Neonatal jaundice

National Collaborating Centre for Women's and Children's Health

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Implementation of this guidance is the responsibility of local commissioners and/or providers

ISBN to be added

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1 Guidance summary

ID.	Recommendations	See chapter/section
	1.1 Key Priorities for implementation	
	Information for parents and carers Offer parents or carers information about neonatal jaundice that is tailored to their needs and expressed concerns. They should receive information on: • factors that influence the development of 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 (recommendation x) and of seeking urgent medical advice (recommendation x) • 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. 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. **Care for all babies** Identify babies as being more likely to develop 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. In all babies: • check whether there are factors associated with an increased likelihood of developing hyperbilirubinaemia soon after birth (see recommendation 2). • examine the baby for jaundice at every opportunity especially in the first 72 hours.	

When looking for jaundice (visual inspection)

- check the naked baby in bright and preferably natural light.
- examination of the sclerae, gums and blanched skin is useful across all skin tones

All Babies with jaundice – measure bilirubin

Do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice

How to Measure the bilirubin level in babies

When measuring the bilirubin level

- use a transcutaneous bilirubinometer in term and near term babies more than 24 hours of age
- 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 check the result by measuring the serum bilirubin
- always use serum bilirubin measurement to determine the bilirubin level in babies with jaundice in the first 24 hours of life
- always use serum bilirubin measurement to determine the bilirubin level in preterm babies less than 34 weeks gestational age
- always use serum bilirubin in babies receiving phototherapy
- do not use an icterometer.

7

When to treat bilirubin

Use serum bilirubin measurement to determine the management of hyperbilirubinaemia in all babies (see table 1 below and graphs A-F).

8

Second line phototherapy treatment in term and pre term babies

Use continous multiple phototherapy to treat hyperbilirubinaemia in term and preterm babies who:

- have a bilirubin level that fails to respond to conventional phototherapy (that is, the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting conventional phototherapy)
- have rapidly rising serum bilirubin levels (more than 8.5 micromol/litre/hour)
- have serum bilirubin at a level for which exchange transfusion is indicated (see table 1 and graphs A-F).

Factors that influence the risk of kernicterus

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

- a serum bilirubin greater than 340 micromol/litre in a term baby
- a rapidly rising bilirubin level of greater than 8.5 micromol/litre/hour
- clinical features of acute bilirubin encephalopathy.

Formal Assessment for underlying disease

	In addition to a clinical examination, carry out all of the following tests in babies with hyperbilirubinaemia requiring treatment (see table 1 and graphs A-F): • 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). 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) **Intravenous immunoglobulin** Use intravenous immunoglobulin (IVIG) as an adjunct to continuous multiple 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/hour.	
	1.2 Summary of all recommendations	
1	**Information to parents and carers** Offer parents or carers information about neonatal jaundice that is tailored to their needs and expressed concerns. They should receive information on: • factors that influence the development of 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 (recommendation X) and of seeking urgent medical advice (recommendation X) • 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 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.	8
	Care for all babies Identify babies as being more likely to develop hyperbilirubinaemia if	

2	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.	3.1
3	Ensure that adequate support is offered to all women who intend to breastfeed exclusively. *Refer to 'Routine postnatal care of women and their babies' (NICE clinical guideline 37) for information on breastfeeding support*.	3.1
4	In all babies: • check whether there are factors associated with an increased likelihood of developing hyperbilirubinaemia soon after birth (see recommendation 2). • examine the baby for jaundice at every opportunity especially in the first 72 hours.	5.1
5	When looking for jaundice (visual inspection) • check the naked baby in bright and preferably natural light • examination of the sclerae, gums and blanched skin is useful across all skin tones.	5.1
6	Parents, carers or healthcare professionals can carry out the visual inspection	5.1
7	Do not measure pre-discharge bilirubin levels routinely in babies who are not jaundiced.	4.7
8	Do not use any of the following to predict hyperbilirubinaemia: • umbilical cord bilirubin • end-tidal carbon monoxide (ETCOc) measurement • umbilicial cord direct antiglobulin test (DAT) (Coombs' test).	4.1, 4.3, 4.5
9	**Additional care** In babies with factors associated with an increased likelihood of developing hyperbilirubinaemia (recommendation 2) conduct an additional clinical examination including a visual inspection for jaundice during the first 48 hours of life.	5.1
10	**All Babies with jaundice – measure bilirubin** Do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice.	5.1
	Urgent care for babies in their first 24 hours	

11	Measure and record the serum bilirubin urgently (within 2 hours) in all babies less than 24 hours old with suspected or obvious jaundice.	4.2
12	If the serum bilirubin is greater than 100 micromol/litre in the first 24 hours of life repeat the serum bilirubin measurement between 6 and 12 hours later.	4.2
13	Refer to ensure an urgent medical review is conducted (as soon as possible and within 6 hours) to exclude pathological causes of jaundice.	4.2
14	Interpret bilirubin levels according to the baby's postnatal age in hours and manage hyperbilirubinaemia according to Table 1 and graphs A -F.	4.2
15	**Care for babies more than 24 hours old** Measure and record the bilirubin level urgently (within 6 hours) in all babies more than 24 hours old with suspected or obvious jaundice.	5.4
16	**How to Measure the bilirubin level** When measuring the bilirubin level • use a transcutaneous bilirubinometer in term and near term babies more than 24 hours of age • 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 check the result by measuring the serum bilirubin • always use serum bilirubin measurement to determine the bilirubin level in babies with jaundice in the first 24 hours of life • always use serum bilirubin measurement to determine the bilirubin level in preterm babies less than 34 weeks gestational age • always use serum bilirubin in babies receiving phototherapy • do not use an icterometer.	5.4
17	**Information for parents or carers on treatment** Offer parents or carers information about treatment, including • anticipated duration of treatment • reassurance that breastfeeding and physical contact with the baby can usually continue.	8
18	Encourage mothers of breastfed babies with jaundice to breastfeed frequently, and to wake the baby for feeds if necessary.	8
	Provide lactation/feeding support to breastfeeding mothers whose baby is visibly jaundiced	8

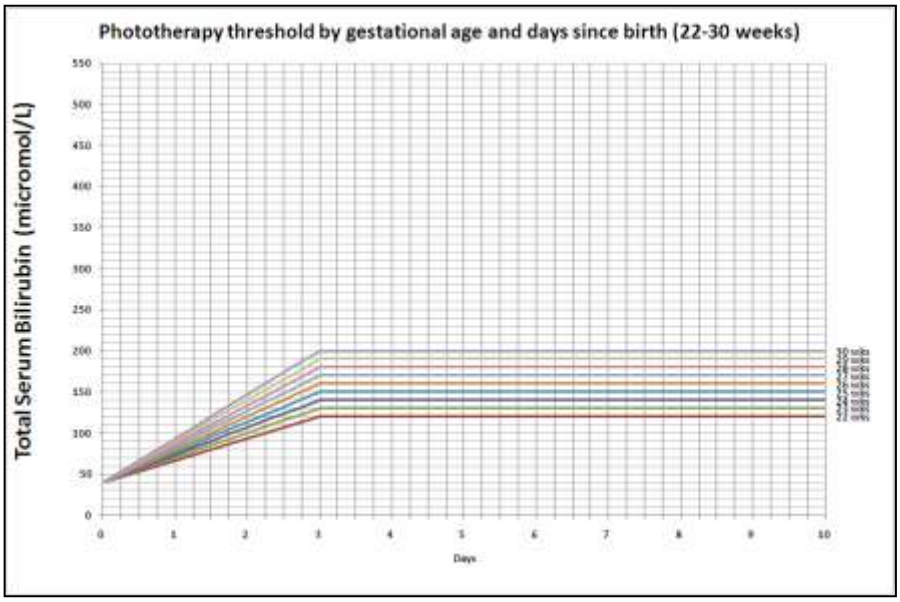
19		
20	**How to manage hyperbilirubinaemia** Use serum bilirubin measurement to determine the management of hyperbilirubinaemia in all babies (see table 1 below and graphs A – F).	7.1.8

Table 1 Consensus based serum bilirubin thresholds for management of babies ≥ 38 weeks gestational age

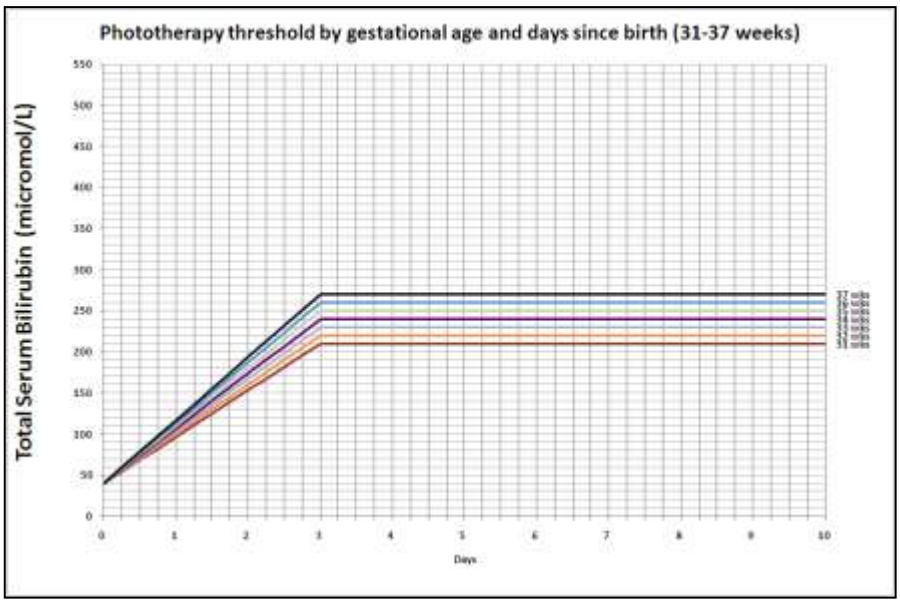
Age (hours)	**Serum Bilirubin measurement** (micromol/litre)			
0			> 100	> 100
6	> 100	> 112	> 125	> 150
12	> 100	> 125	> 150	> 200
18	> 100	> 137	> 175	> 250
24	> 100	> 150	> 200	> 300
30	> 112	> 162	> 212	> 350
36	> 125	> 175	> 225	> 400
42	> 137	> 187	> 237	> 450
48	> 150	> 200	> 250	> 450
54	> 162	> 212	> 262	> 450
60	> 175	> 225	> 275	> 450
66	> 187	> 237	> 287	> 450
72	> 200	> 250	> 300	> 450
78		> 262	> 312	> 450
84		> 275	> 325	> 450
90		> 287	> 337	> 450
96+		> 300	> 350	> 450
Action	↓	↓	↓	↓
	Repeat transcutaneous bilirubin/serum bilirubin (6–12 hours)	**Consider phototherapy (repeat transcutaneous bilirubin/serum bilirubin in 6 hours)**	**Start phototherapy**	**Perform an exchange transfusion**

See also graphs A-F for treatment thresholds for babies < 38 weeks

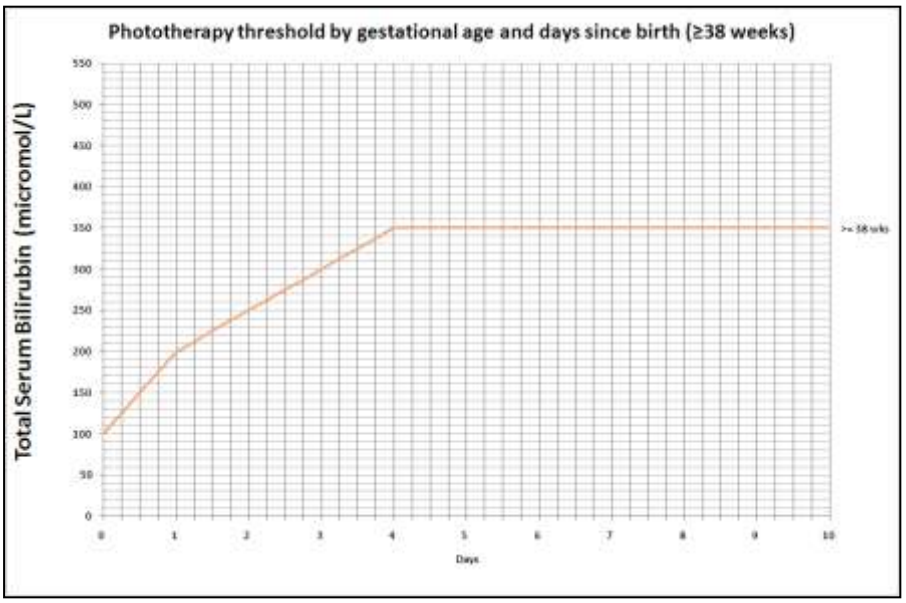
Graph A



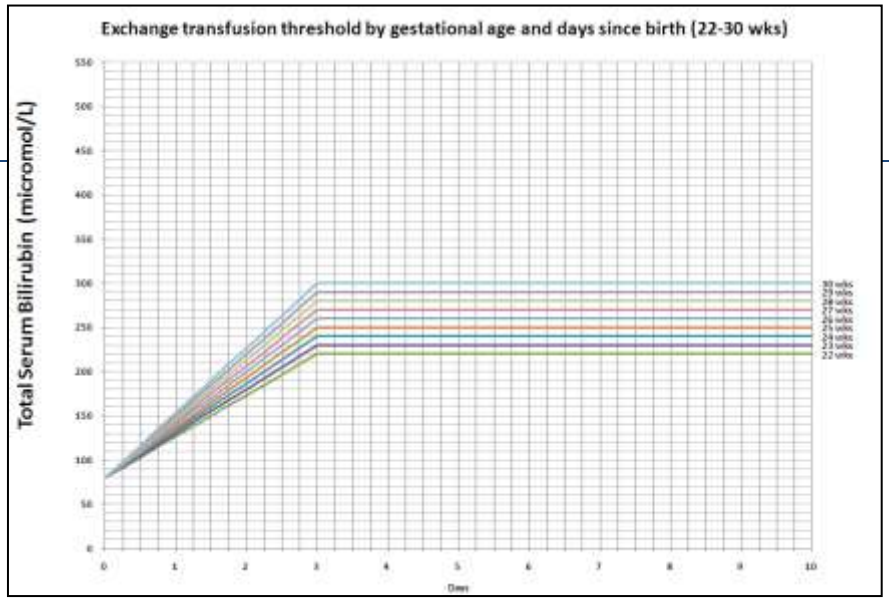
Graph B



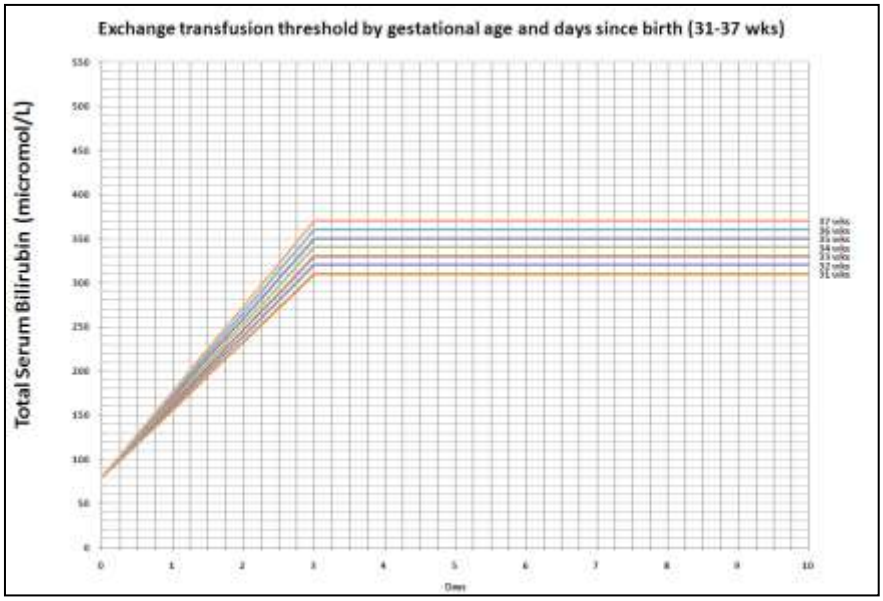
Graph C



Graph D



Graph E



Graph F

21	Do not use the albumin/bilirubin ratio when making decisions about the management of hyperbilirubinaemia.	6.5
22	Do not subtract conjugated bilirubin from total serum bilirubin when making decisions about the management of hyperbilirubinaemia. Please see management thresholds in table 1 and graphs A-F below.	6.6, 6.7
	Measuring and monitoring bilirubin thresholds in phototherapy	
	Starting phototherapy	
21	Use serum bilirubin measurement and the treatment thresholds when considering the use of phototherapy (see Table 1 and graphs A -F).	7.1.8
22	In babies with a gestational age of 38 weeks or more whose bilirubin is in the 'repeat transcutaneous bilirubin/serum bilirubin' category (Table 1) repeat transcutaneous bilirubin/serum bilirubin in 6–12 hours.	7.1.8
23	In babies with a gestational age of 38 weeks or more whose serum bilirubin is in the 'consider phototherapy' category (Table1) repeat serum bilirubin in 6 hours regardless of whether or not phototherapy has subsequently been started.	7.1.8
24	Do not use phototherapy in babies whose bilirubin does not exceed the phototherapy threshold levels (see Table 1 and graphs A -F).	7.1.8
	During phototherapy	
25	If treatment has been started, use serum bilirubin measurement for all subsequent assessments until the baby has been discharged from the care of the maternity or neonatal service.	7.1.8
26	During conventional 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.	7.1.8
	Stopping phototherapy	
27	Stop phototherapy once serum bilirubin has fallen to a level at least 50 micromol/litre below the appropriate phototherapy threshold (see Table 1 and graphs A - F).	7.1.8
28	Check for rebound of hyperbilirubinaemia with a repeat serum bilirubin measurement between 12 and 18 hours after stopping phototherapy – babies do not necessarily have to remain in hospital for this to be done.	7.1.12
	Type of phototherapy to use	
29	Do not use sunlight as phototherapy for hyperbilirubinaemia.	7.1.1

30	**First line phototherapy treatment for term babies** Use conventional blue light phototherapy as first-line treatment for hyperbilirubinaemia in term babies.	7.1.1
31	Do not use fibreoptic phototherapy as first-line treatment for hyperbilirubinaemia in term babies.	7.1.1
32	**First line phototherapy treatment in preterm babies** Use either fibreoptic phototherapy or conventional blue light phototherapy as first-line treatment for hyperbilirubinaemia in preterm babies.	7.1.2
32	**Second line phototherapy treatment in term and pre term babies** Use continuous multiple phototherapy to treat hyperbilirubinaemia in term and preterm babies who: • have a bilirubin level that fails to respond to conventional phototherapy (that is, the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting conventional phototherapy) • have rapidly rising serum bilirubin levels (more than 8.5 micromol/litre/hour) • have serum bilirubin at a level for which exchange transfusion is indicated (see table 1 and Graphs).	7.1.2
33	**Information for parents or carers on phototherapy** Offer parents or carers verbal and written information on all of the following: • why phototherapy is being considered • why phototherapy may be helpful in treating 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 supported as long as the bilirubin levels are not significantly elevated • what might happen if phototherapy fails • rebound jaundice • potential long-term adverse effects of phototherapy • potential impact on breastfeeding and how to minimise this.	8
34	**General Care of the baby during phototherapy** 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	7.1.4

	environment that will minimize energy expenditure (thermoneutral environment) • support parents and carers and encourage them to interact with the baby.	
35	Use eye protection and give routine eye care to the baby during phototherapy.	7.1.6
36	Use tinted headboxes as an alternative to eye protection in term babies undergoing conventional phototherapy.	7.1.6
37	**Monitoring the baby during phototherapy** During conventional phototherapy: • Using clinical judgement encourage breaks (of up to 30 minutes) for breastfeeding, nappy changing and cuddles as long as the bilirubin levels are not significantly elevated • continue lactation/feeding support • do not give additional fluids or feeds routinely. Maternal expressed milk is the additional feed of choice if available, and when additional feeds are indicated.	7.1.11
38	During multiple phototherapy: • monitor hydration by daily weighing and assessing wet nappies • do not interrupt phototherapy for feeding but continue administering intravenous/oral feeds • continue lactation/feeding support so that breastfeeding can start again when treatment stops.	7.1.11
39	Maternal expressed milk is the additional feed of choice if available, and when additional feeds are indicated	7.1.11
40	**Phototherapy equipment** Ensure all equipment is maintained and used according to the manufacturers' guidelines.	7.1.1
41	Use incubators or bassinettes according to clinical need and availability.	7.1.9
43	Do not use white curtains routinely with phototherapy as they may impair observation of the baby.	7.1.7
43	**Factors that influence the risk of kernicterus** Identify babies with hyperbilirubinaemia as being at increased risk of developing kernicterus if they have any of the following:	3.2

	• a serum bilirubin greater than 340 micromol/litre in a term baby • a rapidly rising bilirubin level of greater than 8.5 micromol/litre/hour • clinical features of acute bilirubin encephalopathy.	
	Formal assessment for underlying disease	
44	In addition to a clinical examination, carry out all of the following tests in babies with hyperbilirubinaemia requiring treatment (see treatment thresholds in table 1 and graphs A-F): • 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).	6.4
45	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).	6.4
	Care of babies with prolonged jaundice	
46	In term babies with jaundice lasting more than more than 14 days and more than 21 days in preterm babies (prolonged jaundice): • look for pale chalky stools and/or dark urine that stains the nappy • measure the conjugated bilirubin • refer babies with a conjugated bilirubin greater than 25 micromol/litre for expert investigation.	6.8
47	Carry out the following investigation in babies with prolonged jaundice (that is, persisting more than 14 days in term babies and more than 21 days in preterm babies): • visual inspection of stool and urine • total and conjugated bilirubin • full blood count • 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.) • urine culture. • ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed.	6.8
	In babies with high levels of conjugated bilirubin (more than 25	6.8

48	micromol/litre), arrange urgent referral to a specialist centre, because this may indicate serious liver disease.	
49	**Intravenous immunoglobulin** Use intravenous immunoglobulin (IVIG) as an adjunct to continuous multiple 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/hour.	7.3
50	Offer parents or carers information on IVIG including: • why IVIG is being considered • why IVIG may be helpful in treating significant hyperbilirubinaemia • the possible adverse effects of IVIG • when it will be possible for parents or carers to see and hold the baby.	7.3
51	**Exchange transfusion** Use serum bilirubin measurement and the treatment thresholds when considering the use of an exchange transfusion (see table 1 and graphs A – F)	7.2
52	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 helpful in treating 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.	7.2
53	Use a double-volume exchange transfusion to treat babies: • whose serum bilirubin level (using the threshold levels in Table 1 and graphs A-F) indicate its necessity • with hyperbilirubinaemia that fails to respond to phototherapy • with clinical features and signs of acute bilirubin encephalopathy.	7.2
54	During exchange transfusion do not : • perform a single-volume exchange • use albumin priming • routinely administer intravenous calcium.	7.2
55	**Other therapies** 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.	7.3

1.5 Research recommendations

1.5.1 Key priorities for research

Prediction (3.1)

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

Why this is important

Evidence: Breastfeeding has been shown to be a factor in hyperbilirubinaemia. The reasons for this association have not yet been fully elucidated. Population: Infants in the first 28 days of life. Exposure: Feeding type (breast milk, formula feeds or mixed feeds). Comparison: Infants who do not get hyperbilirubinaemia will be compared with infants with hyperbilirubinaemia requiring treatment. Outcome: Factors to be analysed include I) maternal factors, II) neonatal factors, III) blood analyses. Time stamp: Sept 2009

Prediction (3.1)

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

Why this is important

Evidence: There is good evidence that a risk assessment that combines the result of a timed transcutaneous bilirubin level with risk factors for hyperbilirubinaemia is effective at preventing later hyperbilirubinaemia requiring treatment.Population: Babies in the first 28 days of life. Subgroups should include pre-term and babies with dark skin tones. Exposure: A/ Timed pre-discharge transcutaneous bilirubin level. B/ Timed pre-discharge transcutaneous bilirubin level combined with risk assessment. Comparison: Standard care (discharge without timed transcutaneous bilirubin level). Outcome: i) Hyperbilirubinaemia requiring treatment ii) Cost-effectiveness, III) Parental anxiety. Time stamp: Sept 2009

Recognition (4.7)

How accurate are transcutaneous bilirubinometers in assessing bilirubin levels in preterms babies and babies with dark skin tones or with high levels of bilirubin

Why this is important

Evidence: The accuracy of transcutaneous bilirubinometers has been adequately demonstrated in term babies below treatment levels (bilirubin < 250 micromol/L). New research is needed to evaluate the accuracy of transcutaneous bilirubinometers in babies with, gestational age under 37 weeks, dark skin tones, high levels of bilirubin, and who are or have had received phototherapy for neonatal hyperbilirubinaemia. Population: Babies in the first 28 days of life. Subgroups to include pre-term and babies with dark skin tones. Exposure: Bilirubin levels taken from transcutaneous bilirubin. Comparison: Bilirubin levels assessed using serum (blood) tests. Outcome: Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value), parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

Recognition (5.4)

What is the comparative accuracy of the Minolta JM-103 and the BiliChek when compared to serum bilirubin levels.

