small study.	**Albumin transfusion**. A RCT which evaluated the role of 5% albumin infusion before exchange transfusion in reducing post-exchange unconjugated serum bilirubin levels in 42 low birth weight (1000g-2499g>=32 weeks	New evidence could potentially impact guideline recommendations. Two small RCTS provide evidence that albumin infusion maybe potentially beneficial in neonates with hyperbilirubinaemia. It was noted with the EU that because the potential population for a UK study is so small, conducting a

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
phototherapy was significantly shorter in the albumin group. No infant in the albumin group needed a second exchange transfusion but four infants in the control group did. This study of 50 infants is small, but exchange transfusions for severe hyperbilirubinaemia in otherwise healthy near-term or term babies are rare (around 25 cases per year in the UK.		gestational age) neonates with intensive phototherapy failure was identified[18]. 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. No albumin transfusion-related complications were observed. **Suppositories, other rectal modes of treatment** A systematic review of 3 RCTs found no effect on serum bilirubin and the need for phototherapy by the induction of meconium evacuation on neonatal hyperbilirubinemia in term infants[24]. **Other treatments** Two RCTs that have	larger study would be difficult. However, the definition of 'intensive' phototherapy used in these trials may not represent the high irradiance of multiple phototherapy used in the UK, so fewer such babies in the UK might progress to needing exchange transfusion. NICE CG98 lists albumin priming before exchange transfusion as a 'do not use' intervention. However, within the guideline only one small study from 1976 addressed the use of albumin before exchange transfusion and the GDG therefore stated that albumin priming could not be recommended because of an 'absence of evidence'. The evidence from the 2 RCTs identified indicates that the recommendation could be considered for update **Suppositories, other rectal modes of treatment** Evidence on the use of rectal laxative is in in line with the current do not use recommendation. **Other treatments**

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		investigated the efficacy of using prebiotic/probiotics or probiotics alone as a supplementation on the course of hyperbilirubinemia and duration of phototherapy in very low birth weight neonates (gestational age of <=32 weeks and birth weight of <=1500 g). The RCTs gave conflicting results with a combination of prebiotics and probiotics been ineffective compared to placebo on bilirubin levels or duration of phototherapy but probiotics alone significantly reducing duration of phototherapy and feeding intolerance[25,26]. Two RCTs have examined the effect of massage as an adjunctive treatment to phototherapy in term neonates with hyperbilirubinemia compared to no massage. Both RCTS indicate that massage can reduce bilirubin levels (TBS or mean bilirubin) either during early phototherapy (first 24hr) or over the initial 5 day period.	There was evidence from 2 small RCTs that massage may be beneficial for babies receiving phototherapy. The evidence base for this adjunctive approach is limited and at present may be insufficient to guide clinical practice. There is conflicting evidence on the effectiveness of pre and probiotics which. It is unlikely that this evidence alone would result in recommendations for this approach at this stage

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		However, massage therapy did not show any benefit with regards to weight gain in the neonates[27,28].	
Monitoring and follow-up			
98-09 How to monitor a baby with jaundice? What are the appropriate criteria for monitoring (timing, frequency) of babies with jaundice who are at lower risk of developing neonatal hyperbilirubinaemia/kernicterus? ii) What are the appropriate criteria for monitoring (timing, frequency) of babies diagnosed with neonatal hyperbilirubinaemia who do not require immediate treatment?			
None identified	None identified	None identified	No Impact
98-10 When to discharge a baby treated for hyperbilirubinaemia? What follow-up is required? What is the appropriate criterion for discharge of babies treated for neonatal hyperbilirubinaemia? ii) What is the appropriate timing/frequency of follow-up?			
None identified	None identified	None identified	No Impact
INFORMATION			
98-11 What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia? At the time of birth At the time of recognition of jaundice (FOR ALL BABIES) At the time of formal assessment/diagnosis During monitoring During treatment with phototherapy and other interventions f) At discharge and follow-up			
None identified	None identified	None identified	No impact
Research Recommendations			