Why this is important

Evidence: The accuracy of transcutaneous bilirubinometers has been adequately demonstrated in term babies below treatment levels (bilirubin < 250 micromol/L). New research is needed to compare the accuracy of different device, BiliChek and Minolta JM-103 in different populations including i) gestational age under 37 weeks, ii) dark skin tones, iii) high levels of bilirubin and iv) hyperbilirubinaemia during, and after phototherapy. Population: Term babies in the first 28 days of life. Subgroups to include pre-term and babies with dark skin tones.Exposure: BiliChek and Minolta JM-103 readings of bilirubin levels. Comparison: Bilirubin levels assessed using serum (blood) tests. Outcome: Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value), parental anxiety, satisfaction, and cost effectiveness. Time stamp: Sept 2009

National registries (3.2)

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

Why this is important

Evidence: There is good evidence that prospective surveys in the UK and from a national Kernicterus Register in the US can help is identify root-causes of kernicterus and acute bilirubin encephalopathy. Population: All children with a peak bilirubin level greater than 450 micromol/L which is the threshold for an exchange transfusion recommended by NICE. Exposure: All maternal, pre-natal, peri-natal and neonatal factors. Comparison: Not applicable. Outcome: Shortcomings in clinical and service provision to prevent recurring themes in kernicterus cases. Time stamp: Sept 2009

1.5.2 Other research recommendations

Research recommendation - Pre-discharge risk assessment (4.4)

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?

Why this is important

Evidence: There is good evidence that a risk assessment that combines the result of a timed transcutaneous bilirubin level with risk factors for hyperbilirubinaemia is effective at preventing later hyperbilirubinaemia requiring treatment. Population: Babies in the first 28 days of life. Subgroups should include pre-term and babies with dark skin tones. Exposure: A/ Timed pre-discharge transcutaneous bilirubin level. B/ Timed pre-discharge transcutaneous bilirubin level combined with risk assessment. Comparison: Standard care (discharge without timed transcutaneous bilirubin level). Outcome: i) Hyperbilirubinaemia

requiring treatment ii) Cost-effectiveness, III) Parental anxiety. Time stamp: Sept 2009

Phototherapy (7.1.1)

What is the clinical and cost-effectiveness of:

- LED phototherapy compared to conventional phototherapy in term and preterm babies with hyperbilirubinaemia?

Why this is important.
Existing research has shown that while there is no difference between LED phototherapy and conventional phototherapy, LED phototherapy may be easier to use in clinical setting by reducing over-heating and the potential need for additional fluids. New randomized controlled trials are needed to examine LED phototherapy. Population: Term and pre-term babies in the first 28 days of life. Interventions: LED phototherapy compared with fiberoptic phototherapy or conventional phototherapy. Outcome: Effectiveness in terms of the mean decrease in bilirubin levels and the mean duration of phototherapy. Extra outcomes should include adverse effects, parental bonding and parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

- fibreoptic phototherapy using large pads compared to conventional phototherapy in term babies with hyperbilirubinaemia?

Why this is important.
Existing research has demonstrated the effectiveness of fiberoptic phototherapy in pre-term babies but not in term babies. This is due to that fact that existing fiberoptic pads are small and cannot ensure adequate skin coverage in larger babies. New devices using larger pads may be effective in term babies. New randomized controlled trials are needed to examine fiberoptic phototherapy which uses larger pads. Population: Term babies with hyperbilirubinaemia in the first 28 days of life. Interventions: Fiberoptic phototherapy with larger pads compared with conventional phototherapy. Outcome: Effectiveness in terms of mean decrease in bilirubin levels and mean duration of phototherapy. Extra outcomes should include adverse effects, family adjustment, breastfeeding effects, parental bonding and anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

Other interventions (7.1? do not do)

What is the effectiveness, cost-effectiveness and safety of Clofibrate alongside phototherapy versus phototherapy alone for non-haemolytic hyperbilirubinaemia?

Why this is important.
Existing research has demonstrated that Clofibrate in combination with phototherapy can shorten time spent undergoing phototherapy. This can help minimise the disruption to breast-feeding and mother-baby bonding. However no studies have been carried out in a UK population. New placebo-controlled double-blind randomized controlled trials in a UK population are needed. Population: Term and pre-term babies with hyperbilirubinaemia in the first 28 days of life. Interventions: Clofibrate (a single 100mg/kg dose) combined with phototherapy versus phototherapy with a placebo phototherapy. Outcome: Effectiveness in terms of mean decrease in bilirubin levels and mean duration of phototherapy. Extra outcomes should include adverse effects, parental bonding and parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

What is the clinical and cost-effectiveness of IVIG used to prevent exchange transfusion in newborns with haemolytic disease due to ABO incompatibility and rising bilirubin?

Why this is important.
Existing research has demonstrated that IVIG is effective in reducing the need for an exchange transfusion in one in two hyperbilirubinaemic babies with rhesus haemolysis. The

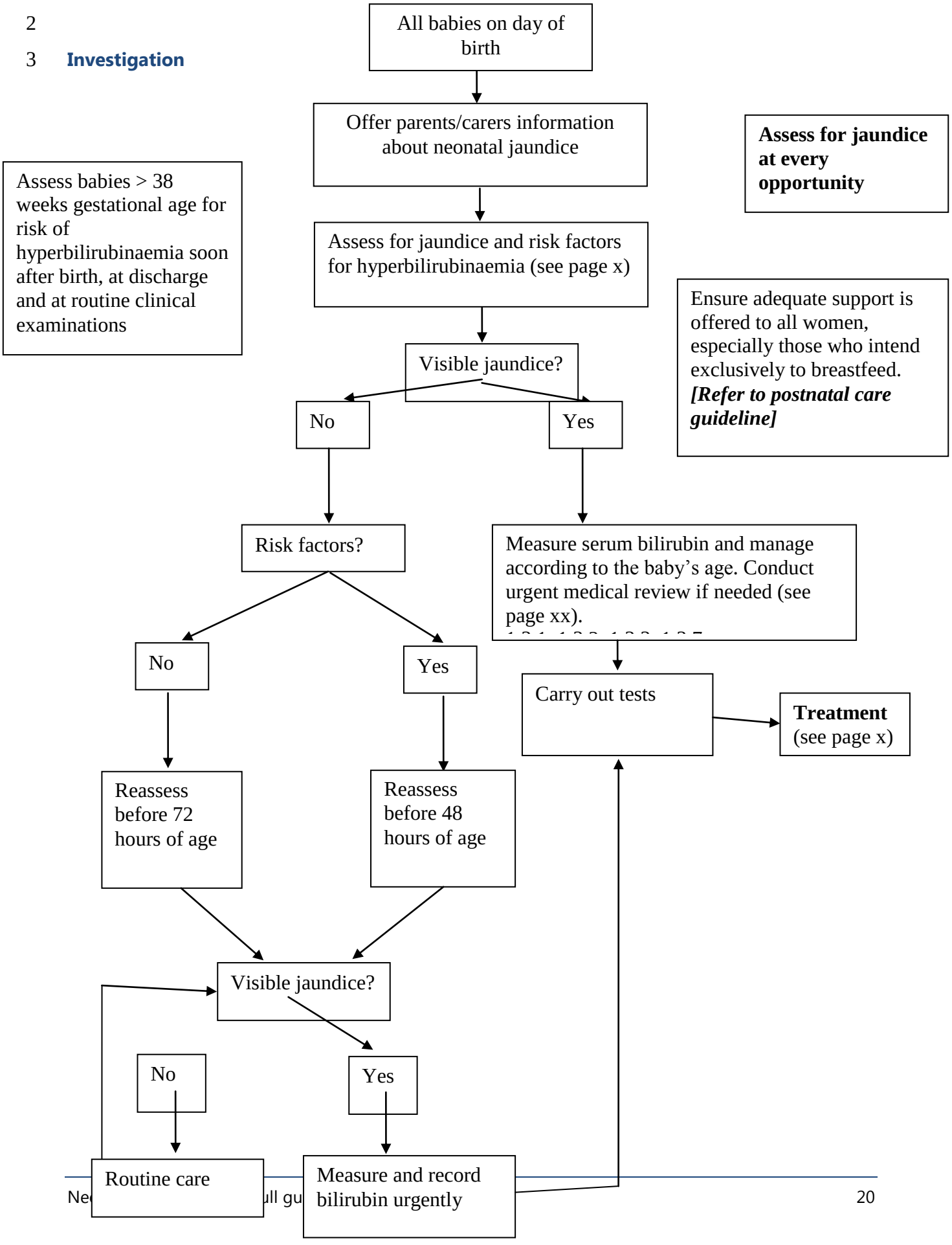
	evidence is less convincing in hyperbilirubinaemic babies with ABO haemolysis. New placebo-controlled double-blind randomized controlled trials are needed to examine if IVIG is effective in sub-groups of babies with ABO haemolysis, ie pre-term babies, babies with bilirubin rising greater than 10 mincromol/L/hr or babies with co-morbid illness such as infections.. Population: Term and pre-term babies with hyperbilirubinaemia in the first 28 days of life. Interventions: IVIG (500mg/kg) alongside phototherapy versus phototherapy alone. Outcome: Number of exchange transfusions needed. Extra outcomes should include adverse effects, mean duration of phototherapy, parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

1

1 **Working draft to be updated**

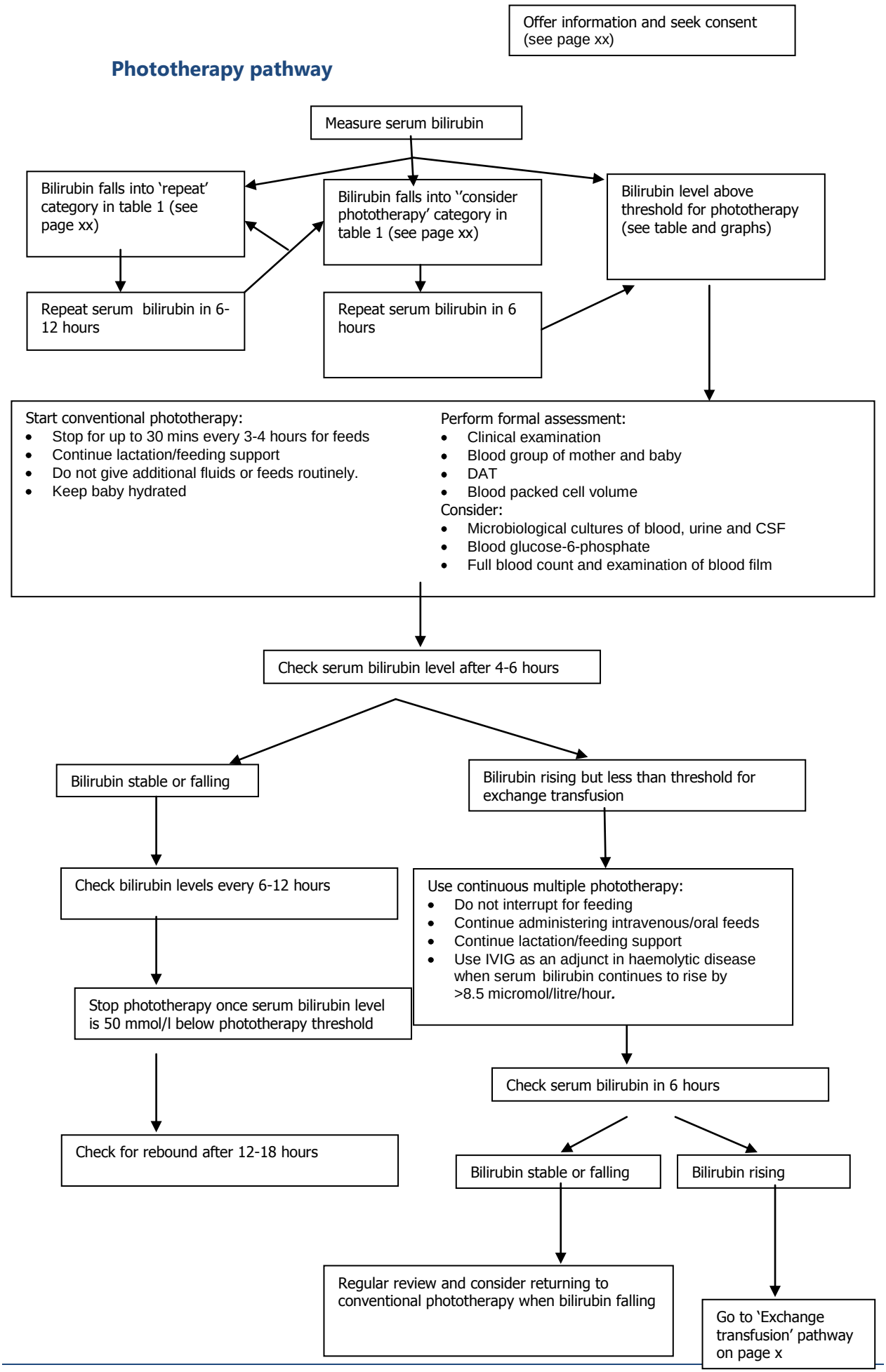
2

3 **Investigation**

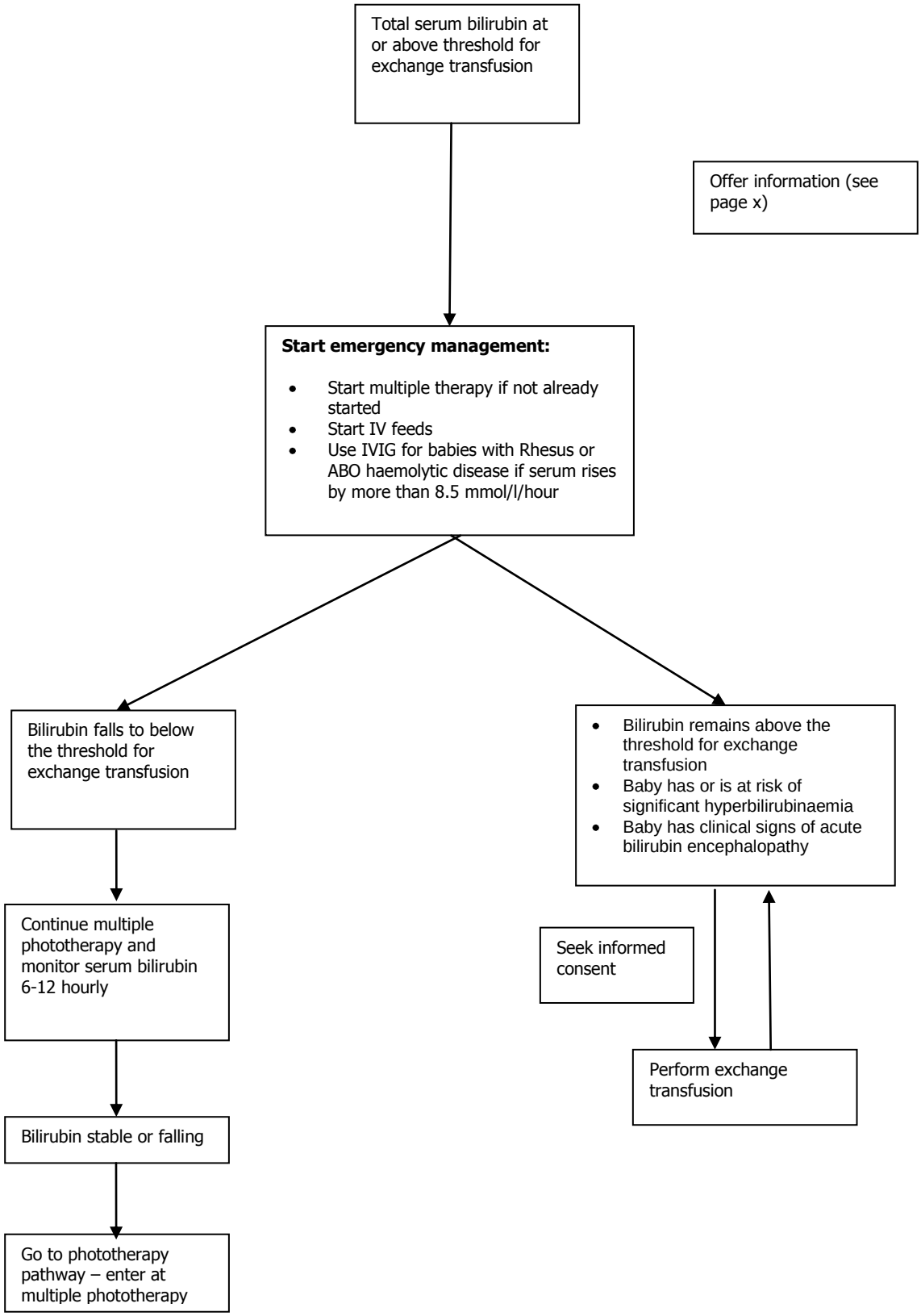


1

Phototherapy pathway



1 Exchange transfusion pathway



2 Introduction

2.1 Neonatal jaundice

Jaundice is one of the most common conditions requiring medical attention in newborn babies. Approximately 60% of term and 80% of preterm babies develop jaundice in the first week of life, and about 10% of breast fed babies are still jaundiced at one month of age. In most babies with jaundice there is no underlying disease, and this early jaundice (termed 'physiological jaundice') is generally harmless. However, there are pathological causes of jaundice in the newborn, which although rare, need to be detected. Such pathological jaundice may co-exist with physiological jaundice.

Neonatal jaundice refers to yellow colouration of the skin and the sclerae of newborn babies that result from accumulation of bilirubin in the skin and mucous membranes. This is associated with a raised level of bilirubin in the circulation, a condition known as hyperbilirubinaemia.

Bilirubin

Bilirubin is a breakdown product of the red cells in the blood. Red cell breakdown produces unconjugated (or 'indirect') bilirubin, which is mostly bound to albumin. Unconjugated bilirubin is metabolised in the liver to produce conjugated (or 'direct') bilirubin, which then passes through the gut and is excreted in the stool. Bilirubin can be reabsorbed again from stools remaining in the gut.

Newborn babies have more circulating red cells, and a shorter red cell lifespan than adults, so bilirubin levels are higher than they are later in life. The metabolism circulation and excretion of bilirubin is also slower than in adults. Thus a degree of hyperbilirubinaemia occurring as a result of this normal physiological mechanism is common in newborn babies and usually benign. It is difficult to tell which babies are at risk of developing high levels of bilirubin which could become dangerous, or who have a serious problem as the explanation for their jaundice, which is why this guideline has been developed.

Physiological jaundice

Breast fed babies are more likely than bottle-fed babies to develop physiological jaundice within the first week of life, but the appearance of jaundice is not a reason to stop breastfeeding. Physiological jaundice refers to the common, generally harmless, jaundice seen in many newborn babies in the first weeks of life and to which there is no underlying cause other than the usual post birth adaptation. The reasons for the association between breastfeeding and neonatal jaundice have not yet been fully elucidated, but may include inadequate breastfeeding support leading to a reduced intake, sluggish gut action leading to an increase in the entero-hepatic circulation of bilirubin or unidentified factors in breast milk. Finally, it may be that this is a relative reduction of bilirubin levels in formula fed babies due to increased clearance of bilirubin from the gut. Current NHS practice of early postnatal discharge, often within 24 hours, also reduces the opportunity to assess that successful lactation has been established and to provide adequate breastfeeding support and advice. Existing guidelines including 'Routine postnatal care of women and their babies', NICE clinical guideline 37 (2006)' (www.nice.org.uk/CG37), deal with breastfeeding and lactation/feeding support so this guideline has been referred to where-ever appropriate.

Prolonged jaundice

Prolonged jaundice, that is jaundice persisting beyond the first 14 days, is also seen more commonly in these infants. The mechanism for this 'breast milk jaundice syndrome' is still not completely understood and the condition appears to be generally harmless. However prolonged jaundice can be a clue to serious underlying liver disease and should be assessed carefully.

Causes of pathological jaundice

Jaundice may also have other, non-physiological, causes, including blood group incompatibility (most commonly rhesus or ABO incompatibility), other causes of haemolysis, sepsis, bruising and metabolic disorders. Gilbert's and Crigler–Najjar syndromes are rare causes of neonatal jaundice and are caused by leiver enzyme problems. Deficiency of a particular enzyme, glucose-6-phosphate-dehydrogenase (G-6-PD), can cause severe neonatal jaundice. G-6-PD deficiency is more common in certain ethnic groups and is familial. Congenital obstruction and malformations of the biliary system, such as biliary atresia, cause an obstructive jaundice with conjugated hyperbilirubinaemia. This condition needs specialist investigation and early surgical treatment, preferably before 8 weeks of life.

Bilirubin encephalopathy and kernicterus

In young babies, unconjugated bilirubin can penetrate the membrane that lies between the brain and the blood (the blood-brain barrier). Unconjugated bilirubin is potentially toxic to neural tissue (brain and spinal cord). Entry of unconjugated bilirubin into the brain can cause both short-term and long-term neurological dysfunction. Acute features include lethargy, irritability, abnormal muscle tone and posture, temporary cessation of breathing (apnoea) and convulsions. This presentation is known as acute bilirubin encephalopathy. Bilirubin is deposited particularly in a part of the brain known as the basal ganglia, part of the 'deep grey matter' of the brain. On pathological examination of the brain, this produces yellow staining; this staining is referred to as 'kernicterus'. The term kernicterus is also used to denote the clinical features of acute or chronic bilirubin encephalopathy. Features of the latter include athetoid cerebral palsy, hearing loss, visual and dental problems. The exact level of bilirubin that is likely to cause neurotoxicity in any individual baby varies, and depends on the interplay of multiple factors which probably include acidosis, gestational and postnatal age, rate of rise of serum bilirubin, serum albumin concentration, and concurrent illness (including infection).

Although neonatal jaundice is very common, kernicterus is very rare. There is a poor correlation between levels of circulating bilirubin and the occurrence of bilirubin encephalopathy. There seems to be tremendous variability in susceptibility towards bilirubin encephalopathy among newborns for a variety of unexplained reasons. However, there are certain factors that probably influence the passage of bilirubin into the brain and hence increase the risk of acute bilirubin encephalopathy. These include prematurity, sepsis, hypoxia, seizures, acidosis and hypoalbuminaemia. The rate of rise of the level of bilirubin is probably important, hence the increased risk of kernicterus in babies with haemolytic disease such as G-6-PD deficiency, ABO or rhesus haemolytic disease.

Kernicterus in healthy term babies with none of the above factors is virtually unknown below a serum bilirubin concentration of 450 micromoles of bilirubin per litre (micromol/L), but the incidence increases above this threshold level and the risk of kernicterus is greatly increased in full term babies with bilirubin levels above 515 micromol/L. Kernicterus is also known to occur at lower levels of bilirubin in term babies who have any of the factors described above.

Treatment of jaundice

Levels of bilirubin can be controlled by placing the baby under a lamp emitting light in the blue spectrum known as phototherapy. Light energy of the appropriate wavelength converts the bilirubin in the skin to a harmless form that can be excreted in the urine. Phototherapy has proved to be a safe and effective treatment for jaundice in newborn babies, reducing the need to perform an exchange transfusion of blood (the only other means of removing bilirubin from the body).

Clinical recognition and assessment of jaundice can be difficult. This is particularly so in babies with darker skin. Once jaundice is recognised, there is uncertainty about when to treat. Currently there is widespread variation in the use of phototherapy, exchange transfusion and other treatments. There is a need for more uniform, evidence-based practice and for consensus-based practice where such evidence is lacking, hence the importance of this guideline.

2.2 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'[1]. This clinical guideline concerns the management of neonatal jaundice in babies from birth up to 28 days of age.

This guideline has been developed with the aim of providing guidance on:

- Recognition and assessment
- Prediction of later significant hyperbilirubinaemia and adverse sequelae
- Treatment
- Information and education for parents/carers of babies with jaundice

2.3 Areas outside the remit of the guideline

- Primary prevention of jaundice;
- Jaundice that requires surgical treatment to correct the underlying cause;
- Management of babies with conjugated hyperbilirubinaemia, although we consider the importance of identifying conjugated hyperbilirubinaemia.

2.4 Related NICE guidance

- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63 (2008). Available from www.nice.org.uk/CG63
- Antenatal care: routine care for the healthy pregnant woman. NICE clinical guideline 62 (2008). Available from www.nice.org.uk/CG62
- Intrapartum care: care of healthy women and their babies during childbirth. NICE clinical guideline 55 (2007). Available from www.nice.org.uk/CG55
- Routine postnatal care of women and their babies. NICE clinical guideline 37 (2006). Available from www.nice.org.uk/CG37

2.5 Guideline methodology

This guideline was developed in accordance with the NICE guideline development process outlined in the 2005 and 2009 editions of the Guidelines technical manual (http://www.nice.org.uk/guidelinesmanual). Table 2.1 summarises the key stages of the guideline development process and which version of the process was followed for each stage.

Table 2.1 Stages in the NICE guideline development process and the guideline versions followed at each stage

Stage	2005	2007	2009
Scoping the guideline (determining what the guideline would and would not cover)	✓		
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution etc)	✓		
Forming and running the guideline development group	✓		
Developing clinical questions	✓		
Identifying the evidence	✓		
Reviewing and grading the evidence	✓		
Incorporating health economics		✓	
Making group decisions and reaching consensus		✓	
Linking guidance to other NICE guidance		✓	

Stage	2005	2007	2009
Creating guideline recommendations		✓	
Developing clinical audit criteria			
Writing the guideline	✓	✓	
Validation (stakeholder consultation on the draft guideline)		✓	✓
Pre-publication check			✓
Internal validity check			✓
Declaration of interests	✓	✓	✓

Literature search strategy

Initial scoping searches were executed to identify relevant guidelines (local, national and international) produced by other development groups. The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Relevant published evidence to inform the guideline development process and answer the clinical questions was identified by systematic search strategies. The questions are presented in Appendix A.

Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases via the 'Ovid' platform: Medline (1966 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (1982 onwards), and PsycINFO (1967 onwards). The most recent search conducted for the three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects) was Quarter 2, 2009. Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluations Database (NHS EED).

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were not applied to searches, although publications in languages other than English were not appraised. Both generic and specially developed methodological search filters were used appropriately.

There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the databases was not undertaken.

Towards the end of the guideline development process searches were updated and re-executed, thereby including evidence published and included in the databases up to June 2009. Studies identified after this date could only be included if they were specifically requested during the consultation process. Evidence published after this date has not been included in the guideline. This date should be considered the starting point for searching for new evidence for future updates to this guideline.

Further details of the search strategies, including the methodological filters employed are presented in Appendix [x see content page for details].

Appraisal and synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[2-6] and classified using the established hierarchical system presented in Table 2.2 (http://www.nice.org.uk/guidelinesmanual). This system reflects the susceptibility to bias that is inherent in particular study designs.

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of the evidence, each study receives a quality rating coded as '++', '+' or '-'. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs; EL=1++) or an individual RCT (EL=1+). Studies of poor quality are rated as '-'. Usually, studies rated as '-' should not be used as a basis for making a recommendation, but they can be used to

inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study (EL=2). A level of evidence was assigned to each study, and to the body of evidence for each question.

Table 2.2 Levels of evidence for intervention studies

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding , bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example, if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy (accuracy) of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity and positive and negative predictive values (PPVs and NPVs) were calculated or quoted where possible (see Table 2.3).

Table 2.3 '2 × 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Test positive	a (true positive)	b (false positive)	a+b
Test negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d = N (total number of tests in study)

Sensitivity = a/(a+c), specificity = d/(b+d), PPV = a/(a+b), NPV = d/(c+d)

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting accuracy of diagnostic tests. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy of evidence that takes into account the various factors likely to affect the validity of these studies (see Table 2.4).[7]

Table 2.4 Levels of evidence for studies of the accuracy of diagnostic tests

Level	Type of evidence
Ia	Systematic review (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]; systematic reviews of level-2 studies
III	Level-3 studies[d]; systematic reviews of level-3 studies

IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are minor or no variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] Level-1 studies are studies that use a blind comparison of the test with a validated reference standard ('gold' standard) in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have only one of the following:

- narrow population (the sample does not reflect the population to whom the test would apply)
- use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- the comparison between the test and reference standard is not blind
- case–control studies.

[d] Level-3 studies are studies that have at least two or three of the features listed above.

Clinical evidence for individual studies was extracted into evidence tables (see Appendix C) and where possible quantitative synthesis (meta-analysis) was carried out. If no meta-analysis was possible a brief summary of each study was included in the guideline text. If an analysis has been carried out the results may be presented pictorially (i.e. forest plots, summary ROC curves) as well as in the text. If no meta-analysis has been carried out the results from each included study will be reported in the text and where appropriate in summary tables. The body of evidence identified for each clinical question was synthesised qualitatively or quantitatively in clinical evidence statements that accurately reflected the evidence.

Lists of excluded studies for each clinical question are presented in Appendix E.

Specific considerations for this guideline

For this guideline, the effectiveness of interventions has been assessed against the following outcome domains:

- Serum bilirubin concentrations (change from baseline)
- Duration of treatment
- Treatment failure
- Adverse effects
- Mortality

If bilirubin concentrations were presented as mg/dl these were converted to systems international (SI) units in micromol/L by multiplying by 17.1

Where data were missing, typically standard deviations of change scores, these were imputed using a standard formula as recommended in section 16.1.3.2 of the Cochrane Handbook (www.cochrane-handbook.org/)

$$SD_{E,change} = \sqrt{SD^2_{E,baseline} + SD^2_{E,final} - \left(2 \times Corr \times SD_{E,baseline} \times SD_{E,final}\right)}$$

Instead of calculating a correlation coefficient for each individual study, it was decided to use a correlation of 0.80 as an arbitrary cut-off value.

The number needed to treat (NNT) was calculated with the following formula

Table 1.5 '2 x 2' table for calculation of number needed to treat (NNT)

	Outcome present	Outcome absent
Treated	A	C
Control	B	D

NNT = 1 / (A/A+B)-(C/C+D)

Health economics

The aim of the economic input in this guideline was to inform the GDG of potential economic issues relating to neonatal jaundice, and to ensure that recommendations represented a cost-effective use of scarce resources.

The GDG sought to identify relevant economic evidence for this guideline, but no published evidence was identified that fully answered the guideline questions. Had any such evidence been identified it would have been assessed using a quality assessment checklist based on good practice in decision-analytic modelling (because no standard system of grading the quality of economic evaluations exists).

Where it is not possible to make recommendations based on published economic evidence, the guideline health economist may undertake de novo economic analysis. Health economic analysis may be required for a clinical question where there are genuine competing alternatives for decision makers which may have implications for health care resources and patient outcomes. Cost effectiveness analysis can provide clarity as to which alternative is currently the best option for the NHS.

After GDG discussion of the clinical questions it became apparent that economic analysis would not actually influence the recommendations as originally expected since genuine alternatives to current practice did not practically exist in the NHS. For example, 'no treatment' would not be considered as a serious alternative to phototherapy or exchange transfusion in any modern health care system.

Therefore, the remaining area where health economics was thought to be important in guiding recommendations was around testing for hyperbilirubinaemia. The results of the economic analysis are summarised briefly in the guideline text, and a more detailed description of the methods is presented in Appendix [x to be added – see content page] and in the section on Cost-effectiveness on page 131.

GDG interpretation of the evidence and formulation of recommendations

For each clinical question, recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree clinical evidence statements. Statements summarising the GDG's interpretation of the clinical and economic evidence and any extrapolation (including economic modelling) from the evidence used to form recommendations were also prepared. In areas where no substantial evidence was identified, the GDG considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The GDG also identified areas where evidence to answer their clinical questions was lacking and used this information to draft recommendations for future research.

Towards the end of the guideline development process formal consensus methods were used to consider all the clinical care recommendations that had been drafted previously. Consensus was again used to agree the wording of recommendations. All recommendations for which at least one GDG member indicated any level of disagreement were discussed at a subsequent GDG meeting, and the final wording was agreed following discussion of the relevant issues.

The GDG identified key priorities for implementation which were those recommendations expected to have the biggest impact on patients' care and patients' outcomes in the NHS as a whole. Each GDG member submitted a paper form indicating their top 10 recommendations in order of priority. The GDG members' votes were collated and priority recommendations were obtained by including all recommendations that had been voted for by at least four GDG members in order of popularity.

Stakeholder involvement in the guideline development process

Registered stakeholder organisations were invited to comment on the draft scope of the guideline and the draft guideline. Stakeholder organisations were also invited to undertake a pre-publication check of the final guideline to identify factual inaccuracies. The GDG carefully

considered and responded to all comments received from stakeholder organisations. The comments and responses, which were reviewed independently for NICE by a Guidelines Review Panel, are published on the NICE website.

3 Risk factors

Introduction

Some disorders cause red cells to be more fragile than normal, and break down more easily (haemolysis), and this process can add significantly to the bilirubin load. Some of these disorders are inherited. Other problems include increased destruction of red cells by circulating antibodies directed against them. Historically rhesus haemolytic disease (involving rhesus blood group antibodies) was a major cause of kernicterus, but thanks to effective prevention and treatment of rhesus incompatibility, other causes of haemolysis, such as ABO incompatibility, have assumed increasing importance. Large areas of bruising with extravasated and damaged red blood cells can also contribute to the bilirubin load requiring clearance by the liver. For reasons which are not understood, babies who are breastfed have higher bilirubin levels than those who are 'formula' fed.

This chapter examines the evidence for and against the factors which have been suggested as candidates for identifying babies at higher risk of developing significant hyperbilirubinaemia, and therefore kernicterus

Clinical question
What are the factors associated with an increased risk of hyperbilirubinaemia? Which factors affect the relationship between neonatal hyperbilirubinaemia and kernicterus or other adverse outcomes (neurodevelopmental, auditory)?

A common literature search was conducted for both the sub-questions and 1865 abstracts and titles were identified from the electronic databases. After primary screening, hard copies of 98 articles were retrieved. There were large numbers of studies which had evaluated the association between various demographic, maternal and neonatal factors with increased or decreased risk of hyperbilirubinaemia, but most did not control for confounding variables and were therefore excluded. For the second sub-question, few good quality studies were identified.

This review includes 16 studies; 10 studies evaluating the risk factors for development of hyperbilirubinaemia and 3 studies each for the risk factors of kernicterus and adverse sequelae.

3.1 Risk factors for hyperbilirubinaemia

Description of included studies

Of the ten studies included under this section, eight are from the USA. Except for one cross-sectional survey, all studies are comparative observational studies, all of EL II. The results of all comparative studies on risk factors have been tabulated in Table 3.1.

Review findings

A nested case-control study was carried out at 11 hospitals of a health maintenance organization in the USA[8] to investigate predictors of hyperbilirubinaemia and evaluate the predictive accuracy of a risk index model. The cohort consisted of 51,387 babies with birth weight (BW) ≥ 2,000 grams and GA ≥ 36 weeks born at these hospitals during a two year period. Babies with peak serum bilirubin levels ≥ 427 micromol/L within the first 30 days after birth were defined as cases (N = 73), while controls were a random sample of babies from the cohort with maximum serum bilirubin levels below this level (N = 423). Information on the risk factors was collected by reviewing hospital records and interviewing parents.

Using bivariate analysis, various clinical and demographic factors were found to be associated with an increased risk of hyperbilirubinaemia. They included maternal factors such as race, maternal age, history of jaundice in a previous sibling or vacuum delivery. Neonatal factors include male sex, lower GA, early jaundice (defined either as bilirubin levels exceeding age specific phototherapy thresholds, or phototherapy during birth hospitalization, or jaundice noted in first 20 hours and bilirubin levels were not taken within 6 hours of that time), cephalohaematoma, bruising, exclusively breast fed at time of discharge. These factors were then entered into multiple regression analysis to find independent predictors of hyperbilirubinaemia. When all cases were included, the presence of early jaundice (adjusted Odds Ratio (OR) 7.3; 95% CI 2.8 to 19.0), GA (in weeks) at birth (adjusted OR 0.6; 95% CI 0.4 to 0.7), exclusive breastfeeding at discharge (adjusted OR 6.9; 95% CI 2.7 to 17.5), Asian race (adjusted OR 3.1; 95% CI 1.5 to 6.3), the presence of bruising (adjusted OR 3.5; 95% CI 1.7 to 7.4) , cephalohaematoma (adjusted OR 3.2; 95% CI 1.1 to 9.2), and maternal age ≥ 25 yrs (adjusted OR 2.6; 95% CI 1.1 to 9.2) were all independently associated with hyperbilirubinaemia. When cases with early jaundice were excluded, the results were similar except that family history of jaundice showed evidence of statistically significant association with later hyperbilirubinaemia (adjusted OR 6.0; 95% CI 1.0 to 36.0). [EL II]

The above study was expanded[9] in order to examine the association between jaundice noted in the first 24 hours of life and the risk of later hyperbilirubinaemia and the need for phototherapy. This study included babies born during a period of four years (compared to two years in the first study[8]) and the baseline cohort population included 105,384 newborn babies. The criteria for study selection and definitions of cases (N = 140) and controls (N = 631) were unchanged. Information on the timing of the appearance of jaundice was extracted by medical records analysts and this process was reliably assessed by a second analyst blindly re-abstracting data from a random sample of 25 medical records (kappa statistic for agreement = 0.75). Data on the use of phototherapy and development of hyperbilirubinaemia (maximum serum bilirubin levels ≥ 427 micromol/L) were also obtained from hospital records. Among the controls, the cumulative probability of jaundice being noticed within 18 hours of birth was 2.8% and within 24 hours of birth it was 6.7% (these proportions were estimated using Kaplan-Meier survival analysis after correcting for age of discharge). On adding the number of newborns who had serum bilirubin measured within 24 hours (as a proxy measure of jaundice noticed in first 24 hours), to the above data the proportions increased to 3.8% by 18 hours and 7.9% at 24 hours. There was no statistically significant association between jaundice noticed within 24 hours and risk factors such as ethnicity, sex, gestational age, breastfeeding, or cephalohaematoma. Although most of the babies did not require any intervention, these babies were 10 times more likely to be treated with phototherapy compared to newborns noted not to have jaundice in the first 24 hours (18.9% vs. 1.7%; Mantel Haenszel OR 10.1, 95% CI 4.2 to 24.4). Moreover the early jaundiced babies were found to have a statistically significant increase in the risk of developing hyperbilirubinaemia > 427 micromol/L (14.3% vs. 5.9%; Mantel Haenszel OR 2.9, 95% CI 1.6 to 5.2). [EL II]

Another nested case control study from the USA[10] estimated the effect of phototherapy and other factors on the risk of developing severe hyperbilirubinaemia (defined as serum bilirubin levels ≥ 427 micromol/L) in babies who had serum bilirubin levels close to the American Academy of Pediatrics (AAP) phototherapy threshold levels [11]. The cohort included 285,295 babies with GA ≥ 34 weeks and BW ≥2000 grams born between 1995 and 2004 in a health maintenance organization. Babies with resolving jaundice, those whose serum bilirubin levels were not fully documented, and those with conjugated bilirubin level ≥ 34 micromol/L were excluded. A subset of babies (N = 13,843) with a serum bilirubin level between 291 and 392 micromol/L at ≥ 48 hours of age was identified. Babies with serum bilirubin concentration ≥ 427 micromol/L were selected as cases (N = 62), and four controls were selected randomly for each case (N = 248). Cases and controls were matched for risk status (low, medium and high risk based on the hour-specific bilirubin centiles, gestational age and DAT tests results) and the difference between their serum bilirubin levels and the AAP phototherapy threshold levels. Data on all variables were extracted from electronic and paper records of admissions, outpatient visits, and home health visits. The cases and controls did not differ significantly by sex, race, birth weight or duration of hospitalization. Moreover the two groups had similar

mean serum bilirubin levels and percentage weight loss from birth. Bivariate analysis showed that lower gestational age, bruising on examination, serum bilirubin concentration between 291 and 392 micromol/L occurring during birth hospitalization, serum bilirubin increase of ≥ 102 micromol/L/day, and exclusive breast feeding (after serum bilirubin levels) were significantly associated with an increased risk of hyperbilirubinaemia ($p < 0.04$), while inpatient phototherapy was found to significantly lower the risk. Multivariate analysis revealed that the strongest predictors of increased risk of severe hyperbilirubinaemia were lower gestational age (adjusted OR 3.1, 95% CI 1.2 to 8.0 for 38 to 39 wks and adjusted OR 3.7, 95% CI 0.6 to 22.7 for 34 to 37 weeks compared to 40+ weeks as the reference), bruising on examination (adjusted OR 2.4, 95% CI 1.2 to 4.8), serum bilirubin increase of ≥ 102 micromol/L/day (adjusted OR 2.5, 95% CI 1.2 to 5.5) and exclusive breast feeding after reaching the qualifying serum bilirubin levels (adjusted OR 2.0, 95% CI 1.03 to 4.0). It was also reported that male sex, race, and the mode of feeding before the bilirubin level did not predict severe hyperbilirubinaemia. [EL II]

In a retrospective cohort study conducted in a community teaching hospital in the USA[12], a clinical risk factor score was developed and its predictive accuracy was compared to pre-discharge serum bilirubin measurements plotted on the bilirubin nomogram. The study population included babies with BW ≥ 2000 grams (if GA ≥ 36 weeks) and BW ≥ 2500 grams (if GA ≥ 35 weeks) who participated in the hospital's early discharge programme and who had both pre and post-discharge serum bilirubin measured. Hyperbilirubinaemia was taken as post-discharge serum bilirubin level > 95th centile on the nomogram. Hospital records were reviewed retrospectively to collect information on various risk factors (baby, maternal, pregnancy and delivery factors) and their association with hyperbilirubinaemia was explored by univariate analysis. All factors found to be associated with the outcome at $p < 0.2$ level of significance were considered for the final risk factor score based on logistic regression modelling. For univariate analysis, the baby factors found to be associated with an increased risk of hyperbilirubinaemia (at $p < 0.2$ level of significance) included GA < 38 weeks and ≥ 40 weeks, large for gestational age (LGA), high pre-discharge serum bilirubin and higher birth weight; the maternal factors included maternal diabetes, breast feeding and combined breast and bottle feeding; the pregnancy, labour and delivery factors included vacuum extraction, prolonged rupture of membranes and oxytocin use. Three factors were found to be associated with decreased risk of hyperbilirubinaemia; small for gestational age (SGA), parity and caesarean section. All these factors were then analyzed for the final risk factor model using step-wise logistic regression, except for pre-discharge serum bilirubin level/risk zone which was analyzed separately. Results from the regression analysis showed the following factors to be significantly associated with hyperbilirubinaemia – GA < 38 wks (adjusted OR 2.6, 95% CI 1.5 to 4.5), oxytocin use during labour (adjusted OR 2.0, 95% CI 1.2 to 3.4), vacuum delivery (adjusted OR 2.2, 95% CI 1.5 to 3.6), exclusive breastfeeding (adjusted OR 2.6, 95% CI 1.5 to 4.5), combination of breast and bottle feeding (adjusted OR 2.3, 95% CI 1.1 to 4.9), and birth weight (for every 0.5 kg increase above 2.5 kg – adjusted OR 1.5, 95% CI 1.2 to 1.9). The predictive accuracy of pre-discharge serum bilirubin level/risk zone was evaluated separately from the risk factor model, and it was shown to predict hyperbilirubinaemia more accurately than the risk factor model alone. [EL II]

A prospective cohort study from Israel[13] evaluated the ability of prenatal and intrapartum characteristics and early serum bilirubin measurements to predict hyperbilirubinaemia in healthy term babies. The study included 1,177 babies (≥ 37 weeks gestation). Babies with either blood group incompatibility with a positive direct DAT or G6PD deficiency were excluded. Serum bilirubin levels were obtained within the first 8 to 24 hours of life and repeated daily for the next 4 days. In all, 5.1% (60 of 1,177) of babies developed hyperbilirubinaemia (defined as serum bilirubin level > 171 micromol/L at day 2, > 239 micromol/L at day 3, and > 291 micromol/L at day 4-5. Using multiple logistic regression analysis serum bilirubin level > 85 micromol/L on 'day 1' per 17 micromol/L on 'day 1' and change in serum bilirubin from 'day 1' to 'day 2' per 17 micromol/L were found to have a significant association with hyperbilirubinaemia with adjusted OR = 36.5, 95% CI 15.9 to 83.6, adjusted OR = 3.1, 95% CI 2.4 to 4.1, and adjusted OR = 2.4, 95% CI 1.9 to 3.0 respectively. Other factors found to be associated with hyperbilirubinaemia were maternal blood group O (adjusted OR 2.9, 95% CI 1.5 to 5.8), maternal age per year (adjusted OR 1.1, 95% 1.0 to 1.2),

maternal education per year (adjusted OR 0.8, 95% CI 0.7 to 0.9), and exclusive breastfeeding (adjusted OR 0.4, 95% CI 0.2 to 0.9). [EL II]

Another prospective cohort study from the USA[14] aimed to evaluate the predictive accuracy of clinical risk factors, pre-discharge bilirubin levels expressed as risk zones, and a combination of pre-discharge bilirubin levels and additional risk factors. The study population comprised babies managed exclusively in the well baby nursery of an urban tertiary care hospital. Since the population served by the hospital was predominantly black, stratified sampling was used to obtain a representative sample. The study included 812 term and near-term healthy newborns managed exclusively in the well baby nursery with GA ≥36 weeks and BW ≥ 2,000 grams, or GA ≥ 35 weeks and BW ≥ 2,500 g. About 7% babies were lost to follow-up and of the remaining babies, 6.4% (48 of 751) developed significant hyperbilirubinaemia (Day 3-5 serum bilirubin or transcutaneous bilirubin levels exceeding or within 17 micromol/L of the hour-specific phototherapy treatment thresholds recommended by the AAP). Using univariate analysis, the factors which were statistically associated with the development of significant hyperbilirubinaemia (at $p < 0.05$) were pre-discharge bilirubin in the high and high-intermediate risk zones, GA < 38 weeks, mother's intention to breastfeed, either exclusively or combined with bottle feeds, grade 4 or higher jaundice observed clinically as per Kramer scale (only for non-black babies), vacuum delivery and female sex. When all these factors were added in a step-wise logistic regression model (except the pre-discharge bilirubin risk zones), only five factors were found to be independently associated with significant hyperbilirubinaemia; GA < 38 weeks (OR 19, 95% CI 6.3 to 56), mother's intention exclusively to breastfeed (OR 3.7, 95% CI 1.1 to 13), black race (OR 0.22, 95% CI 0.08 to 0.61), grade 4 or higher jaundice observed clinically (OR 1.7, 95% CI 1.2 to 2.6), and female sex (OR 3.2, 95% CI 1.2 to 8.4). [EL II]