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
What are the factors that underlie the association between breastfeeding and jaundice?			
None identified	None identified	None identified	No impact
What is the clinical and cost-effectiveness of: LED phototherapy compared to conventional phototherapy in term and preterm babies with significant hyperbilirubinaemia?			
None identified	None identified	Six studies (2 systematic reviews and 4 RCTs) were identified that have investigated the effectiveness of light emitting diodes (LEDs) phototherapy as compared to conventional phototherapy. A Cochrane systematic review which identified 6 RCTs evaluated the effect of light emitting diodes (LEDs) phototherapy as compared to conventional phototherapy (compact fluorescent tubes, halogen spotlight) in decreasing TSB levels and duration of treatment in neonates (term and pre-term) with unconjugated hyperbilirubinaemia[4]. The duration of phototherapy (630 neonates), rate of decline of	New evidence could potentially impact on recommendations From the new evidence it would appear that LED phototherapy is efficacious in bringing down levels of TSB at rates that are similar to phototherapy with conventional (compact fluorescent lamp or halogen) light sources. LED phototherapy has potentially less frequent side effects, less energy consumption, longer life span, and lower costs and may therefore potentially be a more cost effective approach than current conventional phototherapy. The guideline indicated that there was existing evidence that there is no difference between LED and conventional phototherapy. However it was noted that LED phototherapy maybe easier to use in clinical setting by reducing the need for

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		TSB (511 neonates), treatment failure and adverse events were comparable in LED and non-LED phototherapy groups. Likewise a systematic review which included 511 neonates in the meta-analysis found that LED and other phototherapy devices appeared to be equally effective in reducing TSB in term or late preterm neonate[5]. Two RCTs (n=45- 58) also found no difference in the outcomes of duration of phototherapy, bilirubin levels (rate of decline or maximal level) or the frequency of skin eruptions for pre-term neonates undergoing phototherapy for hyperbilirubinemia when comparing LED with conventional phototherapy devices[6, 7] . Two RCTs comparing phototherapy for neonates with hyperbilirubinemia by 'special blue fluorescent' or by LED were	additional fluids. Hence the research recommendation requested RCTs with the outcome of effectiveness in terms of the mean decrease in bilirubin levels and the mean duration of phototherapy. In addition extra outcomes were requested in terms of adverse effects, parental bonding and parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. It is unclear from only an assessment of the abstracts if the 'extra' outcomes have also been reported. Due to word limitations abstracts tend to only report on the primary outcomes. There may now be sufficient evidence to determine if LED phototherapy should be specifically recommended.

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		identified[8,9]. One RCT was in 40 healthy infants aged between 1 and 5 days and the other in 64 preterm neonates (gestational age of 33.5 + 1.2 weeks) produced conflicting results. In full term neonates the 6 special blue fluorescent tubes phototherapy resulted in an increased median rate of plasma bilirubin decline compared to LEDs however the duration of phototherapy was comparable between the types of phototherapy. Whereas in the preterm neonates there was no difference in TBS rate of reduction, treatment duration, treatment failure rates in the LED and fluorescent groups. However, there were more cases of mild hyperthermia in the fluorescent group.	
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?			
None identified	None identified	None identified	No impact
What is the comparative accuracy of the Minolta JM-103 and the BiliChek when compared to serum bilirubin levels in all babies?			

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
None identified	None identified	A systematic review to assess the reliability of transcutaneous bilirubin (TcB) devices in preterm infants identified 22 studies[29]. It was noted that results from transcutaneous bilirubinometers in neonates with 32 weeks' gestation were similar to the overall preterm population. A comparison of the 2 most common TcB devices, the JM103 and BiliCheck, found that these devices were comparable at the forehead site, although the JM103 device exhibited better correlation at the sternum, and overall the JM-103 device exhibited better precision than the BiliCheck. The authors concluded that the TcB devices used in the studies could reliably estimate bilirubin levels in preterm infants and could be used in clinical practice to reduce blood sampling.	New evidence may impact recommendations. Within CG98 it was noted that there were no published studies directly comparing the BiliChek and the JM-103. Hence the GDG was unable to recommend a particular device over another and recommended the use of ' transcutaneous bilirubinometer' only when a case of jaundice is suspected via visual inspection in babies with a gestational age of 35 weeks or more and postnatal age of more than 24 hours. However it was noted that measurement over the sternum was more acceptable to parents and babies and sternal measurement avoided the problem of failing to obtain a reading associated with forehead methods. The current systematic review indicates that there may now be sufficient evidence to allow recommendations on specific transcutaneous bilirubinometers to be made and that this approach may also be effective in younger preterm neonates.
How frequently and for how long can conventional phototherapy be interrupted without adversely effecting clinical outcomes?			