In another nested case-control study from Israel[15], data were collected retrospectively from the charts of 10,122 term singleton babies born at a tertiary hospital over a 4 year period. Bilirubin levels were routinely measured in all clinically jaundiced newborns and all mothers were interviewed within 48 hours of delivery. A total of 1,154 term babies (11.4%) who developed serum bilirubin levels ≥ 221 micromol/L constituted the test group, while from the remainder, every tenth admission with serum bilirubin levels < 221 micromol/L was randomly selected as the comparison group (N = 1,154). Univariate analysis was done to compare the two groups and it showed high serum bilirubin levels to be significantly associated with a number of maternal, baby and delivery variables. These variables were then included in a stepwise logistic regression analysis and the final model revealed six factors to be independently associated with development of high serum bilirubin levels. These factors were maternal age more than 35 years (adjusted OR 1.7, 95% CI 1.3 to 2.3), male sex (adjusted OR 1.4, 95% CI 1.2 to 1.7), primiparity (adjusted OR 2.7, 95% CI 2.1 to 3.5), previous sibling with jaundice (adjusted OR 2.3, 95% CI 1.9 to 2.8), early gestation (for 37 weeks adjusted OR 4.5, 95% CI 3.2 to 6.3; for 38 weeks adjusted OR 2.1, 95% CI 1.6 to 2.8), and vacuum extraction (adjusted OR 3.0, 95% CI 2.1 to 4.4). [EL II]

In a retrospective study from the USA[16], the risk of recurrence of hyperbilirubinaemia in siblings was studied in 3,301 offspring of 1,669 male US Army veterans participating in a nationwide study of veterans' health. Babies who had a different mother's name from the rest of the sibling relationship (paternal half siblings), stillbirths, and babies with records showing evidence of haemolytic disease of newborns were excluded. In case of a twin delivery (N = 34), only one baby was randomly included for the study. Birth details of each baby were obtained by interviews and detailed information extracted from hospital medical records by trained staff. Hyperbilirubinaemia (defined as peak serum bilirubin levels ≥ 205 micromol/L) was present in 4.5% of the babies (147/3,301). Newborns who had one or more prior sibling with hyperbilirubinaemia showed a threefold risk of developing hyperbilirubinaemia compared to those who had prior sibling without hyperbilirubinaemia (10.3% vs. 3.6%; OR 3.1, 95% CI 1.4 to 6.8). In the next stage of analysis, potential confounding factors (race, sex, GA, maternal age, year of birth, delivery type, gravidity, breastfeeding, obstetric anaesthesia and neonatal asphyxia) were adjusted in a logistic regression analysis and the risk of recurrence assessed for different degrees of jaundice – mild (peak serum bilirubin levels ≤ 205 micromol/L), moderate (205 to 256 micromol/L) and severe hyperbilirubinaemia (≥ 256

micromol/L). The results showed a clear trend of increasing sibling risk with increasing severity of hyperbilirubinaemia. There was a 2.7 times higher risk of mild jaundice in newborns who had a prior sibling with mild jaundice (25.3% vs. 11.1%; OR 2.7, 95% CI 1.8 to 4.1), and the risk was 4 times greater for the moderate jaundice group (8.8% vs. 2.3%; OR 4.1, 95% CI 1.5 to 10.8). Babies who had a prior sibling with severe hyperbilirubinaemia showed a 12 times higher risk of developing jaundice compared to those who had no sibling with severe hyperbilirubinaemia (10.5% vs. 0.9%; OR 12.5, 95% CI 2.3 to 65.3). [EL II]

In another nested case-control study from the USA[17], the charts of 11,456 babies were searched electronically to identify babies who had been re-admitted for hyperbilirubinaemia TSB > 291 micromol/L. Babies who had received phototherapy before discharge were excluded. A total of 75 babies (0.7%) constituted the test group, and these were matched with 75 randomly selected controls who had not been readmitted. The two groups were compared and a stepwise logistic regression analysis to determine the smallest subset of predictors of the difference between the groups.

Three factors were identified, early gestation (for 35 – 36 6/7 weeks adjusted OR 20.79, 95% CI 2.34 to 184.74; for 37 to 37 6/7 weeks adjusted OR 14.86, 95% CI 1.91to 115.38), exclusive breastfeeding (adjusted OR 10.75, 95%CI 2.37 to 48.82 and finally TcB above the 95th percentile on the Bhutani nomogram (adjusted OR 149.89 95%CI 20.41 to > 999.99) [EL II]

A survey of mothers of babies with GA ≥ 35 weeks discharged from a well baby nursery of a health maintenance organization (HMO) in the USA[18] was conducted to evaluate how closely mother's race documented in medical records correlated with self-reported race, and to analyze the correlation between mother's and newborn's race in the context of risk for neonatal hyperbilirubinaemia. Maternal and neonatal data were extracted from the organization's database and maternal race was placed in one of 7 categories. Further information from the mothers about their experience of breastfeeding, neonatal care, hyperbilirubinaemia detection, interventions and education, and racial ancestry for mother, father and newborn (allowing ≤ 5 responses for ancestry of each) was elicited through a computerized telephone survey. Of the 3,021 mothers available for potential inclusion, only 41% could be contacted and of them 69% (866 of 1,248) completed the survey. Of these 145 mothers were documented as white in the medical records, but only 64% self-reported as white, while of 427 mothers documented as black in medical records, only 70% self-reported as black. For mothers of Asian and Middle Eastern origin, the agreement between the two sources was 35% and 50% respectively.

About 15% of the mothers described themselves of multiracial (≥ 2 races) origin and 9% reported that the father was multiracial, but only 11% (93 of 866) reported their baby as multiracial. When racial ancestry was further explored among the newborns reported as of ≥ 2 races, the primary race matched that of the parents in 41% cases only. In 23% babies the primary race was assigned to mother's race and in 25% to father's race with 11% assigned to the race of neither mother nor father. Moreover of the 70 newborns born to parents of different ethnic origins, only 64% were reported as multiracial [EL III]

Insert Table 3.1 here

Evidence summary

There is consistent evidence from good quality studies to show that four factors are independently associated with an increased risk of hyperbilirubinaemia – gestational age < 38 weeks, jaundice within 24 hours of birth, increase in severity of jaundice and intention exclusively to breastfeed. Five studies evaluated family history of jaundice as a risk factor and four found it to be significantly associated with hyperbilirubinaemia. Bruising was reported as a significant risk factor in only two studies. Results from most studies show no significant association between cephalohaematoma, vacuum delivery, male sex or race with hyperbilirubinaemia.

GDG translation from evidence

Factors significantly associated with hyperbilirubinaemia were gestational ages < 38 weeks, visible jaundice within 24 hours of birth and history of a previous sibling with neonatal

jaundice. The GDG refined the latter to family history of neonatal jaundice requiring treatment with phototherapy because neonatal jaundice is so common.

This evidence is consistent with the NICE guideline on 'Postnatal care' which recommends that "babies who develop jaundice within the first 24 hours after birth should be evaluated as an emergency action" (www.nice.org.uk/CG037)

The GDG have used the term 'Intention exclusively to breastfeed' in a practical sense because most babies are discharged home before breastfeeding has been fully established. At this time the only risk factor which can be identified is the intention exclusively to breastfeed as opposed to 'exclusively breastfeeding'. Early postnatal discharge also limits the opportunity to assess lactation, and to provide adequate breastfeeding support and advice.

The GDG acknowledges the strong evidence that the intention exclusively to breastfeed is a risk factor for hyperbilirubinaemia whilst also recognising the benefits of breastfeeding to both mother and child. This was discussed at length as the GDG did not want to give the message that breast milk feeding should be replaced by formula milk if a baby was being treated for jaundice. The GDG have recommended that adequate lactation / feeding support be provided, including support for expressing breast milk if the baby requires treatment. The GDG feel that this support would be augmented if more was known about factors underlying the association between breastfeeding and jaundice and to this end have made a research recommendation on this topic.

It is commonly believed that bruising, cephalohaematoma and vacuum delivery all contribute towards development of hyperbilirubinaemia, however the evidence was inconclusive.

Recommendations – Risk factors for hyperbilirubinaemia

Identify babies as being more likely to develop hyperbilirubinaemia becausethey 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
- jaundice in the first 24 hours of life.

Ensure that adequate support is offered to all women who intend to breastfeed exclusively. Refer to 'Routine postnatal care of women and their babies' (NICE clinical guideline 37) for information on breastfeeding support.

Prediction (3.1)

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

Why this is important

Evidence: Breastfeeding has been shown to be a factor in hyperbilirubinaemia. The reasons for this association have not yet been fully elucidated. Population: Infants in the first 28 days of life. Exposure: Feeding type (breast milk, formula feeds or mixed feeds). Comparison: Infants who do not get hyperbilirubinaemia will be compared with infants with hyperbilirubinaemia requiring treatment. Outcome: Factors to be analysed include I) maternal factors, II) neonatal factors, III) blood analyses. Time stamp: Sept 2009

Prediction (3.1)

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

Why this is important

Evidence: There is good evidence that a risk assessment that combines the result of a timed transcutaneous bilirubin level with risk factors for hyperbilirubinaemia is effective at preventing later hyperbilirubinaemia requiring treatment.Population: Babies in the first 28 days of life. Subgroups should include pre-term and babies with dark skin tones. Exposure: A/ Timed pre-discharge transcutaneous bilirubin level. B/ Timed pre-discharge transcutaneous bilirubin level combined with risk assessment. Comparison: Standard care (discharge without timed transcutaneous bilirubin level). Outcome: i) Hyperbilirubinaemia requiring treatment ii) Cost-effectiveness, III) Parental anxiety. Time stamp: Sept 2009

3.2 Risk factors for kernicterus and/or adverse sequelae

Description of included studies

Three studies were identified that examined the association between risk factors and the development of kernicterus – two comparative studies [EL II] and one descriptive study [EL III].

For adverse sequelae, two studies [EL II] looked at the association between hyperbilirubinaemia and neurodevelopmental outcomes (one in term babies and the other in

extremely low birth weight babies) while the third [EL II] evaluated risk factors for hearing loss.

Review findings

A prospective study conducted over a one-year period in a tertiary referral neonatal unit in India[20] sought to determine the risk factors for the development of kernicterus in term babies with non-haemolytic jaundice. The inclusion criteria were total serum bilirubin levels > 308 micromol/L, absence of haemolysis and absence of major malformations. Laboratory investigations were carried out to rule out haemolysis, meningitis, intracranial haemorrhage and other pathology. Exchange transfusions were done whenever serum bilirubin levels reached 342 micromol/L. There were 64 babies eligible for the study, of whom 14 (21.8%) had kernicterus. In all cases, stage II encephalopathy was reported; all the babies with kernicterus had stage II bilirubin encephalopathy characterized by presence of opisthotonos, rigidity and paralysis of upward gaze. There was no statistically significant difference between affected and unaffected babies in gender, mean GA, mean BW, proportion exclusively breastfed and postnatal weight. Mean peak serum bilirubin levels, free bilirubin levels, bilirubin/albumin ratio and free fatty acid levels were significantly higher in cases than in babies without kernicterus. Multiple logistic regression analyses showed birth asphyxia (OR 8.3, 95% CI 1.2 to 111.8; p = 0.03), serum bilirubin levels (OR 1.15, 95% CI 1.04 to1.3; p<0.01) and free bilirubin levels (OR 1.1, 95% CI 1.04 to 2.2; p<0.01) to be significantly associated with the development of kernicterus. [EL II]

In a retrospective matched case-control study from a university hospital in the USA[21], all babies showing kernicterus at autopsy during a 6 year period were classified as cases (N = 32) while babies without kernicterus at autopsy constituted the control group (N = 32). Both groups were matched for the year of birth, gestational age, birth weight, and duration of survival. Data on multiple clinical, historical and laboratory variables were derived from hospital records. Gestational age ranged from 25 to 41 weeks with a mean GA of 31 weeks for both the groups, while birth weight ranged between 750 to 5,000 grams (mean 1,800 grams). Variables evaluated included maternal gravidity, maternal age, 1-minute Apgar scores, lowest haematocrit, lowest pH, average pH, hypoxia, peak serum bilirubin, hypercarbia and lowest temperature. There was no statistically significant difference between the cases and the controls for any of the variables evaluated on univariate or multivariate analysis. Multivariate analysis also failed to determine any factor which was statistically significant. [EL II]

A retrospective study from the USA[22] compared clinical and demographic histories of late preterm babies who suffered kernicterus to those of affected term babies, all of whom were entered in the Pilot Kernicterus Registry. Babies were included if they had been discharged well after birth and subsequently suffered kernicterus. A total of 125 of the 142 cases reported to the Registry met the inclusion criteria. The mean birth weight of the study population was 3,281 grams and the mean GA 38 weeks. Mortality among cases was 4.8%. The total serum bilirubin levels, age at re-hospitalization, and birth weight distribution were similar for the late preterm (34 to < 37 weeks, N = 29) and the term babies (> 37 weeks, N = 96). More late preterm babies developed kernicterus as compared with term babies (38% vs. 25%, p>0.05). Similarly severe post-icteric sequelae occurred in 83% of the late preterm babies compared to 71% in the term babies. However the percentage of large for gestational age babies among the late preterm group who developed kernicterus was significantly higher compared to that in the term group (34.9% vs. 24.7%, p<0.01). [EL III]

A multi-centre prospective cohort study from the USA[23] examined the association between serum bilirubin concentration and neurodevelopmental outcomes. The study population included first- born white and black singleton babies with birth weight ≥ 2,500 grams who survived for at least 1 year and had at least one bilirubin measurement recorded (N = 41,324). Each baby had serum bilirubin measured between 36 and 60 hours of age (as close to 48 hours as possible) and subsequent sampling was done on clinical grounds. The outcomes evaluated were intelligence quotient (IQ) assessment by psychologists (using Wechsler Intelligence Scale for Children) at the age of 7 years, blinded neurological examination by paediatric neurologists or other trained clinicians at the age of 7 years, and

hearing evaluation performed at 8 years of age using pure-tone audiometry. Multiple logistic regression analysis was performed to control for potential confounding variables (maternal education level, parity, feeding method during nursery stay, oxytocin use, birthweight, maternal age). The study also looked for variables (race, gender, gestational age, DAT result, exchange transfusion) that could act as effect modifiers for the relationship between bilirubin levels and the defined outcomes. Follow-up data were available for 80% of the study population. About 1% of the white babies (N = 21,375) had peak serum bilirubin level ≥ 342 micromol/L while the proportion among the black babies (N = 19,949) was 0.6%. No statistically significant association was seen between high serum bilirubin levels and IQ scores or sensorineural hearing loss. Abnormal neurological examination was reported more commonly in children with high serum bilirubin levels (≥ 342 micromol/L) compared to those with lower serum bilirubin levels, but the difference was statistically not significant (4.5% vs. 3.8%; RR 1.2, 95% CI 0.7 to 2.1). However it was observed that there was a significant linear increase in the risk of 'suspicious' abnormal neurological examination with an increase in the serum bilirubin levels (OR 1.12, 95% CI 1.06 to 1.2). This association was not significant when serum bilirubin levels were analyzed as a dichotomous variable. Sensorineural hearing loss was not associated with high bilirubin levels, but only 50% of study participants had undergone hearing evaluation. [EL II]

A prospective cohort study conducted in a university hospital neonatal unit in Malaysia[24] evaluated the risk factors associated with hearing loss in term babies with serum bilirubin levels > 339 micromol/L. The study included 128 jaundiced term babies with a mean age of jaundice onset being 3.4 days. Babies with congenital anomalies and those receiving aminoglycoside antibiotics were excluded. Screening for hearing loss was done using brain stem-evoked response on the day of discharge. The outcome assessors were blinded to treatment and serum bilirubin levels. Altogether 35% of the babies had hyperbilirubinaemia (defined as serum bilirubin levels ≥ 340 micromol/L); hearing loss was detected in 22% babies. Though there was a higher percentage of babies with hearing loss among those with hyperbilirubinaemia compared to babies with serum bilirubin levels < 340 micromol/L, the difference was not statistically significant (33% vs.16%, p = 0.11). After controlling for various confounding factors in a logistic regression analysis, variables significantly associated with hearing were jaundice which required exchange transfusion and an earlier onset of hyperbilirubinaemia. [EL II]

Another retrospective multi-centre study from the USA[25] assessed the association between peak serum bilirubin levels and neurodevelopmental outcomes in extremely low birth weight (ELBW) babies (BW range 401 to 1,000 grams) born during a 4-year period who survived to 14 days of age. Trained and certified personnel performed a comprehensive history, physical examination and neurodevelopmental assessment at 18 to 22 months age. Blinding was not reported. The variables indicative of abnormal neurodevelopment included Psychomotor Developmental Index (PDI) <70, Mental Developmental Index (MDI) <70, moderate or severe cerebral palsy (CP), hearing impairment (needing hearing aids), and a composite category designated as neurodevelopmental impairment (NDI). Of 3,167 babies eligible for the study, 2,575 (81%) were followed up. Regression analysis showed various demographic and clinical variables to be associated with poor neurodevelopmental outcomes. However after adjustment for these risk factors, significant associations were found only between peak serum bilirubin levels and death or NDI (OR 1.07, 95% CI 1.03 to 1.11), PDI <70 (OR 1.06, 95% CI 1.00 to 1.12), and hearing impairment requiring hearing aids (OR 1.14, 95% CI 1.00 to 1.30). There was no significant association between peak serum bilirubin levels and CP, MDI <70, and NDI in ELBW babies. [EL II]

Evidence summary

There is a lack of good quality evidence on the association between hyperbilirubinaemia and kernicterus or other adverse sequelae.

One small cohort study reported a history of birth asphyxia, higher serum bilirubin levels and free bilirubin levels as significant risk factors for kernicterus in term babies. A poor quality retrospective study found no significant difference between babies diagnosed with kernicterus at autopsy and those without. In a third study, a higher proportion of late preterm

babies developed kernicterus and post-icteric sequelae compared to term babies, but the difference was not statistically significant.

Three studies evaluated the association of high serum bilirubin levels (> 340 micromol/L) with adverse sequelae – two in term babies and one in babies with birthweight less than 1000 grams. One study in term babies found no significant association between hyperbilirubinaemia and IQ, abnormal neurological examination or sensorineural hearing loss. Another study reported severe jaundice requiring exchange transfusion and early onset of jaundice as significant risk factors for hearing loss. The third study found a weak association between high serum bilirubin levels and neurodevelopmental impairment, hearing impairment and psychomotor impairment in babies with birthweight less than 1,000 grams.

GDG Translation from evidence

No good quality studies identified risk factors for kernicterus.

Poor quality studies have shown a link between kernicterus and both high serum bilirubin levels and free bilirubin levels in all babies.

Severe jaundice requiring exchange transfusion (criteria was bilirubin > 340 micromol/L) and early onset of jaundice (within 24 hours) are significant risk factors for hearing loss. Deafness is a clinical manifestation of Kernicterus. Haemolytic disorders e.g. G6P-d deficiency and ABO incompatibility may cause a rapid increase in bilirubin level, and these disorders have been over-represented in international kernicterus registries and population studies of significant hyperbilirubinaemia (see chapter 6 Formal Assessment). A study of low birthweight babies found a weak association between high serum bilirubin levels (> 340 micromol/L) and neurodevelopmental impairment, hearing impairment and psychomotor impairment.

There was no evidence to support race, sex, or maternal age as significant risk factors.

The GDG has made a research recommend to for surveys of severe hyperbilirubinaemia and kernicterus which would lead to better understanding of the risk factors for kernicterus.

Recommendations – Risk factors for kernicterus

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

- a serum bilirubin greater than 340 micromol/litre in a term baby
- a rapidly rising bilirubin level of greater than 8.5 micromol/litre/hour)
- clinical features of acute bilirubin encephalopathy.

Research recommendation

National registries

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

Why this is important

Evidence: There is good evidence that prospective surveys in the UK and from a national Kernicterus Register in the US can help is identify root-causes of kernicterus and acute bilirubin encephalopathy. Population: All children with a peak bilirubin level greater than 450 micromol/L which is the threshold for an exchange transfusion recommended by NICE. Exposure: All maternal, pre-natal, peri-natal and neonatal factors. Comparison: Not applicable. Outcome: Shortcomings in clinical and service provision to prevent recurring themes in kernicterus cases. Time stamp: Sept 2009

Table 3.1 Table of risk factors for hyperbilirubinaemia (results from multivariate analysis reported as Odds Ratio with 95% CI)

Study details [EL]	Study population	Family H/O jaundice	GA < 38 wks or early gestation	Sex	Race	Exclusive breast feeding	Early clinical jaundice	Severity of jaundice	Bruising or cephalohaematoma	Delivery characteristics	Maternal characteristics
Newman et al 2000 [8] [EL II]	BW ≥ 2000 grams and GA ≥ 36 weeks	OR = 6.0 (1.0-36.0)	GA per week OR = 0.6 (0.4-0.7)	Male sex NS	Asian race OR = 3.1 (1.5-6.3)	OR = 6.9 (2.7-17.5)	OR = 7.3 (2.8-19)		Bruising OR = 3.5 (1.7-7.4) Cephalohaematoma OR = 3.2 (1.1-9.2)	Vacuum delivery NS	Maternal age ≥ 25 years OR = 2.6 (1.1-9.2)
Newman et al 2002 [9] [EL II]	BW ≥ 2000 grams and GA ≥ 36 weeks						RR = 2.9 (1.6-5.2)				
Kuzniewics et al 2008 [10] [EL II]	GA ≥ 34 wks and BW ≥2000 grams with serum bilirubin levels of 291 to 392 micromol/L at ≥ 48 hrs of age	OR = 3.8 (0.9-15.7) NS	For 34-37 wks OR = 3.7 (0.6-22.7) For 38-39 wks OR = 3.1 (1.2-8.0) 40 wks as reference	Male sex NS	Asian and African American race NS	OR = 2.0 (1.03-4.0) Risk after reaching qualifying serum bilirubin levels		serum bilirubin increase of ≥ 102 micromol/ L/day OR = 2.5 (1.2-5.5)	Bruising OR = 2.4 (1.2-4.8) Cephalohaematoma NS		
Keren et al 2005 [12] [EL II]	BW ≥ 2000 grams if GA ≥ 36 wks & BW ≥ 2500 grams if GA ≥ 35 wks		GA < 38 wks OR = 2.6 (1.5-4.5)	Male sex NS	Asian, Hispanic, Black NS	OR = 2.6 (1.5-4.5	Analyzed separately as pre-discharge risk zones	Analyzed separately as pre-discharge risk zones	Bruising NS Cephalohaematoma NS	Vacuum delivery OR = 2.2 (1.5-3.6) Oxytocin use OR = 2.0 (1.2-3.4)	Maternal age, parity, HT, diabetes NS

Study details [EL]	Study population	Family H/O jaundice	GA < 38 wks or early gestation	Sex	Race	Exclusive breast feeding	Early clinical jaundice	Severity of jaundice	Bruising or cephalohaematoma	Delivery characteristics	Maternal characteristics
Seidman et al 1999 [13] [EL II]	Healthy term babies (GA ≥ 37 weeks)	Jaundice in sibling NS		Male sex NS	Jewish ethnicities NS	Full breast feeding NS	Day-1 serum bilirubin level > 85 micromol/L OR = 36.5 (15.9-83.6)	Change in serum bilirubin from day-1 to day-2 per 17 micromol/L OR = 2.4 (1.9-3.0)	Cephalohaematoma NS	Vacuum delivery NS	Maternal age per year OR = 1.1(1.0-1.2) Maternal blood type O OR = 2.9(1.5-5.8) Maternal education per year OR = 0.8(0.7-0.9)
Keren et al 2008 [14] [EL II]	GA ≥ 36 wks and BW ≥ 2000 grams or GA ≥ 35 wks and BW ≥ 2500 grams		GA < 38 wks OR = 19 (6.3-56)	Female sex OR = 3.2 (1.2-8.4)	Black race OR = 0.22 (0.08-0.61)	Mother's plan of exclusive breast feeding OR = 3.7 (1.1-13)	Analyzed separately as pre-discharge risk zones	Clinical jaundice grade 4 or higher OR = 1.7 (1.2-2.6)		Vacuum delivery NS	Maternal smoking, ethnicity NS
Gale et al 1990 [15] [EL II]	Term singleton babies (≥ 37 weeks)	Previous sibling with jaundice OR = 2.3 (1.9-2.8)	For 37 weeks OR = 4.5 (3.2-6.3) For 38 weeks OR = 2.1 (1.6-2.8) 40 weeks as reference	Male sex OR = 1.4 (1.2-1.7)						Vacuum extraction OR = 3.0 (2.1-4.4)	Maternal age > 35 years OR = 1.7(1.3-2.3) Primipara OR = 2.7(2.1-3.5)

Study details [EL]	Study population	Family H/O jaundice	GA < 38 wks or early gestation	Sex	Race	Exclusive breast feeding	Early clinical jaundice	Severity of jaundice	Bruising or cephalohaematoma	Delivery characteristics	Maternal characteristics
Khoury et al 1988 [16] [EL II]	Both term and preterm babies	Risk of recurrence in siblings depending on degree of jaundice (in micromol/L) Mild: serum bilirubin ≤ 205 OR = 2.7 (1.8-4.1) Moderate: serum bilirubin 205-257 OR = 4.1 (1.5-10.8) Severe: serum bilirubin ≥ 257 OR = 12.5 (2.3-65.3)									
Maisels et al 2009[17] ELII	Both term and preterm babies		For 35 – 36 6/7 weeks OR = 20.79 (2.34-184.74) For 37 – 37 6/7 weeks OR = 14.86 (1.91-115.38) 40 40 6/7 weeks as reference			OR = 10.75 (2.37-48.82)					

1

4 Prediction

Introduction

This chapter builds on the work which has been done in recognition and risk factor assessment for neonatal hyperbilirubinaemia. A tool or test which could be used to distinguish babies who were likely to develop significant, potentially serious hyperbilirubinaemia from those whose jaundice would only ever be mild would be extremely valuable in clinical practice, particularly in the modern era of very short hospital stays. Tests which have been reported as potentially useful in this area in the past include markers of haemolysis and early timed bilirubin measurements. The evidence has been systematically evaluated.

Clinical question

What is the accuracy of the following tests in predicting neonatal hyperbilirubinaemia?

a) Umbilical cord bilirubin levels
b) Timed serum bilirubin levels
c) Transcutaneous bilirubin levels
d) End tidal CO levels
e) Nomograms
f) Risk assessment
g) Coombs' test

Since the tests routinely used for recognizing/detecting jaundice have also been studied to predict hyperbilirubinaemia at a later age, it was decided to conduct a combined systematic

Literature search to answer two questions –the diagnostic accuracy of tests in recognizing jaundice, and the prediction of hyperbilirubinaemia at a later age. Primary screening of 2,840 titles and abstracts from the database led to the retrieval of 148 papers.

Altogether 22 studies have been selected for inclusion in the prediction chapter. Four studies each were included for evaluating the predictive accuracy of umbilical cord bilirubin levels and serum bilirubin levels measured within the first 24 hours of age respectively. A meta-analysis of these studies was conducted for these tests to calculate the summary predictive values. End tidal CO levels were assessed in two studies with different population characteristics and threshold values. Eight studies have been grouped together under 'Pre-discharge risk assessment' since they all evaluated different strategies (serum bilirubin, transcutaneous bilirubin or clinical risk factors) during the pre-discharge period, to predict subsequent hyperbilirubinaemia. DAT tests were assessed in four studies. Moreover two or more strategies were compared in three of these studies.

4.1 Umbilical Cord Bilirubin (CB)

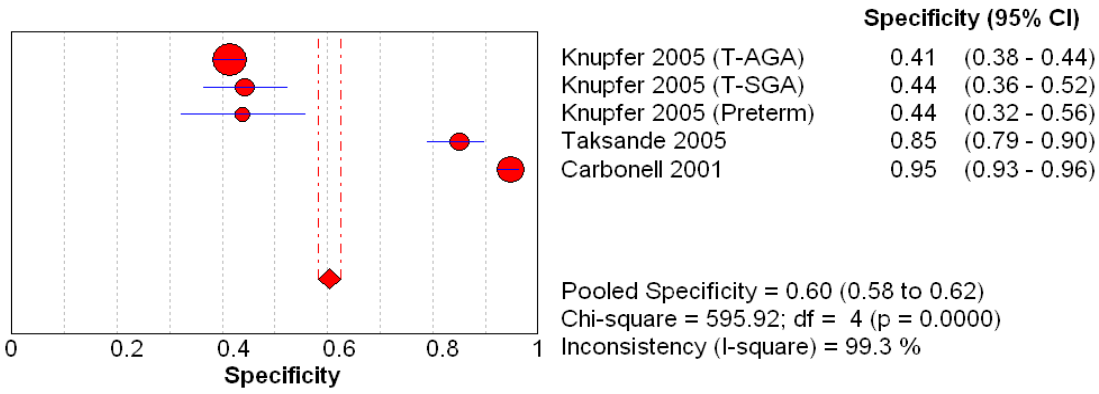
Description of included studies

Four studies of EL II conducted out in different countries (Germany[27], India[28], Denmark[29] and Spain[30]) have been included. The study population was made up of healthy term babies in three studies while in the German study the population included healthy term babies who were appropriate for gestational age (AGA), healthy term who were small for gestational age (SGA) and healthy preterm babies (GA < 34 weeks). In three studies CB was measured within 2 hours of birth and the standard reference test (laboratory serum bilirubin measurement) was carried out within 3-4 days, while in the German study blood testing was done only in those babies who had a Minolta JM-102 transcutaneous bilirubin reading >16 reflectance

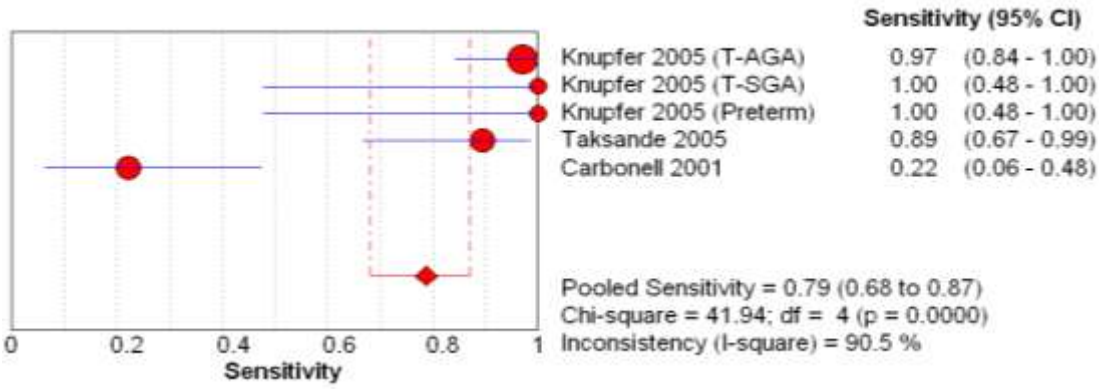
units. A meta-analysis was conducted with data from 3 studies[27,28,30] which had defined hyperbilirubinaemia as serum bilirubin levels ≥ 290 micromol/L. The threshold values of CB in these studies were ≥ 30 micromol/L, > 34 micromol/L and ≥ 37 micromol/L respectively. In the Danish study the ability of CB at levels ≥ 35 micromol/L (best cut-off value derived from the ROC curve) to predict serum bilirubin levels ≥ 200 micromol/L was calculated. Blinding of the outcome assessors was not specified in three studies.

Review findings

The prevalence of hyperbilirubinaemia (serum bilirubin ≥ 290 micromol/L) varied between 2.9% and 9.5% in the three studies, while in the Danish study 20.3% of the babies had serum bilirubin levels ≥ 200 micromol/L. The sensitivity of CB to predict serum bilirubin levels ≥ 290-300 micromol/L ranged from 22% to 100%, while the specificity ranged from 41% to 95%. The pooled sensitivity was 79% (95% CI 68% to 87%) and the pooled specificity 60% (95% CI 58% to 62%), but there was strong evidence of statistical heterogeneity for both the pooled results. The Danish study showed that CB levels with threshold value ≥ 35 micromol/L had a sensitivity of 71% and specificity of 68% in predicting serum bilirubin ≥ 200 micromol/L.



Forest plot 4.1.1 Pooled specificity



Forest plot 4.1.2 Pooled sensitivity

Evidence summary

Results from three EL II studies indicate great variation in the ability of CB to predict hyperbilirubinaemia in healthy term and preterm babies. Sensitivity ranged from 22% to 100% and specificity from 41% to 95%. The pooled sensitivity and specificity were 79% and 60% respectively, but the results were marred by strong evidence of statistical heterogeneity.

GDG translation from evidence

Current evidence does not support measuring umbilical cord bilirubin levels for the prediction of subsequent hyperbilirubinaemia in healthy babies.

Recommendations – Umbilical cord bilirubin

Do not use any of the following to predict hyperbilirubinaemia:

- umbilical cord bilirubin
- end-tidal carbon monoxide (ETCOc) measurement
- umbilical cord direct antiglobulin test (DAT) (Coombs' test)

(See other sections in this chapter for information on the last 2 bullet points in this recommendation)

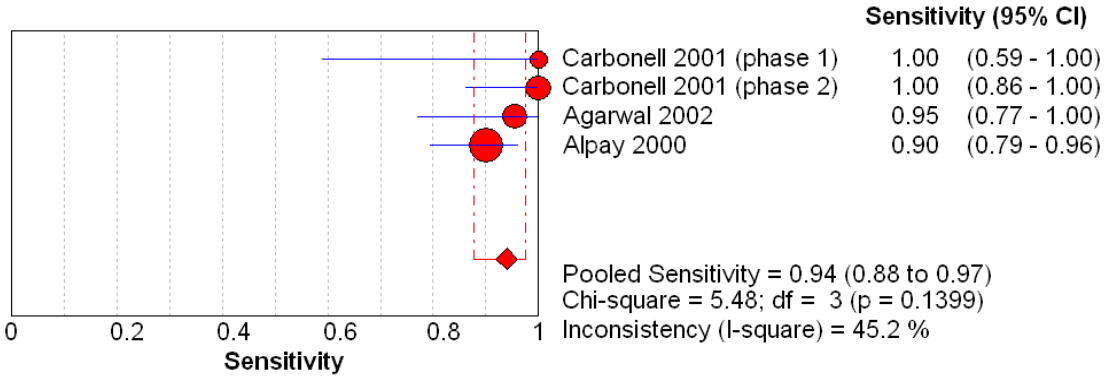
4.2 Serum bilirubin levels in the first 24 hours of life (serum bilirubin-Day 1)

Description of included studies

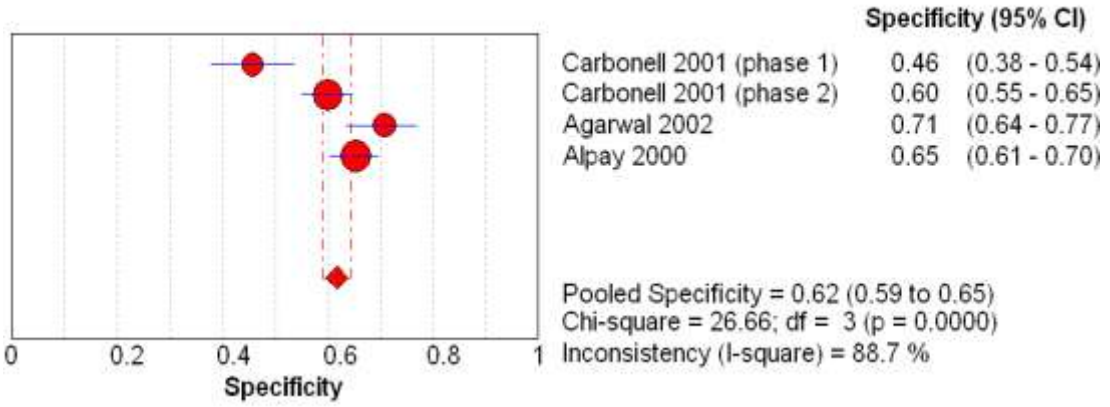
Four studies with ELII have been included. They were conducted in Spain[30], India[31], Turkey[32] and Israel[13]. The study population in three studies included healthy term babies (≥ 37 weeks) and serum bilirubin was measured within 24 hours of birth. The Indian study included healthy babies with GA > 35 weeks and serum bilirubin was measured at 24 ± 6 hours of age. In three studies the ability of serum bilirubin-Day 1 (threshold value ≥ 102 micromol/L) to predict hyperbilirubinaemia (defined as serum bilirubin ≥ 290 micromol/L on day 3 – 5) was calculated, and results from these studies were pooled to obtain the summary results. Since the Spanish study was conducted in two phases, data have been given separately for both phases. The fourth study, from Israel, used multiple regression analysis to investigate the association of various factors (maternal age, education, O blood group, breastfeeding, serum bilirubin-Day 1 and change in serum bilirubin levels) with hyperbilirubinaemia.

Review findings

In three studies used in the meta-analysis, hyperbilirubinaemia was defined as serum bilirubin levels ≥ 290 micromol/L and its prevalence ranged from 2.9% to 12.0%. The pooled sensitivity of serum bilirubin-Day 1 in predicting hyperbilirubinaemia was 94% (95% CI 88% to 97%) with values in individual studies ranging from 90% to 100%, and the results were statistically homogeneous. On the other hand there was strong evidence of statistical heterogeneity for specificity with the pooled value being 62% (95% CI 59% to 65%) and individual values ranging from 46% to 71%. The study from Israel showed serum bilirubin value > 85 micromol/L on Day 1 to have a sensitivity of 63% and specificity of 94%, while the model with all other variables (except serum bilirubin on Day 1) showed 58% sensitivity and 90% specificity. The addition of serum bilirubin > 85 micromol/L on Day 1 to the model with all other variables increased the sensitivity to 82% but the specificity decreased to 80%.



Forest plot 4.2.1 Pooled sensitivity



Forest plot 4.2.2 Pooled specificity

Evidence summary

Evidence from three EL II studies indicates that serum bilirubin ≥ 102 micromol/L on Day 1 is a sensitive predictor of later hyperbilirubinaemia. In another study, combining serum bilirubin > 85 micromol/L at less than 24 hours with maternal variables (blood group O, age, exclusive breastfeeding and education) resulted in an increase in sensitivity but a decrease in specificity.

GDG translation from evidence

Evidence shows that serum bilirubin > 102 micromol/L in the first 24 hours of life is predictive of serum bilirubin > 290 micromol/L between days 3-5. This supports the evidence reviewed in Chapter 3: Risk factors, that visible jaundice in the first 24 hours is a risk factor

for significant later hyperbilirubinaemia. In babies with light skin tones jaundice is usually visible at levels of bilirubin > 90 micromol/L[33] Some studies show that the sensitivity can be improved using a model combining serum bilirubin with maternal variables.

The GDG is of the opinion that visible jaundice in the first 24 hours remains an important predictor of later clinically important hyperbilirubinaemia. Any visible jaundice in the first 24 hours requires urgent medical review, which must include serum bilirubin measurement and an investigation of the underlying causes (see Chapter 6: Formal assessment)

Recommendations – in first 24 hours of life

Measure and record the serum bilirubin urgently (within 2 hours) in all babies less than 24 hours old with suspected or obvious jaundice.

If the serum bilirubin is greater than 100 micromol/litre in the first 24 hours of life repeat the serum bilirubin measurement between 6 and 12 hours later.

Refer to ensure an urgent medical review is conducted (as soon as possible and within 6 hours) to exclude pathological causes of jaundice.

Interpret bilirubin levels according to the baby's postnatal age in hours and manage hyperbilirubinaemia according to Table 1 and graphs A-F.

4.3 End-tidal carbon monoxide measurement (ETCOc)

Description of included studies

Two studies with EL II have been included in this section. The first study had a large sample size of both term and near-term babies while the second, smaller, study included only term babies. In both studies, ROC curves were developed to evaluate the accuracy of end-tidal carbon monoxide (CO) production corrected for ambient CO (ETCOc) in predicting hyperbilirubinaemia.

Review findings

The first study was an international study[34] carried out at 9 sites (4 in the USA, 2 in China, 2 in Israel and 1 in Japan). All newborn babies with GA ≥ 35 weeks were enrolled in the first 36 hours of life. Of the 1,895 babies enrolled, 1,370 (72%) completed the study. All babies had measurements of ETCOc and serum bilirubin performed at 30 ± 6 hours, and serum bilirubin only at 96 ± 12 hours. Between these times, serum bilirubin could be measured for clinical reasons. ETCOc was measured using a breath analyzer with single-use disposable nasal sampler. Hyperbilirubinaemia was defined as laboratory serum bilirubin ≥ 95th centile at any time during the study period. Threshold centile values were taken as those defined by Bhutani[35] and adopted by the AAP[11]. Inclusion and exclusion criteria were well defined. Babies with age-specific serum bilirubin ≥ 95th centile at up to 96 ± 12 hours were withdrawn from the study. About 9% (120 of 1,370) babies had serum bilirubin levels ≥ 95th centile at 30 ± 6 hours or at 96 ± 12 hrs. The mean ETCOc levels in this group were significantly higher than the mean levels in the non-hyperbilirubinaemic group ($p<0.001$). Logistic regression analysis was conducted with variables found to be associated with hyperbilirubinaemia (serum bilirubin percentile at 30 hours, bruising, maternal blood type, race maternal diabetes, feeding type, gravidity, and ETCOc) Models to evaluate diagnostic accuracy of ETCOc, laboratory serum bilirubin and their combination in predicting hyperbilirubinaemia were developed. ETCOc at 30 ± 6 hours with a threshold value above the population mean (1.48 ± 0.49 ppm) predicted hyperbilirubinaemia with 13% positive predictive value (PPV) and 96% negative predictive value (NPV), while laboratory serum bilirubin levels > 75th centile showed 17% PPV and 98% NPV. When both tests were combined, NPV increased to 99% but PPV decreased to only 6%. It was concluded that serum bilirubin measurement before discharge (at 30 ± 6 hours) may provide some assistance in predicting risk of hyperbilirubinaemia, but the addition of ETCOc does not improve its predictive accuracy.[EL II]

In the second study, from Japan[36], ETCOc levels were measured every 6 hours during the first 3 days of life in 51 healthy, full-term babies. The Minolta JM-102 was used to record transcutaneous bilirubin measurements every 12 hours during the first 5 days and serum bilirubin levels were measured if the JM-102 index was ≥ 22 reflectance units. A ROC curve was developed to evaluate the accuracy of ETCOc at different ages in predicting hyperbilirubinaemia, which was defined as serum bilirubin ≥ 257 micromol/L. Hyperbilirubinaemia occurred in 7 babies, while 44 babies had serum bilirubin levels < 257 micromol/L. There were no statistically significant differences between the hyperbilirubinaemic and non-hyperbilirubinaemic babies in terms of sex, GA, mode of delivery, Apgar score at 1 min, age at peak transcutaneous bilirubin, and mode of feeding. Moreover the mean levels of ETCOc were similar for the two groups from 6 to 36 hours of age, but the hyperbilirubinaemic group had higher mean levels at 42, 48, 54 and 66 hours. The ROC curve indicated that ETCOc at 42 hours of age showed the best accuracy in predicting hyperbilirubinaemia. At the threshold value of 1.8 ppm, it showed 86% sensitivity, 80% specificity, 40% PPV and 97% NPV. [EL II]

Evidence summary

ETCOc levels were measured at different times and their accuracy evaluated with different threshold values in two studies with EL II. While one study reported ETCOc to have a PPV of 40% and NPV of 97%, the other study reported 13% PPV and 96% NPV for subsequent hyperbilirubinaemia. The second study also found no additional benefit from combining this test with pre-discharge laboratory serum bilirubin levels.

GDG translation to recommendation

Although ETCOc shows good negative predictive value, it is not routinely available and does not accurately predict neonatal hyperbilirubinaemia.

Recommendation - End-tidal carbon monoxide measurement (ETCOc)

See section 4.1 in this chapter

4.4 Pre-discharge risk assessment

Description of included studies

Seven studies have been included in this section, 6 from the USA[35,8,38,,39,14,12] and one from Italy[37]. Four cohort studies were conducted prospectively and two retrospectively, while one study was a nested case-control study. Apart from one study with EL I, the studies are of EL II. Two main strategies were employed in these studies to predict subsequent hyperbilirubinaemia; pre-discharge bilirubin or early bilirubin measurement combined with clinical risk factors. Three studies[35;37] evaluated the predictive accuracy of pre-discharge serum bilirubin plotted on an hour-specific nomogram, while one study[38] assessed pre-discharge transcutaneous bilirubin measurements using BiliChek. Clinical risk factors were evaluated in four studies, either alone or in combination with pre-discharge bilirubin measurement. In one nested case-control study[8;8] a risk index model was assessed; in two retrospective cohort studies[14;39] the risk index was compared with pre-discharge serum bilirubin plotted in risk zones, and in one prospective study[14] the predictive value of multiple risk factors was first compared with pre-discharge bilirubin (transcutaneous bilirubin or serum bilirubin) levels, and later their combined accuracy assessed.

Review findings

The first study, conducted in the USA[35], evaluated the predictive ability of an hour-specific pre-discharge serum bilirubin measurement. The study population included 13,003 term and near-term appropriate for gestational age (AGA) babies admitted to the well baby nursery of a tertiary hospital over a 5 year period. Pre-discharge (18-72 hours) serum bilirubin was measured as part of routine metabolic screening. Babies admitted to the intensive care unit,

those with a positive DAT, and babies who started phototherapy before serum bilirubin measurement were excluded. After discharge, the babies were followed up by home care nurses, who could request laboratory serum bilirubin if they had clinical concerns. Based on the pre and post-discharge serum bilirubin measurements in 2,840 eligible babies (recorded in epochs of 4 hrs for the first 48 hrs of age, 12 hrs for 48-96 hrs of age, and 24 hrs for age 5-7 days), an hour-specific serum bilirubin nomogram was constructed. This was divided into zones – high risk (≥ 95th centile), high intermediate risk (between 75th and 95th centile), low intermediate risk (between 75th and 40th centile) and low risk (below 40th centile). The nomogram was used as the reference standard to determine the ability of pre-discharge serum bilirubin (measured between 18 to 72 hours of age) to predict subsequent severe hyperbilirubinaemia – defined as serum bilirubin level in the high-risk zone (≥ 95th centile). For 8.1% (230 of 2,840 babies), serum bilirubin fell within this zone at some time. In 58 babies (2.0%), this occurred after discharge. Among 172 of 2,840 babies with pre-discharge serum bilirubin ≥ 95th centile, 68 had subsequent hyperbilirubinaemia giving pre-discharge serum bilirubin ≥ 95th centile a sensitivity of 54.0% and a specificity of 96.2% in predicting hyperbilirubinaemia. Pre-discharge serum bilirubin ≥ 75th centile showed a sensitivity of 90.5% and a specificity of 84.7%. None of the 126 babies with pre-discharge serum bilirubin < 40th centile developed subsequent hyperbilirubinaemia. The predictive accuracy of each risk zone was also calculated in terms of the likelihood ratio (LR) for predicting serum bilirubin ≥ 95th centile. The LR was 14.1 for the high risk zone (and 54% babies continued in the same zone), 3.2 for the high intermediate risk zone (12.9% moved up to the high risk zone), 0.5 for the low intermediate risk zone (2.2% moved up to the high risk zone), and 0 for the low risk zone (none moved into the high risk zone). [EL II]

The second study, from Italy[37], was conducted in two phases. In the first phase, serum bilirubin curves were developed from blood samples obtained at 6 hours of age and then every 4-6 hours during the day and every 6-12 hours during the night. 438 full term AGA babies without "asphyxia" and without Rh or ABO incompatibility were included. Serum bilirubin curves for babies with levels > 12 mg/dl (205 micromol/L) and those with serum bilirubin > 15 mg/dl (255 micromol/L) were devised, and their percentile values (for each hour of life) connected to form percentile tracks. Any serum bilirubin value exceeding the 1st percentile track of babies with serum bilirubin > 12 mg/dl was (Trend 12), and serum bilirubin value exceeding the 1st percentile track of babies with serum bilirubin > 15 mg/dl (Trend 15). Trend 12 and trend 15 were taken as indicative of hyperbilirubinaemia.