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
None identified	None identified	None identified	No impact
National registries are needed of cases of significant hyperbilirubinaemia, kernicterus and exchange transfusions.			
None identified	None identified	None identified	No impact
What is the effectiveness, cost-effectiveness and safety of clofibrate alongside phototherapy versus phototherapy alone for non-haemolytic significant hyperbilirubinaemia?			
None identified		Two systematic reviews (1 Cochrane) were identified that evaluated the effect of clofibrate with phototherapy versus phototherapy alone for unconjugated hyperbilirubinaemia in neonates[19].The Cochrane systematic review which include 15 studies (two including preterm neonates and 13 including term neonates) indicated that for preterm neonates, clofibrate significantly lowered bilirubin levels at 48hrs, and for term neonates significantly lower bilirubin levels at both 24 and 48 hours of treatment. For both ages of neonates the duration of phototherapy was significantly reduced by the adjunctive addition of clofibrate group to phototherapy. However, the	Potential impact on guideline recommendations The meta-analysis of good quality RCTs within CG98 indicated that a single dose of clofibrate led to statistically significant reductions in mean serum bilirubin levels and duration of phototherapy compared with phototherapy alone. However, as all the studies were carried out in one country the GDG felt that the results were not generalisable to UK clinical practice. Hence the current recommendation states 'do not use' clofibrate to treat hyperbilirubinaemia. The new evidence identified indicates the same clinical benefit but is not from a diverse range of countries.

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		review concluded that there was insufficient data from different countries on the use of clofibrate in combination with phototherapy for hyperbilirubinaemia to make recommendations for practice. The second systematic review which included 13 studies (867 infants) also found that a single oral administration of clofibrate was associated with decreased need of phototherapy, shortened duration of phototherapy and reduced peak TSB[20]. Two RCTs which evaluated a single dose of clofibrate as an adjunctive to phototherapy in term neonates with hyperbilirubinemia were identified[21] . The first RCT conducted on 52 new-borns with pathologic unconjugated hyperbilirubinemia found that clofibrate adjunctive therapy resulted in a reduction in serum bilirubin at 24 hours and 48 hours after treatment. The	

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		second RCT conducted on 60 healthy term neonates found that clofibrate adjunctive therapy resulted in reduced mean TSB after 12, 24, 48hrs of treatment, reduced mean of hospital stay days and duration of phototherapy[22]. In addition 1 RCT was identified that compared, the efficacy of clofibrate to phenobarbital in 60 full-term neonates with non-haemolytic jaundice as adjunctive treatment to phototherapy[23]. The mean TSB in phenobarbital group was significantly lower at 24hrs, and after 72 hours of significantly more neonates were discharged with TBS of <10 mg.	
What is the clinical and cost-effectiveness of IVIG when used to prevent exchange transfusion in newborns with haemolytic disease and rising bilirubin?			
None identified	None identified	A systematic review of intravenous immunoglobin for treatment of haemolytic disease	No impact on guideline recommendations. The results of the systematic review were

Conclusions from previous review (2 year EU)	Impact at 2 years	Evidence summary of clinical area at 4 year and GDG/clinical perspective	Impact and comments
		in neonates due to rhesus , ABO or any other blood group antibodies was identified that meta-analysed 14 studies (942 infants)[37]. The results indicated that intravenous immunoglobin reduced the need for exchange transfusion.	in line with current guideline recommendations to offer intravenous immunoglobulin as an adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease or ABO haemolyticdisease when the serum bilirubin continues to rise by more than 8.5 micromol/litre per hour.

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