In the second phase the nomogram was validated in a prospective study carried out at two hospitals (Hospital A, n = 1,244, Hospital B, n = 498). The study population included term babies who had serum bilirubin measured between 30-72 hours because of clinical jaundice. Most of the babies had a single serum bilirubin measurement, but 514 of 1,244 babies in Hospital A and 175 of 498 babies in Hospital B had two serum bilirubin determinations 12 hours apart. The ability of serum bilirubin measurements exceeding trends 12 and 15 to predict subsequent hyperbilirubinaemia was evaluated. In Hospital A, 18.5% babies had serum bilirubin values > 12 mg/dl while 8.0% had serum bilirubin > 15 mg/dl. With a single serum bilirubin measurement and trend 12 as the threshold, a sensitivity of 99% and a specificity of 49% were obtained, while applying trend 15 gave 100% sensitivity and a specificity of 75%. In Hospital B, trend 12 gave similar results (98% sensitivity and 36% specificity) to Hospital A but trend 15 was less accurate, with 88% sensitivity and 78% specificity. Two consecutive serum bilirubin determinations accurately identified all babies reaching serum bilirubin levels > 12 mg/dl in the two hospitals (100% sensitivity), and all but one baby reaching serum bilirubin levels > 15 mg/dl in Hospital B.[EL II]

The third study, conducted in two tertiary hospitals in the USA[38], compared transcutaneous bilirubin measurement to serum bilirubin for prediction of hyperbilirubinaemia in a multiracial population. The study population comprised 490 healthy babies with GA ≥ 36 wks and BW ≥ 2000 grams or GA ≥ 35 wks and BW ≥ 2500 grams, and included 59% White, 29.5% Black, 3.5% Hispanic and 4.5% Asian babies. At the time of routine metabolic screening (24-72 hours of age), transcutaneous bilirubin readings were recorded from the forehead with a BiliChek device and simultaneously two blood samples were taken for serum bilirubin estimation – one at the local laboratory and the other sent for HPLC assay. The laboratory

technicians, clinicians and investigators were all blinded to the transcutaneous bilirubin and serum bilirubin data. Paired transcutaneous bilirubin and HPLC serum bilirubin values were then plotted on the hour-specific nomogram developed by Bhutani et al 35. Hyperbilirubinaemia was defined as serum bilirubin levels ≥ 95th centile on the nomogram (ie in the high-risk zone). Altogether 30 of 490 (6.1%) babies had HPLC serum bilirubin values above the 95th centile and only 1.1% had serum bilirubin levels > 255 micromol/L. The correlation between transcutaneous bilirubin and serum bilirubin values was linear and significant ($r = 0.91$, $p<0.001$), and the values for correlation coefficient were similar when the data were categorized by race. The mean difference between paired serum bilirubin and transcutaneous bilirubin values was 8 micromol/L (95% CI -38.9 to 54.9 micromol/L). For predicting hyperbilirubinaemia, pre-discharge transcutaneous bilirubin above the 75th centile showed a sensitivity of 100%, specificity of 88% and a likelihood ratio of 8.4. None of the babies with serum bilirubin levels in the high-risk zone had a transcutaneous bilirubin recording below the 75th centile on the nomogram, while all babies with serum bilirubin levels below the 40th centile also had transcutaneous bilirubin values below the 40th centile. No adverse events were reported using the BiliChek device. [EL II]

A nested case-control study was carried out at 11 hospitals in a health maintenance organization in the USA[8] to investigate predictors of hyperbilirubinaemia and evaluate the predictive accuracy of a risk index model. This study has been described in an earlier chapter on risk factors. Information on risk factors was collected by reviewing hospital records and interviewing parents. Using bivariate analysis, several clinical and demographic variables were found to be associated with an increased risk of hyperbilirubinaemia. They included maternal factors (race, age, family history of jaundice in a newborn, vacuum delivery) and neonatal factors (male sex, lower GA, early jaundice, cephalohaematoma, bruising, breast feeding at time of discharge). These variables then underwent multiple regression analysis to identify independent predictors of hyperbilirubinaemia. This was done by including and later excluding cases of early jaundice (N = 14) in order to predict hyperbilirubinaemia after initial hospital discharge. When all the cases were included, early jaundice (OR 7.3; 95% CI 2.8-19), GA in weeks (OR 0.6; 95% CI 0.4-0.7), breast feeding at discharge (OR 6.9; 95% CI 2.7-17.5), Asian race (OR 3.1; 95% CI 1.5-6.3), bruising (OR 3.5; 95% CI 1.7-7.4) , cephalohaematoma (OR 3.2; 95% CI 1.1-9.2), and maternal age ≥ 25 yrs (OR 2.6; 95% CI 1.1-9.2) were all independently associated with hyperbilirubinaemia. After excluding cases with early jaundice, similar findings were reported, with two exceptions – history of jaundice in a newborn was significant in the second model and black race was not included in it as all the early jaundice cases were black. A simple risk index was then developed by assigning points to the risk factors (approximately equal to their OR in the second model) which were found to be significant after exclusion of early jaundice cases. The accuracy of the risk index in predicting hyperbilirubinaemia was good (c = 0.85). With a threshold risk score > 10 points, the likelihood ratio of babies having serum bilirubin levels ≥ 428 micromol/L was 2.2 but it increased to 18.8 when a score of > 20 points was used as the threshold. [EL II]

In the fifth study, from the USA[39] a risk index score for predicting hyperbilirubinaemia was validated, and a subset of this index was combined with pre-discharge serum bilirubin measured at < 48 hrs for predicting subsequent hyperbilirubinaemia. To validate the risk index score in predicting serum bilirubin ≥ 427 micromol/L, 67 cases and 208 randomly sampled controls were selected from a cohort of 53,997 babies using similar study design, case definitions and selection criteria to the previous study8. The baseline characteristics of the 1997-98 cohort study group were similar to those of the previous (1995-96) cohort. After excluding family history of jaundice, a modified risk index was developed and it showed accuracy in predicting significant hyperbilirubinaemia (serum bilirubin levels ≥ 427 micromol/L) with a c-statistic of 0.83 (95% CI 0.77 to 0.89). The results were similar to those from the previous study (c-statistic 0.84; 95% CI 0.79 to 0.89). In the second part of the study, the records of 5,706 babies born in the same setting over a period of 4 years and who had serum bilirubin measured at < 48 hrs of age were reviewed retrospectively. A partial clinical risk index was derived by deleting family history of jaundice, breast feeding and bruising, and by substituting scalp injury with cephalohaematoma. The serum bilirubin levels measured at < 48 hrs were classified into age-specific percentile groups (< 40th centile, 40th to < 75th centile, 75th to < 95th centile, ≥95th centile), and then transformed into hour-specific z

scores but subtracting the observed value from the calculated median for that age and dividing by the calculated standard deviation. Significant hyperbilirubinaemia was defined as maximum serum bilirubin levels ≥ 342 micromol/L. Pre-discharge serum bilirubin levels expressed as hour-specific centiles showed better accuracy for predicting hyperbilirubinaemia than the partial risk index score (c-statistic 0.79 vs. 0.69). Within each percentile category there was a 5- to 15-fold increase in the risk of hyperbilirubinaemia for those with a risk index score > 10 compared to those with a score > 4 Transforming the pre-discharge serum bilirubin centiles into the hour-specific z scores improved their predictive ability (c-statistic from 0.79 to 0.83), but the best results were obtained by combining pre-discharge serum bilirubin z scores with the partial risk index score (c-statistic 0.86). [EL II]

Another retrospective cohort study, conducted in a urban teaching hospital in the USA[12] also compared the predictive performance of combined clinical risk factor assessment and pre-discharge serum bilirubin measurement. The study population (N = 899) and the methodology has been described in detail under chapter on risk factors. The population was the same as that used in a previous study38 but for this study it was restricted to the time interval when ≥ 75% of babies had both samples collected. Out of 996 eligible babies, 899 (90%) were finally included. Hospital records were reviewed retrospectively to collect information on risk factors. Their association with hyperbilirubinaemia was explored by univariate analysis and a risk factor score was derived from regression modelling using the factors independently associated with significant hyperbilirubinaemia. The final risk factor model included birth weight, GA < 38 wks, oxytocin use during labour, vacuum delivery, breastfeeding, and combined breast and bottle feeding. Pre-discharge serum bilirubin levels were expressed as risk zones on the hour-specific bilirubin nomogram. Significant hyperbilirubinaemia (serum bilirubin > 95th centile on the nomogram) was present in 98 of 899 (11%) babies. The predictive accuracy of pre-discharge serum bilirubin risk zone (c-statistic 0.83; 95% CI 0.80 to 0.86) was better than the clinical risk factor score (c-statistic 0.71; 95% CI 0.66 to 0.76). By decreasing the thresholds of a positive test for the risk factor score (higher to lower score) and pre-discharge serum bilirubin risk zones (> 95th centile to < 40th centile), sensitivity increased but neither test could predict hyperbilirubinaemia with more than 98% sensitivity without seriously compromising specificity (13% for risk factor score, 21% for serum bilirubin risk zone). [EL II]

In the last study, from the USA[14], the predictive accuracy of clinical risk factors, pre-discharge bilirubin levels expressed as risk zones, and a combination of pre-discharge bilirubin and additional risk factors was evaluated prospectively. Study methodology and population is described in detail in the chapter on risk factors. All babies (N = 812) had pre-discharge bilirubin measured before 52 hours of age with daily transcutaneous bilirubin readings from the forehead using BiliChek, and these were recorded on the hour-specific nomogram. Bilirubin levels (transcutaneous bilirubin or serum bilirubin) were also measured on day 3-5 in all babies either in hospital or at home. If transcutaneous bilirubin readings exceeded the 75th centile or were ≥ 205 micromol/L, blood samples were taken for laboratory serum bilirubin measurement. Both the transcutaneous bilirubin and serum bilirubin readings were expressed as risk zones on the hour-specific nomogram. In cases where both transcutaneous bilirubin and serum bilirubin levels were measured in the same baby, the serum bilirubin readings were used for the final analysis. Information on clinical risk factors was extracted from hospital records, and their association with hyperbilirubinaemia assessed using univariate analysis. The variable most strongly associated with an increased risk of hyperbilirubinaemia was the pre-discharge bilirubin level. As this was included in a separate model, the final clinical risk model included 5 other factors; GA, gender, intended method of feeding, black race and extent of jaundice. Using logistic regression modelling, the accuracy of three tests was compared for the prediction of significant hyperbilirubinaemia. In all, 6.4% babies developed hyperbilirubinaemia, (bilirubin levels on day 3-5 exceeding or within 17 micromol/L of the hour-specific AAP phototherapy treatment thresholds). The predictive accuracy of pre-discharge bilirubin risk zone assignment was not significantly different from that of multiple risk factors (c-statistic 0.88 vs. 0.91). After combining clinical risk factors with pre-discharge bilirubin risk zone assignment, the only factors that remained significant were GA and percentage weight loss per day. This combination model showed improved predictive accuracy (c-statistic 0.96) when compared to the pre-discharge bilirubin levels. [EL II]

Evidence summary

Results from two studies with EL II indicate that pre-discharge serum bilirubin plotted on hour-specific percentile charts ("nomograms") shows good accuracy in predicting subsequent hyperbilirubinaemia. The studies used different threshold values and definitions of hyperbilirubinaemia. In one study two consecutive serum bilirubin readings plotted on the nomogram had greater predictive accuracy than a single measurement. Another study with EL I indicated that pre-discharge transcutaneous bilirubin plotted on an "hour specific" nomogram of bilirubin levels generated from a study of healthy babies could predict hyperbilirubinaemia with 100% sensitivity and 88% specificity. The threshold values for defining hyperbilirubinaemia were different for the transcutaneous (≥ 75th centile) and serum (≥ 95th centile) bilirubin levels. Other studies have compared the predictive accuracy of clinical risk index scores with pre-discharge bilirubin levels. Their results suggest that pre-discharge bilirubin is more accurate in predicting subsequent hyperbilirubinaemia than clinical risk factors alone, but the best results are seen when pre-discharge bilirubin measurement is combined with risk factors. A major limitation of the evidence is that the hour-specific bilirubin nomogram was devised using a small population of babies in a single city, and that babies with conditions such as ABO incompatibility were excluded. The nomogram may not, therefore, be applicable to other populations of newborn infants. Similar nomograms need to be devised for other populations.

GDG translation from evidence

Current evidence suggests that it is possible to identify babies who are likely to develop significant hyperbilirubinaemia using a predischarge assessment. The GDG considered that assessment of risk factors was important.

Another approach has been based on hour-specific bilirubin estimation. Hour specific bilirubin levels were interpreted using a nomogram such as that devised by Bhutani et al., however, the universal application of hour-specific bilirubin estimation could not be relied on as data was lacking for babies in first 24 hours of life and also for those with jaundice due to haemolytic disease of the newborn.

The GDG review of the evidence supports our recommendations, namely that parents and carers need to made aware of the risk factors for hyperbilirubinaemia (see recommendations in Chapter 8: Information for parents and carers).

All those responsible for the care of newborn babies should also be aware of the importance of risk factors (See section 3.1), and should take them into account when examining the baby (see 5.1) deciding on management options (see 7.1.8).

Research recommendation - Pre-discharge risk assessment

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?

Why this is important

Evidence: There is good evidence that a risk assessment that combines the result of a timed transcutaneous bilirubin level with risk factors for hyperbilirubinaemia is effective at preventing later hyperbilirubinaemia requiring treatment. Population: Babies in the first 28 days of life. Subgroups should include pre-term and babies with dark skin tones. Exposure: A/ Timed pre-discharge transcutaneous bilirubin level. B/ Timed pre-discharge transcutaneous bilirubin level combined with risk assessment. Comparison: Standard care (discharge without timed transcutaneous bilirubin level). Outcome: i) Hyperbilirubinaemia requiring treatment ii) Cost-effectiveness, III) Parental anxiety. Time stamp: Sept 2009

4.5 Direct Antiglobulin (Coombs') Test (DAT)

Review findings

One study with EL2[40] and three with EL3[41,42,44] examining the predictive ability of the Direct Antiglobulin, Test (DAT) have been included but no meta-analysis was possible as the studies used different criteria for defining hyperbilirubinaemia.

In the first study, from the USA[40], universal DAT was evaluated with reference to ETCOc, and its accuracy in predicting hyperbilirubinaemia was then assessed. The study population included 660 babies (mean GA = 38.9 ± 1.4 weeks, mean BW = 3,267 ± 480 grams) admitted consecutively to the postnatal ward of a tertiary hospital. In all cases cord blood was collected and DAT was conducted by the gel test. In positive cases the baby was investigated for haemolytic disease. The reference standard for haemolysis was ETCOc measured in all babies at 12 ± 6 hrs and again at 24 ± 6 hrs. Significant haemolysis was defined as ETCOc ≥ 95th centile. Since maternal cigarette smoking was shown to influence ETCOc measurement results were given separately for babies of non-smoking and smoking mothers. Bilirubin measurement (transcutaneous bilirubin in the majority with subsequent serum bilirubin if required) was performed in all babies at the time of hospital discharge or earlier if clinically indicated. Hyperbilirubinaemia was defined as a bilirubin reading ≥ 75th centile on the Bhutani nomogram. Blinding of outcome assessors was not specified. More than 80% of the study population was black. The DAT was positive in 3.5% of babies (23 of 659). In babies of non-smoking mothers, DAT could predict haemolysis (ETCOc levels ≥ 3.2 µl/l) with a sensitivity of 38.5% and specificity of 98.5%, while in babies of all mothers it showed a sensitivity of 8.5% and specificity of 97.6% in detecting haemolysis (ETCOc levels ≥ 2.5 microl/l). The accuracy of DAT test in predicting hyperbilirubinaemia was evaluated and compared to that of high ETCOc levels. A positive DAT test showed a sensitivity of 14.7% while ETCOc showed 27.9% sensitivity in predicting subsequent hyperbilirubinaemia in babies of non-smoking mothers. The specificity of DAT testing combined with ETCOc was 98.2% and 97.9% respectively. [EL II]

The second study, from the USA[41], evaluated selective DAT and cord bilirubin measurement (CB) in predicting hyperbilirubinaemia. The study population included 91 ABO incompatible babies in a state-sponsored neonatal program; Rh incompatible babies were excluded. Demographic information on GA, birth weight, gender or ethnicity was not provided. Cord blood was obtained from all babies of group O mothers, and bilirubin estimations were carried out at 12, 24, 36 and 48 hours of life in cases of ABO incompatibility. The CB threshold for a positive test was a measurement > 68 micromol/L. Babies with serum bilirubin levels > 273 micromol/L between 12 and 36 hours were classed as severely hyperbilirubinaemic. Blinding of outcome assessors was not specified. DAT was positive in 34.1% (31 of 91) babies. A positive DAT test and the CB threshold ≥68 micromol/L both showed a sensitivity of 92.3%.in predicting subsequent severe hyperbilirubinaemia. Specificities for both positive DAT and CB tests were 75.6% and 100% respectively [EL III]

A Norwegian study[42] examined the ability of universal DAT testing to predict the need for phototherapy, using the Hillingdon Hospital bilirubin chart[43] to inform treatment. The study population included 2,463 babies born in a general hospital. Exclusion criteria included high-risk deliveries and severe neonatal illness but no more details were given. Information on GA, BW, gender and ethnicity was not provided. Phototherapy was started in term babies at serum bilirubin > 350 micromol/L-1 at >72 hours and >250 micromol/L-1 at > 120 hours. Blinding of outcome assessors was not specified. DAT was positive in 4.1% (100 of 2,463) of babies. The DAT test showed a sensitivity of 14.4% and specificity of 96.6% in predicting the need for phototherapy. [EL III]

A Taiwanese study[44] evaluated selective DAT testing and CB as predictors of hyperbilirubinaemia. The study population included 88 babies with BW > 2500 grams born to group O, Rh positive mothers; 53 babies were ABO incompatible. Information on ethnicity, GA and gender was not provided. Serum bilirubin levels were measured daily for 1 week. Hyperbilirubinaemia was defined as serum bilirubin > 255 micromol/L within 96 hours of birth and/or early jaundice with serum bilirubin > 171 micromol/L within 24 hours of birth.

Blinding of outcome assessors was not specified. DAT was positive in 26.4% (14 of 53). The DAT test and the CB threshold level > 68 micromol/L showed sensitivity of 44.8% and 41.4% in predicting subsequent hyperbilirubinaemia. The specificity for the DAT and CB tests was 95.8% and 100% respectively [EL III]

A Turkish study[45] examined selective DAT to predict serum bilirubin levels at 6, 30, 54, 78 and 102 hours. All babies > 38 weeks gestation with blood groups A or B born to mothers with blood group O, without a simultaneous rhesus blood factor incompatibility, (N = 150) were included. The mean birth weight was 3,212 ± 415 grams and 51% were male. Ethnicity was not specified. No exclusion criteria were specified but data from 14 babies were excluded from the final analysis for clinical reasons (transferred to intensive care or no informed consent given). Severe hyperbilirubinaemia was defined as serum bilirubin > 85 micromol/L with an increase of 8.5 micromol/L/hr in the first 24 hours, levels > 205 micromol/L on day 2, > 255 micromol/L on day 3 or > 289 micromol/L on days 4 and 5. Blinding of outcome assessors was not specified. DAT was positive in 4.4% (6 of 136) of babies. A positive DAT test showed a sensitivity of 20.1% and a specificity of 100% in predicting subsequent severe hyperbilirubinaemia in babies with ABO incompatibility [EL III].

Evidence summary

Each study compared DAT with varying threshold levels of bilirubin. In the EL2 study the DAT test showed a sensitivity of 8.5% and specificity of 97.6% in detecting hemolysis. Similar levels of sensitivity and specificity in predicting subsequent hyperbilirubinaemia were found in three of the other four EL3 studies. Sensitivity ranged from 14.4% to 44.8% and specificity from 95.8% to 100%. The fourth EL3 study showed a sensitivity of 92.3% and specificity of 75.6%.

GDG translation to recommendation

Routine DAT (Coombs') testing does not accurately predict subsequent hyperbilirubinaemia in healthy newborns.

The GDG appreciates that the current widespread use of antenatal anti-D prophylaxis in rhesus negative women has influenced the interpretation of an early DAT in their newborns. Passive antibody transfer commonly results in a weakly positive DAT in the absence of haemolysis.[46] However, a strongly positive DAT, particularly in a baby in this group of a woman who did not receive anti-D during pregnancy, should still be considered an important marker of haemolysis and forms part of the formal assessment of a baby with significantly elevated bilirubin levels (see also Chapter 6: Formal assessment).

Recommendation – Direct Antiglobulin Test

See section 4.1

4.6 Effectiveness of transcutaneous bilirubin measurement

Clinical question
What is the effectiveness (clinical & cost) of various tests in predicting hyperbilirubinaemia and preventing morbidity/mortality?

Nine studies have been included; four evaluating transcutaneous bilirubin measurement, two evaluating pre-discharge bilirubin estimation and three evaluating DAT. No studies were identified which evaluated the effectiveness of clinical assessment, risk index scoring, umbilical cord bilirubin or ETCOc measurement.

Description of included studies

Four studies have been included in this section. One retrospective study from the USA compared the number of blood samples for bilirubin measurement, treatment with

phototherapy, length of hospital stay and readmission rates before and after implementation of transcutaneous bilirubin measurement. The other three studies evaluated the impact of transcutaneous bilirubin measurement on the need for blood sampling. These three studies have already been described in detail in the chapter on recognition of jaundice.

Review findings

A retrospective cohort study from the USA[47] evaluated the impact of pre-discharge transcutaneous bilirubin measurement on laboratory bilirubin testing and readmission rate for hyperbilirubinaemia within 7 days of initial discharge. All healthy babies born in a tertiary hospital between August 2002 and December 2003 were included. Since transcutaneous bilirubin testing with Bilichek was introduced in the hospital in April 2003, babies born during this month were excluded from the analysis. The study population was divided into two groups; babies born in the 8 months before (August 2002 to March 2003), and those born in the 8 months after, (May 2003 to December 2003), transcutaneous bilirubin testing was introduced. The decision to measure transcutaneous bilirubin or serum bilirubin was made by the attending physician, and Bhutani's nomogram was used to decide whether to start phototherapy or obtain additional blood samples. In all 6,603 babies were included in the study; 6.8% developed significant hyperbilirubinaemia requiring phototherapy as determined by the attending clinician. No baby was treated with home phototherapy or required ET. The two groups were similar with regard to gender or ethnicity. There was no significant difference in terms of total monthly births or the number of readmissions for hyperbilirubinaemia within 7 days of discharge. No significant change was observed in the proportion of newborns tested by serum bilirubin (31.8% vs. 36.7%, p = 0.21) or in the mean number of laboratory measurements per baby (1.51 vs. 1.56, p = 0.33) after the introduction of transcutaneous bilirubin testing. Similarly no difference was seen in the mean length of hospital stay, either for healthy babies or for babies treated with phototherapy. There was a significant increase in the total number of bilirubin measurements (transcutaneous bilirubin ± serum bilirubin) per baby (mean before transcutaneous bilirubin 0.37, mean after transcutaneous bilirubin 0.61, p = 0.007). The proportion of babies tested for serum bilirubin also increased from 31.8% to 36.7% after introduction of transcutaneous bilirubin, but the difference was not statistically significant. However the mean number of readmissions for hyperbilirubinaemia decreased significantly from 4.5 to 1.8 per 1000 births per month (p = 0.04), and the number of babies treated with phototherapy per month increased from 5.9% to 7.7% (p = 0.014). The authors concluded that there appeared to be a trend towards an increase in laboratory-based bilirubin testing associated with the introduction of transcutaneous bilirubin measurement, but more importantly it led to reduction in the number of hospital readmissions for significant hyperbilirubinaemia. [EL II]

Of the three studies which evaluated the impact of transcutaneous bilirubin measurement on the need for blood sampling for serum bilirubin, the BiliChek device was used in two studies, from Denmark and the UK, while the third study, also from the UK, used the Minolta JM-102. In the Danish study[48], the BiliChek was evaluated both in sick babies in the NICU and in healthy newborn babies. The authors used 70% of serum bilirubin limits (defined by the Danish Paediatric Society guidelines) as a threshold for transcutaneous bilirubin. A retrospectively analysis of this transcutaneous bilirubin threshold showed that 35% (178 of 504) of the NICU babies and 80% (254 of 317) of the healthy term and near-term babies would have avoided blood sampling for serum bilirubin estimation In the UK study using BiliChek[49], a reduction of 55% in blood sampling was reported if serum bilirubin testing was limited to babies with transcutaneous bilirubin levels > 195 micromol/L only. The third study evaluated Minolta JM-102 in 285 healthy babies > 34 weeks gestation in a UK setting[50]. The study reported a reduction of 34% in the number of blood samples if serum bilirubin was levels had only been measured from babies with JM-102 reading > 18 reflectance units.

Evidence summary

There is lack of good quality prospective studies evaluating the impact of routine transcutaneous bilirubin measurement on clinical outcomes. Results from a retrospective cohort study show a reduction in the frequency of hospital readmissions after the introduction of transcutaneous bilirubin measurement. However there was an associated

increase in the number of babies treated with phototherapy and also in the proportion of babies tested for serum bilirubin, though the difference was statistically not significant for the latter. Evidence from three other studies suggests that routine use of transcutaneous bilirubin measurement may lead to a reduction in the number of blood samples collected for bilirubin estimation.

GDG translation from evidence

Low quality evidence suggests that routine pre-discharge transcutaneous bilirubinometer use is accompanied by an increase in the use of phototherapy and a small reduction in the number of hospital readmissions for significant hyperbilirubinaemia. Some studies suggest that the number of serum bilirubin estimations is reduced, whereas others found an increase in the number of these tests.

4.7 Effectiveness of a pre-discharge bilirubin screening program

Description of included studies

Two studies from the USA have been included in this section. The first study was a non-comparative observational study evaluating the impact of the introduction of universal pre-discharge bilirubin screening and a comprehensive post-discharge follow-up program. The second study was a retrospective cohort study which assessed the effectiveness of a universal pre-discharge bilirubin screening program on the number of readmissions and incidence of hyperbilirubinaemia.

Review findings

An observational study was conducted in a large urban hospital in the USA[51] to evaluate the effectiveness of an incremental systems approach to the management of neonatal hyperbilirubinaemia. The study cohort included all near term and full term babies born from 01 January 1990 to 31 December 2000 who were discharged from the well-baby nursery of the hospital. Low birthweight (LBW) preterm babies and babies admitted to the intensive care nursery for any neonatal illness were excluded. The sample population was 31,059 babies of mean BW 3318 ± 457 grams and mean GA 38.7 ± 1.3 weeks.

The approaches implemented in chronological order were (a) selective pre-discharge serum bilirubin measurements (1990-1992) (b) universal serum bilirubin measurement at the time of metabolic screening, with nurses having discretion to order serum bilirubin in individual babies on clinical grounds (1993-95) (c) universal serum bilirubin screening along with post-discharge follow-up based on the serum bilirubin position on the hour-specific nomogram[35] (1996-98) and (d) comprehensive, systems-based management of newborn jaundice (1999-2000), the impact of which was assessed in 2001-2003.

In the systems-based approach all babies had pre-discharge bilirubin estimation (serum bilirubin or transcutaneous bilirubin), and follow-up care for jaundice was provided either at the hospital (more than 85% cases) or at home within 24-48 hours of discharge. Other components of the approach included lactation support, provision of information and advice about jaundice to parents, and close follow-up of jaundiced babies based on their hour-specific bilirubin levels. Clinical evaluation for jaundice severity was recommended for all babies at about 4 days of age, along with targeted follow-up of at-risk babies at 7 days and 14 days. Phototherapy was initiated according to the AAP guidelines 11. Adverse outcomes included exchange transfusion conducted for severe hyperbilirubinaemia or following failure of phototherapy to prevent rise in serum bilirubin levels during both the pre-discharge and post-discharge period, readmission for phototherapy following discharge, and presence of clinical signs of acute bilirubin encephalopathy.

A significant decline in the use of intensive phototherapy and the need for exchange transfusion during the first 7 days after birth was observed following the introduction of the systems-based approach. From 1990 to 1998 the incidence of intensive phototherapy use was about 4%, but it declined to 2.5% during 1999-2000 and was 1.3% during 2001 to 2003. During 1990 to 2000, the incidence of exchange transfusion following the failure of intensive

phototherapy was 1:1827, and it declined to 1:11,995 during 2001-2003. A similar reduction in readmission rates for intensive phototherapy was reported – from 14 per 1,000 babies discharged in 1994 to 5.5 per 1,000 in 2001-2003. No babies developed serum bilirubin levels ≥ 513 micromol/L during the study period, while the frequency of reported serum bilirubin levels ≥ 427 micromol/L was 1:15,000 compared to the reported incidence of 1:625 in previous studies 8 [EL 3]

Another historical cohort study from the USA[52] evaluated the effectiveness of a bilirubin screening program in a private health care organization involving 18 hospitals. The program, started in December 2002, involved measurement of bilirubin in every newborn baby either on recognition of jaundice or before discharge from hospital. Two hospitals used BiliChek to measure transcutaneous bilirubin levels while others used serum bilirubin; the bilirubin measurements were plotted on the hour-specific nomogram. Any bilirubin level ≥ 40th centile was notified to the relevant health care provider and the baby managed according to his/her discretion. All babies born at GA ≥ 35 weeks were enrolled in the study. Those born after the initiation of the program (01 January 2003 to 31 December 2004) formed the cohort group (N = 52,483), while those born before the program started (01 March 2001 to 31 December 2002) formed the comparison group (N = 48,798). Other details of the two groups were not given and no comparison was made between their baseline characteristics.

Compliance with the program was good - within 2 months of starting it, more than 99% of the babies had at least one pre-discharge bilirubin level measured. After the first 3 months of the study, the percentiles of the hour-specific nomogram were modified since a large number of babies were reported to have bilirubin measurements in the high or intermediate-high zones.

A significant decline in the incidence of hyperbilirubinaemia was reported after implementation of the screening program. The proportion of babies with serum bilirubin levels ≥ 342 micromol/L declined from 1 in 77 to 1 in 142 ($p<0.0001$), while the proportion with serum bilirubin levels ≥ 427 micromol/L) declined from 1 in 1,522 to 1 in 4,037 ($p<0.005$). The incidence of hospital readmission for hyperbilirubinaemia also fell significantly, from 5.5 per 1,000 before the program to 4.3 per 1,000 babies after its introduction ($p<0.005$). The authors concluded that a universal screening program coupled with evaluation of bilirubin using a percentile-based nomogram can lead to significant reduction in the incidence of hyperbilirubinaemia and hospital readmissions for phototherapy. [EL II]

Evidence summary

There is no good quality prospective comparative study assessing the impact of universal pre-discharge bilirubin testing. Results from two studies with EL3 and EL2+ suggest that the introduction of universal bilirubin screening is followed by reduction in the number of hospital readmissions for phototherapy. The non-comparative observational study also found a reduction in the incidence of intensive phototherapy and exchange transfusion, while the retrospective study reported a decrease in the frequency of reported serum bilirubin levels ≥ 342 micromol/L.

GDG translation from evidence

Low quality evidence suggests that universal pre-discharge bilirubin testing may reduce the need for intensive phototherapy and exchange transfusions, and the readmission rate for significant hyperbilirubinaemia. These studies did not report on bilirubin encephalopathy and stated that there were no recorded cases of kernicterus. However the lack of high quality evidence to show that universal pre-discharge bilirubin measurement reduces the frequency of hospital re-admission, exchange transfusions and bilirubin encephalopathy means that it is not possible to make a conclusion on role of universal pre-discharge bilirubin testing in the UK but have made a research recommendation on this topic.

Recommendation – pre-discharge bilirubin

Do not measure pre-discharge bilirubin levels routinely in babies who are not jaundiced.

Recognition (4.7)

How accurate are transcutaneous bilirubinometers in assessing bilirubin levels in preterms babies and babies with dark skin tones or with high levels of bilirubin

Why this is important

Evidence: The accuracy of transcutaneous bilirubinometers has been adequately demonstrated in term babies below treatment levels (bilirubin < 250 micromol/L). New research is needed to evaluate the accuracy of transcutaneous bilirubinometers in babies with, gestational age under 37 weeks, dark skin tones, high levels of bilirubin, and who are or have had received phototherapy for neonatal hyperbilirubinaemia. Population: Babies in the first 28 days of life. Subgroups to include pre-term and babies with dark skin tones. Exposure: Bilirubin levels taken from transcutaneous bilirubin. Comparison: Bilirubin levels assessed using serum (blood) tests. Outcome: Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value), parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

4.8 Effectiveness of DAT

Description of included studies

Three EL3 studies from the USA were identified. Two studies compared selective versus universal DAT while a third study compared readmission rates and phototherapy rates for tested and untested babies.

Review findings

A retrospective observational study from the USA[53] studied the effectiveness of DAT testing in a sample of births within a 1 year period (Jan – Dec 2000). Mean GA, mean birth weight and gender were not specified; 46% of babies studied were Asian and 36.8% were white. Cord blood DAT was performed on 2,443 babies of mothers with blood group O or Rh negative while 2,097 babies of mothers with groups A, B, AB or Rh positive were not tested. The records of all DAT positive babies were reviewed for information relating to the presence of jaundice and serum bilirubin results if measured in first 24 – 48 hours. DAT was positive in 193 (7.9%) of tested babies. Phototherapy was used in 36 (18.6%) of DAT positive babies. Data for use of phototherapy in DAT negative babies was not provided. Readmission for phototherapy was needed for 26 (1.1%) of all DAT tested babies, and for 19 (0.9%) of untested babies. This difference was not significant (OR 1.17, 95% CI 0.65 to 2.13). [EL III]

A cohort study from a tertiary centre in the USA[54] compared universal and selective newborn cord blood testing (NCBT). In the retrospective cohort group, all cord blood specimens received by the blood bank in 1989 were tested while in the prospective cohort group selective testing (all babies in intensive care, babies with clinical jaundice, babies of Rh negative mothers and/or positive maternal antibody screening, maternal blood group unknown) was carried out on admissions between July 1990 and June 1991. Of the retrospective cohort, 2,253 of 4,003 eligible babies (56.3%) were tested. Of the prospective cohort, 1,048 of 4,498 babies (23.3%) were tested selectively. Cord blood collection difficulties and specimen handling problems were given as reasons for the 1,750 missing test results in the retrospective sample. 15 babies were re-admitted for hyperbilirubinaemia in both study periods. The prevalence of DAT positive tests was not specified. The rate of

readmission for hyperbilirubinaemia was 0.4% (15 of 4003) among universally tested babies and 0.3% (15 of 4498) among selectively tested babies. This difference was not statistically significant (OR 1.12, 95% CI 0.56 to 2.30). [EL III]

A third study from the USA[55] also examined the effectiveness of universal versus selective DAT testing. A retrospective analysis of all records for 1990 and 1991 was carried out to identify babies of group O, Rh positive, mothers. Altogether 301 babies with a mean GA of 39.4 weeks and mean BW of 3343.6 grams were included; 50.5% were male, 44.5% were white and 16.3% were black. Of 113 babies tested 29 (25.7%) were ABO incompatible and 14 (12.4%) were DAT positive. A total of 188 babies were not tested routinely. Of these, 34 (18.1%) had DAT tests requested by their treating doctor; 18 (9.6% were ABO incompatible and 13 (6.9%) were DAT positive. The overall prevalence of DAT positivity was 9.0% (14 of 301 babies). Phototherapy was used in 4 of 113 universally tested babies (3.9%) and 8 of 188 selectively tested babies (4.3%). The OR was 0.83 (95% CI: 0.24 to 2.81). The rate of readmission for phototherapy was 1.8% (2 of 113) among universally tested babies and 0.5% (1 of 188). Again, this difference was not statistically significant (OR 1.12, 95% CI 0.56 to 2.30). [EL III]

Evidence summary

Three EL3 studies using undefined criteria for readmission for hyperbilirubinaemia were included. Two studies compared universal versus selective DAT testing and one compared DAT tested and DAT untested cohorts. No significant difference was found in the readmission rates or phototherapy rates between those undergoing universal testing and those tested selectively. In the 3rd study readmission rates for phototherapy among DAT tested babies were 1.1% and among untested babies were 0.9%.

GDG translation from evidence

There is no good quality prospective comparative study assessing the impact of universal DAT. EL3 studies found no significant difference between universal and selective screening or between babies who received a DAT and those who had not received the test.

See section 4.5 above for recommendation

5 Recognition

Introduction

This chapter addresses the problem of recognition of jaundice and discusses visual assessment and the measurement of jaundice.. Although bilirubin causes yellow discolouration of the skin, the whites of the eyes and the palate, detection of this discolouration can be surprisingly difficult. Even babies with very pale skin can appear "suntanned" rather than yellow, and detection of jaundice in babies with dark skin tones can be almost impossible. In jaundice caused by liver disease the total bilirubin level is variable. Sometimes a baby may not be obviously jaundiced yet has a serious, potentially lethal disease. In babies with liver disease the degree of jaundice does not correlate to the severity of the liver disease. Traditional teaching on examination for jaundice has recommended "blanching" a small area of skin (often on the nose) by pressing it, and inspecting at the whites of the eyes and palate. Jaundice is thought to spread from the head to the toes in a "cephalo-caudal" progression. The "zones of Kramer"[33] attempt to quantify this progression. This review of the evidence was a crucial part of the guideline, because if babies are not recognised to be jaundiced in the first place they will not enter the care pathway.

Clinical question
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?

For answering the question on diagnostic accuracy of various tests in the recognition of jaundice or detection of its severity, these studies were reviewed against the following pre-defined criteria:

- prospective studies
- diagnostic accuracy of the test or its correlation evaluated against the reference standard (serum bilirubin levels)
- test and the reference test performed within 1 hour of each other

A total of 30 studies have been included in this review. Except for four studies with quality EL I (one on visual inspection and three on transcutaneous bilirubin measurement with BiliChek) and six studies with EL III, the rest of the studies are of EL II with the main reason for downgrading their quality being the absence or non-reporting of blinding among the test/reference test operators. Only one study was identified on the diagnostic accuracy of urine or stool examination and limited evidence was available for the icterometer. As few diagnostic accuracy studies had been carried out in preterm and dark skinned babies, the selection criteria were relaxed in studies related to these populations. Diagnostic accuracy of three devices used for transcutaneous bilirubin measurements – Minolta JM-102, Minolta JM-103 and BiliChek, has been reviewed.

Most of the studies have reported the correlation coefficient (r) of the test results with the serum bilirubin values. This statistical measure indicates a degree of association between the two tests, but it is largely dependent on the distribution of serum bilirubin values in the sample population and does not adjust for various biases. Efforts were made to convert the unit of bilirubin measurement from mg/dl to micromol/L (1mg/dl = 17.1 micromol/L) and present the diagnostic accuracy results in terms of sensitivity and specificity where the data were sufficient. Meta-analysis was performed to calculate the diagnostic accuracy of Minolta JM-102 and JM-103 using the statistical programme MetaDisc (http://www.hrc.es/investigacion/metadisc_en.htm). As the reported thresholds of transcutaneous bilirubin levels in the included studies were variable, results were pooled

using the summary ROC curve analysis and Area under ROC curve (AROC) calculated. In order to get a baseline test performance value for the various tests, their sensitivity and specificity were also pooled using the random effects model.

5.1 Visual / Clinical examination

Description of included studies

Seven studies have been included in this section. All the studies evaluated the correlation of clinical assessment of jaundice by experienced healthcare professionals, while one study also evaluated parental assessment. Six studies were conducted in a hospital setting and one in a community setting.

Review findings

In the first study, from Israel[56], 1,129 term and late preterm babies of Jewish (73%) and Arab (26%) ethnicity were clinically assessed for jaundice by experienced clinicians (5 neonatologists and 17 nurses) in a hospital. All the babies were examined by the observers for cephalo-caudal progression of jaundice, and they were unaware of the serum bilirubin levels which were collected simultaneously at the time of visual inspection. The clinical assessment (called "BiliEye") and serum bilirubin values were grouped into risk zones according to a nomogram developed by Bhutani et al35, and the ability of BiliEye to detect significant hyperbilirubinaemia (defined as zones C+D on the nomogram) was analyzed by calculating the area under the ROC curve.

Although BiliEye and serum bilirubin values were moderately positively correlated ($r = 0.75$, $p<0.001$), there was generally a poor agreement between the different observers (kappa = 0.363) for the degree of clinical jaundice. Visual assessment also led to a high false-negative rate, that is, a large number of babies were misclassified into either the lower or higher risk zones and 61.5% (67 of 109) of babies with serum bilirubin in the high-risk zones (zones C ± D on the nomogram) were clinically misclassified as being in the lower risk zones. Moreover 8.1% (230 of 2,857) of babies with clinical estimation determined to be in zone A had serum bilirubin values in the higher risk zones (zone B, C or D), indicating that BiliEye readings in the low risk zone had a NPV of 92% in ruling out serum bilirubin values in the higher risk zones. The area under the ROC curve plotted for the high-risk zones C ± D was 0.82. After adjusting for postpartum age and gestational age (GA), the best results for the diagnostic accuracy of BiliEye to detect significant hyperbilirubinaemia were seen when the observations were made after 60 hours of age in babies ≥ 37 wks GA (AROC = 0.93). The results were poor for observations made before 36 hours of age (AROC = 0.64) and in babies born at less than 37 weeks GA (AROC = 0.61). [EL I]

The second study was conducted in an urban public hospital in the USA[57]. The sample population comprised 122 healthy full term babies with jaundice, with an Rh-negative mother or with a positive DAT. Two observers (paediatric residents, nurse practitioners or physicians) independently recorded their clinical assessment of jaundice in babies for pre-specified parts of the body, and serum bilirubin was measured within 1 hour of the assessment. The clinical assessment included subjective evaluation of jaundice at each site (absent, slight or obvious), subjective evaluation of the skin tone (light or dark), and estimation of serum bilirubin level based on clinical appearance. Ethnic origins were not recorded. Results of the clinical assessment were kept in sealed envelopes until serum bilirubin results were available. Though there was good agreement between pairs of observers regarding the baby's skin tone (k = 0.56), agreement for jaundice at each site was generally poor (only marginally better than chance) with the best agreement seen at the 'nipple to umbilicus' site (k = 0.23, 95% CI 0.09 to 0.38). Linear correlation between the estimated serum bilirubin levels and actual serum bilirubin levels was poor but statistically significant ($r = 0.43$ and 0.54 for the 2 groups of observers, $p<0.01$). The presence of visible jaundice extending between the 'nipple line and the umbilicus' or the lower chest had the best diagnostic accuracy (among all the sites) for detecting serum bilirubin levels > 205 micromol/L with a sensitivity of 97% but a specificity of 19% only. If visible jaundice was

absent in the lower chest, it had a negative predictive value (NPV) of 94% in ruling out serum bilirubin levels above 205 micromol/L. [EL II].

The third study was conducted in a community setting in the USA[58] and involved follow-up visits by 12 home nurses to babies (N = 164) delivered in a hospital setting. The sample population was multi-ethnic; 60% of babies were white, 18% black, 6% Asian, 7% Hispanic and 9% were of other ethnicity. Babies who were in the intensive care nursery, had received phototherapy, whose mothers were not proficient in English or who lived more than 10 miles from the hospital were excluded. The mean age of babies at examination was 6.4 ± 2.5 days. If the baby was felt to be jaundiced, nurses obtained blood for serum bilirubin measurement followed by assessment in three different ways – clinical assessment using their usual method (e.g blanching skin, looking for jaundice at sclera, nose), judging cephalo-caudal progression, and taking an Ingram icterometer reading from the nose. Eighty-two babies were judged to have jaundice. The nurses' usual method of clinical assessment showed the best correlation with serum bilirubin levels ($r = 0.61$, $p<0.01$), while assessment of cephalo-caudal progression and use of the icterometer showed lower levels of correlation ($r = 0.47$ and $r = 0.48$ respectively, $p<0.01$ for both). Only 3 babies had serum bilirubin > 291 micromol/L and nurses were able to correctly predict the levels in two of them. For detecting serum bilirubin > 205 micromol/L, the presence of jaundice caudal to the nipple line had a sensitivity of 76% and specificity of 60%, while an Ingram icterometer reading ≥ 2.5 showed a sensitivity of 75% and specificity of 72% [EL II].

The fourth study, from Israel[59], sought to determine whether clinical impression of jaundice could be used as a primary screening tool for hyperbilirubinaemia in a sample of Jewish (76%) and Arab (24%) babies. All full term babies (N = 283) with jaundice were assessed by four neonatologists before discharge regarding severity of jaundice (sufficient to collect a blood sample) and their estimated serum bilirubin levels. Laboratory serum bilirubin levels were measured within 30 minutes. The physicians were unaware of the baby's previous history and serum bilirubin levels. Their clinical estimates of serum bilirubin were statistically significantly correlated with the actual serum bilirubin values but with varying degree of linear correlation (correlation coefficients ranging from 0.62 to 0.79). On combining the results of all the four physicians, the correlation coefficient was 0.68 ($p<0.001$) [EL II]

In the fifth study, conducted in a newborn nursery in the USA[60], 171 babies over 2 days of age were initially assessed for the severity of jaundice by nurses and physicians using both cephalo-caudal progression and their clinical estimate. The maternal ethnic origins were described as white (50%), black (24%), Asian (13%), Hispanic (9%) and 'other' (4%). The assessment was done at the time of serum bilirubin estimation but serum bilirubin values were measured for only 89 babies. The parents of these babies were then given written and verbal instructions on how to assess jaundice using assessment of cephalo-caudal progression, and a researcher used the Ingram icterometer to record readings from the nose. Only 11 babies had serum bilirubin values above 205 micromol/L. There was poor agreement between physicians, nurses and parents about whether a baby was jaundiced ($k = 0.48$ for all the 3 paired comparisons). Parental assessment of cephalo-caudal progression of jaundice correlated best with the serum bilirubin values ($r = 0.71$), followed by the icterometer ($r = 0.57$) and the nurses' and physicians' clinical estimates ($r = 0.52$ and 0.55). The nurses' and physicians' assessment of cephalo-caudal progression correlated poorly with serum bilirubin values, the coefficients being 0.48 and 0.35 respectively. [EL II]

Two studies[61;62] with EL II conducted in the same setting in Switzerland compared the clinical assessment of jaundice (Kramer method) and two transcutaneous bilirubinometers (Minolta JM-102 and BiliChek) with serum bilirubin levels. The population in the first study included 140 healthy term babies, of whom 66% were white. In the second study the sample population comprised healthy preterm babies (N = 69) with gestational age between 34 to 37 weeks, of whom 87% were white. Both studies babies with birthweight of at least 2000 grams and age not older than 6 days were included and evaluated for clinical jaundice at regular intervals. When jaundice reached zone 3 on the Kramer scale, transcutaneous bilirubin measurements were made from the sternum with Minolta JM-102 and from the forehead and sternum with the BiliChek. Simultaneously blood was collected for serum bilirubin estimation and analysed within 30 minutes. Apart from analyzing the linear

correlation between the 3 tests and serum bilirubin levels, their diagnostic accuracy was evaluated by measuring the area under the ROC curve for serum bilirubin > 250 micromol/L in term babies and serum bilirubin > 190 micromol/L in pre-term babies.

In term babies, transcutaneous bilirubin recordings using the Minolta JM-102 showed the best results in terms of linear correlation and diagnostic accuracy (R2 = 0.82, p < 0.01 and AROC = 0.98). Clinical assessment showed variable results for the correlation coefficient among the white and non-white babies (R2 = 0.74 by nurse and 0.70 by investigator for white babies, R2 = 0.71 by nurse and 0.65 by investigator for non-white babies). The area under the ROC curve for the Kramer method was 0.88. It was also seen that a grading of jaundice below 2 on the Kramer scale (determined by the nurses) had 100% NPV in ruling out serum bilirubin levels > 250 micromol/L. The second study done on healthy pre-term babies showed similar results – Minolta JM-102 showed the best performance with an area under the ROC curve of 0.96 and squared correlation coefficient R2 = 0.76 (p<0.001). BiliChek performed worse than Minolta JM-102 but better than clinical assessment with AROC of 0.88 and 0.89 at forehead and sternum respectively. Values for squared correlation coefficients and AROC for the Kramer method were poor, 0.22 and 0.73 for nurses' observations respectively, and 0.20 and 0.70 for the principal investigator observations.

Evidence summary

Evidence from EL I and EL II studies shows that clinical estimation of the degree of jaundice by experienced healthcare professionals and nursery staff is moderately correlated with actual serum bilirubin levels. The value of the correlation coefficient was much less for the preterm babies and babies with dark skin tones compared to babies with light skin tones and term babies respectively. In one study parental assessment of cephalo-caudal progression showed better correlation than assessment by nurses and paediatricians. Variable results were seen regarding the diagnostic accuracy of clinical assessment in detecting severity of jaundice. In one study visible jaundice 'caudal to nipple line' had a sensitivity of 97% and a specificity of 19% in detecting serum bilirubin levels > 205 micromol/L, while the other study reported 76% sensitivity with 60% specificity. Results from the EL1 study show that visual assessment led to more than 60% of babies being misclassified into the lower risk zones on the nomogram when their serum bilirubin values were actually in the high-risk zones. Moreover this study found clinical assessment to have poor diagnostic accuracy in detecting jaundice in high-risk zones when the observations were made before 36 hours of age and in babies born before 37 weeks of gestational age.

Nevertheless results from three studies show that if clinical examination carried out on the second or third day indicates absence of jaundice, it has high NPV for ruling out the presence of hyperbilirubinaemia (5.1).

Table 5.1 NPV of low degree of jaundice assessed by visual inspection

Study details	Sample characteristics	Timing of assessment	Indicator of absent jaundice or low grade jaundice	Definition of severe hyperbilirubinaemia	Results
Riskin A et al 2007 [56]	Healthy full term and late pre-term babies ≥ 35 wks before discharge (N = 1129)	Mean: 62 ± 24 hrs (median 55 hrs; range 9 to 252 hrs)	Clinical icterus assessed to be in Zone A / low risk zone on Bhutani's nomogram (< 40th centile)	serum bilirubin levels in Zone B, C and D or in intermediate (low, high) and high risk zones on Bhutani's nomogram (> 40th centile)	NPV: 91.9% (2627/2857) Negative LR: 0.45
Moyer VA et al 2000 [57]	Full-term healthy babies with BW > 2000 grams and GA > 36 wks (N = 122)	Mean age 2 days (range 8 hrs to 7 days)	Presence of icterus in lower chest (nipple line to umbilicus)	serum bilirubin levels > 205 micromol/L	NPV: 94.3% (33/35) Negative LR: 0.15
Szabo P et al 2004 [61]	Healthy full-term babies with BW > 2000 grams and no older than 6 days. (N = 140) Excluded – jaundice within 36 hrs	Data not given	Kramer zone 2 assessed by nurses (data not given for zone 0 or 1)	serum bilirubin levels > 250 micromol/L	NPV: 100%

GDG translation of evidence

The experience of the GDG is that it is important to examine the naked baby in good light, preferably natural light. Review of the evidence shows that in most term babies, health care professionals and parents are capable of recognising jaundice, but not very good at assessing its severity clinically.

GDG experience is that jaundice is more difficult to recognise in babies with dark skin tones. The GDG recognised that international kernicterus registries and population studies of hyperbilirubinaemia report over-representation of babies from ethnic groups with dark skin tones. This difficulty may be ameliorated by a careful of all infants including examination of sclera, gums and blanched skin.

Parents can recognise the head-to-toe progression of jaundice. In one study parents recognition of visible jaundice was better that that of clinical staff.

When parents or health professionals consider that a baby is not visibly jaundiced, this assessment is generally reliable in ruling out hyperbilirubinaemia. The negative predictive value of absence of jaundice ranged from 91 - 100% in the studies used in the meta-analysis.

Whenever parents or health professionals consider that a baby is visibly jaundiced, the bilirubin level needs to be measured within hours so the depth of jaundice can be accurately assessed and appropriate care initiated.

Recommendations – Visual / clinical examination:

In all babies:

- check whether there are factors associated with an increased likelihood of developing hyperbilirubinaemia soon after birth (see recommendation 2).
- examine the baby for jaundice at every opportunity especially in the first 72 hours.

When looking for jaundice in all babies (visual inspection)

- check the naked baby in bright and preferably natural light.
- examination of the sclerae, gums and blanched skin is useful across all skin tones

Parents, carers or healthcare professionals can carry out the visual inspection

In babies with factors associated with an increased likelihood of developing hyperbilirubinaemia (recommendation 2) conduct an additional clinical examination including a visual inspection for jaundice during the first 48 hours of life

Do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice

5.2 Urine / Stool examination

Description of included studies

A single non-diagnostic study (project report) from the UK[63] was identified to provide evidence for this test. This study reported the results of a community programme conducted in three phases in which stool colour charts were used to determine liver disease during the neonatal period. In the first phase, parents were asked to record the colour of their babies' stools during the first 28 days of age. 109 parent-baby pairs were recruited and 5,053 stool observations made. The six most commonly selected stool colours were then combined with three pale colours to develop a simplified stool colour chart during the second phase. In the third phase, acceptability and specificity of this chart was evaluated among 3,629 mothers the time of first health visitor visit (usually around 10-14 days). During the second visit (at 28 days), the health visitors collected the information and examined the babies. Any baby thought to be jaundiced or with a history of passing 'pale stools' was referred, investigated for the presence of cholestatic jaundice and followed up for 6 months. In total, 127 babies were jaundiced at 28 days of age with the incidence of jaundice in breastfed babies being 9.2% (95% CI 7.8-11.0%). Many of these babies had abnormal liver function tests but none had abnormal stool/urine colour and none was found to have liver disease. Four non-jaundiced babies were reported to pass pale stools (less than 3 occasions in all), but they were not investigated as stools returned to normal colour and all were thriving at the 6 months follow-up. The authors concluded that though prolonged jaundice is common in breast-fed babies, serious pathology is rare and the combination of prolonged jaundice with persistently pale stools and/or dark urine is very uncommon. Hence, referral of babies with this combination of signs should be considered necessary and all such babies should be investigated immediately. [ELIII]

Evidence summary

No diagnostic study on the accuracy of urine or stool examination to detect liver disease in jaundiced babies was found. A community programme reports that though prolonged jaundice is common in breast-fed babies, these babies rarely have serious liver pathology or pale stools/dark urine. No baby was diagnosed with liver disease during the study period and hence the sensitivity of the stool colour chart could not be evaluated, but it showed a high specificity.

GDG translation from evidence

There is no evidence to show that the examination of stool colour is helpful in the recognition of jaundice in babies. Babies' stools undergo a sequence of colour changes as part of normal postnatal adaptation. GDG experience is that the majority of breast fed babies with prolonged jaundice pass stools and urine of normal colour. (See section 6.8 for prolonged jaundice)

5.3 Icterometers

Description of included studies

Five studies have been included – four in term babies including two in dark skinned babies, and one in preterm babies. The studies were carried out between 1974 and 1998 in the USA(2), Rhodesia, Tanzania and Turkey. The Ingram and the Gosset icterometers were used in two studies each while the fifth study did not report the type of icterometer evaluated.

Review findings

The first study, conducted in a community setting in the USA[60], has already been described in detail in the section on visual examination. The sample population in the study was multi-ethnic and comprised 164 neonates discharged from hospital. During home visits by the nurses, clinical examination and icterometer recordings were done at the time of blood sampling for serum bilirubin estimation. The Ingram icterometer showed a poor linear correlation with serum bilirubin values ($r = 0.48$, $p<0.01$), and had a sensitivity of 75% and specificity of 72% in predicting serum bilirubin > 205 micromol/L with a threshold reading ≥ 2.5 [EL II]

Another study, from Turkey[64], compared the correlation of both the Ingram icterometer and the Minolta JM-102 bilirubinometer with serum bilirubin levels. The study sample comprised 96 full term jaundiced babies between 1 and 5 days of age with a mean birthweight of 3,380 ± 419 grams. Within 30 minutes of blood sampling for serum bilirubin levels, and without the knowledge of the result, transcutaneous bilirubin levels were obtained from the forehead with the Minolta JM-102 and from the nose with the Ingram icterometer. Results showed a significant positive linear correlation between serum bilirubin values and the readings from both the Minolta JM-102 ($r = 0.83$) and the Ingram icterometer ($r = 0.78$). The diagnostic accuracy of the instruments was also assessed in predicting serum bilirubin > 220 micromol/L. The Minolta JM-102 showed a sensitivity of 100% with 56% specificity, while the icterometer had the same value for sensitivity but with 48% specificity [ELII]

In the third study, from the USA[65], varying degrees of jaundice were evaluated using the Gosset icterometer on 90 preterm babies in a hospital setting, and compared with serum bilirubin values obtained within 30 minutes of the icterometer reading. The instrument was used by three observers – two with experience in its use and one with no experience. The mean birthweight of the sample population was 1,676 grams and the mean gestational age 31.7 weeks; the sample was predominately white (95%). The linear correlation between the serum bilirubin levels and icterometer readings by the two experienced observers was moderately positive ($r = 0.71$ and $r = 0.75$ respectively ($p<0.001$)), while for the inexperienced observer the correlation coefficient was 0.63 [EL II]

Two studies with EL III measured the correlation of icterometer readings with serum bilirubin values in black newborn babies. In the first study from Tanzania[66], icterometer gradings were recorded in 70 babies (gestational age 30 to 42 weeks) with jaundice who were admitted to the neonatal unit. No exclusion criterion was defined. Icterometer grading was done by blanching the gum, and at the same time venous blood was drawn for serum bilirubin estimation. Results showed a significant positive correlation ($r = 0.91$, $p<0.001$) between the icterometer readings and serum bilirubin levels. The second study, from Rhodesia[67], investigated the usefulness of the icterometer as a screening test in 55 babies with jaundice. The birthweight of the study sample ranged from 1,050 to 3,925 grams, and age at testing varied from 2 to 24 days. Icterometer gradings were done by a single person who was

unaware of the serum bilirubin levels. The results showed a highly significant positive linear correlation between the icterometer gradings and serum bilirubin levels with a correlation coefficient of 0.96 ($p<0.001$).

Evidence summary

Results on the diagnostic accuracy of icterometer in term babies from two studies with ELII were variable. While one study reported a correlation of 0.48 with 75% sensitivity and 72% specificity in detecting serum bilirubin levels > 205 micromol/L, the other study showed correlation of 0.78 and 100% sensitivity with 48% specificity in detecting high serum bilirubin levels (> 220 micromol/L). In preterm babies a value of 'r' was reported as 0.71 and 0.75 by two experienced observers. There is lack of good quality evidence in babies with dark skin tones. Results from the two studies with ELIII indicate high correlation between icterometer gradings and serum bilirubin values.

GDG translation from evidence

An icterometer can be used to confirm the clinical suspicion of jaundice in term babies but it does not provide a reliable measure of severity. For preterm babies, good quality evidence shows a moderately positive association with serum bilirubin levels. Findings from poor quality studies suggest that icterometer readings in babies with dark skin tones correlate well with serum bilirubin levels, but the GDG opinion is that better quality evidence is needed before icterometer use can be recommended in either preterm babies or babies with dark skin tones. Overall the GDG concluded that icterometers should not be used.

See recommendation at end of section 5.4 below

5.4 Transcutaneous bilirubinometers

5.4.1 Review of devices

Three devices are reviewed in this section. Since a large number of studies were identified that evaluated transcutaneous bilirubinometers, it was decided to include studies with EL II or above only. A large number of studies reported the sensitivity and specificity based on the ROC curves without specifying exact values and therefore preference was given to those studies which reported sufficient data for meta-analysis.

5.4.1.1 Minolta JM-102

Description of included studies

Seven studies are included in this section – one each from Denmark [68], Turkey[64], the UK[50], Spain[30], Saudi Arabia[69], the USA[70] and Taiwan[71]. The sample population was made of term babies in six studies while in the seventh study both term and near term babies > 34 weeks of gestational age were included. Five of the studies are of EL II quality with blinding not reported in most while two are of EL III. Exclusion criteria were not defined in three studies. Transcutaneous bilirubin levels were measured on the forehead in all studies, while in two studies readings were also taken from the sternum and reported separately. Although all studies reported diagnostic accuracy in terms of correlation coefficient and six studies reported on sensitivity/specificity of the test for different thresholds, only 4 studies gave sufficient data to be used for meta-analysis.

Review findings

The sample size in the studies ranged from 76 to 2,004. There was a statistically significant positive linear correlation between the transcutaneous bilirubin reading at the forehead and serum bilirubin levels in all the studies. The correlation coefficients ranged from 0.76 to 0.93.

In the two studies for which detailed data were not available for meta-analysis, sensitivity and specificity were reported separately. One study showed transcutaneous bilirubin (JM-102 threshold value 19.9 reflectance units) to have a sensitivity of 86% and specificity of 78% for

detecting serum bilirubin levels > 249 micromol/L, while the other study reported 98% sensitivity and 72% specificity for detecting serum bilirubin levels > 222 micromol/L.

Data from the other four studies were pooled to examine the diagnostic accuracy of transcutaneous bilirubin readings (with different thresholds) with the Minolta JM-102 in detecting serum bilirubin levels > 220 micromol/L in term babies. The pooled sensitivity was 85% (95% CI 76% to 91%) and the pooled specificity was 83% (95% CI 79% to 86%) but there was strong evidence of statistical heterogeneity for both results (12 = 78.5% and 92.8% for sensitivity and sensitivity respectively). In the summary ROC curve (see Figure 5.4.1.3), AROC was 0.93 but a threshold effect could not be seen indicating further evidence of heterogeneity among the included studies.

Study	Sen	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Bilgen 1998	1.000	0.805 - 1.000	17/17	44/79
Karrar 1989	0.735	0.589 - 0.851	36/49	95/106
Maisels 1982	1.000	0.715 - 1.000	11/11	105/124
Tsai 1988	0.905	0.696 - 0.988	19/21	141/157
Pooled Sen	0.847	0.760 - 0.912		

Heterogeneity chi-squared = 13.98 (d.f. = 3) p = 0.003

Inconsistency (I-square) = 78.5 %

No. studies = 4.

Filter OFF

Add 1/2 to all cells of the studies with zero

Figure 5.4.1 Summary Sensitivity

Study	Spe	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Bilgen 1998	0.557	0.441 - 0.669	17/17	44/79
Karrar 1989	0.896	0.822 - 0.947	36/49	95/106
Maisels 1982	0.847	0.771 - 0.905	11/11	105/124
Tsai 1988	0.898	0.840 - 0.941	19/21	141/157
Pooled Spe	0.826	0.789 - 0.859		

Heterogeneity chi-squared = 41.74 (d.f. = 3) p = 0.000

Inconsistency (I-square) = 92.8 %

No. studies = 4.

Filter OFF

Add 1/2 to all cells of the studies with zero

Figure 5.4.2 Summary Specificity

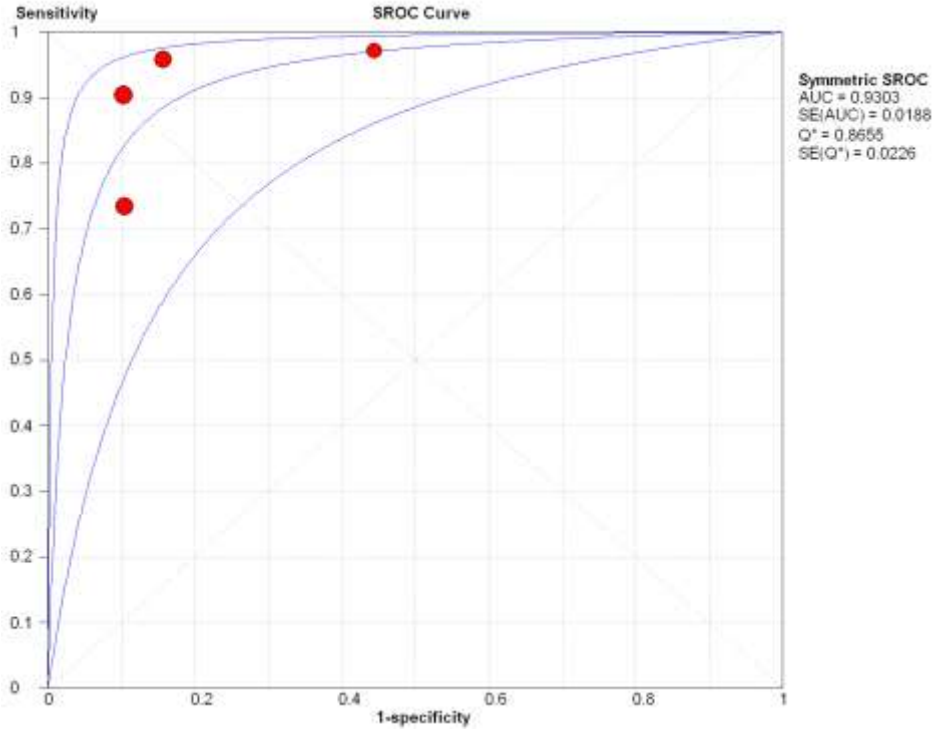


Figure 5.4.3 Summary ROC curve

Evidence summary Minolta JM-102

Results from EL 2 studies show great variation in the accuracy of transcutaneous bilirubin measurement using Minolta JM-102 at the forehead. The correlation coefficient ranged from 0.76 to 0.93 in the included studies. Meta-analysis showed that transcutaneous bilirubin reading at the forehead to have an AROC of 0.93 for the detection of serum bilirubin levels > 220 micromol/L in term babies. The pooled sensitivity was 85% and the pooled specificity 83%, but again these results were marred by strong evidence of statistical heterogeneity. The studies on the Minolta JM 102 were confined to healthy term babies with light skin tones and Chinese babies.

GDG translation from evidence Minolta JM-102

Forehead measurement of transcutaneous bilirubin using the Minolta JM-102 is more accurate than visual assessment for the recognition of jaundice in babies with light skin tones or in those with yellow skin tones.

The Minolta JM-102 is no longer available for purchase from the manufacturers.

5.4.1.2 Minolta JM-103

Description of included studies

Of the 6 included studies in this section, three have been conducted in the USA[72-74], two in Thailand[75;76], and one in Taiwan[77]. The study population in one study from Thailand and one

form the USA comprised healthy preterm babies with gestational age < 36 weeks, while all the other studies included either term babies or both term and near term babies. In the studies from the USA, the population was multi-ethnic in one study, while in two it was predominantly Hispanic. No exclusion criteria were specified in two studies. Transcutaneous bilirubin was measured at the forehead in four studies in term babies and in one study in preterm babies, while the sternum was used as the only site in two studies. Detailed data for meta-analysis were available from 3 studies, but they all reported different thresholds and thus a summary ROC was developed. All the studies are of EL II.

Review findings

The sample size in the studies in term babies ranged from 90 to 849 babies, while there were 196 babies with mean birthweight of 1,887 ± 344.4 grams in the study on preterm babies and in the other study of preterm babies the birthweight ranged from 370 grams to 2989 grams. All the studies showed a statistically significant linear correlation between the transcutaneous bilirubin observations and serum bilirubin levels. In the term babies, correlation coefficients ranged from 0.77 to 0.93 and one study from USA reported variable coefficients for different ethnicities; 0.95 for white babies, 0.82 for black babies and 0.92 for all other babies. This study also reported the difference between the laboratory serum bilirubin levels and transcutaneous bilirubin readings in different ethnicities. The results showed that transcutaneous bilirubin values overestimated serum bilirubin levels by ≥ 51 micromol/L in 17.4% of the black babies compared to 2.0% of white babies and 3.3% of other babies. However in the other three studies in term babies, transcutaneous bilirubin readings were found to underestimate serum bilirubin levels by a mean of 12 micromol/L, 17 micromol/L and 27 micromol/L. This discrepancy did not increase with a rise in the serum bilirubin levels in two of the studies. One study on preterm babies reported a correlation coefficient of 0.79 and reported that the JM-103 overestimated serum bilirubin levels in the first 3-4 days of life but underestimated the serum bilirubin after this age. The second study reported r = 0.92 for GA between 24 and 28 weeks, r = 0.91 for GA between 29 and 31 weeks and r = 0.82 between GA 32 and 34 weeks. This study also noted that the JM-103 underestimated the serum bilirubin by 19 ± 32 micromol/ L in babies with GA between 24 and 28 weeks, by 14 ± 22 micromol/Lin GA between 28 and 31 weeks and by 17 ± 27 micromol/L in babies with GA between 32 and 34 weeks. Data from 3 studies in term babies were pooled to calculate the predictive accuracy of the device in detecting serum bilirubin levels > 255 micromol/L when transcutaneous bilirubin was measured from the forehead with threshold level > 200-204 micromol/L. The pooled sensitivity and specificity were 85% (95% CI 78% to 91%) and 80% (95% CI 77% to 82%) respectively. There was strong evidence of statistical heterogeneity for both results (I2 = 55% and 93% for sensitivity and specificity respectively). The summary ROC curve showed an AROC of 0.87 but there was variation in the individual study results and it showed no indication of a threshold effect.

Study	Sen	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Chang 2006	0.791	0.674 - 0.881	53/67	301/380
Sanpavat 2004	0.929	0.661 - 0.998	13/14	373/446
Engle 2005	0.912	0.807 - 0.971	52/57	34/64
Pooled Sen	0.855	0.785 - 0.909		

Heterogeneity chi-squared = 4.44 (d.f. = 2) p = 0.109

Inconsistency (I-square) = 54.9 %

No. studies = 3.

Filter OFF

Add 1/2 to all cells of the studies with zero

Figure 5.4.4 Summary sensitivity

Study	Spe	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Chang 2006	0.792	0.748 - 0.832	53/67	301/380
Sanpavat 2004	0.836	0.799 - 0.869	13/14	373/446
Engle 2005	0.531	0.402 - 0.657	52/57	34/64
Pooled Spe	0.796	0.767 - 0.822		

Heterogeneity chi-squared = 27.17 (d.f. = 2) p = 0.000

Inconsistency (I-square) = 92.6 %

No. studies = 3.

Filter OFF

Add 1/2 to all cells of the studies with zero

Figure 5.4.5 Summary specificity

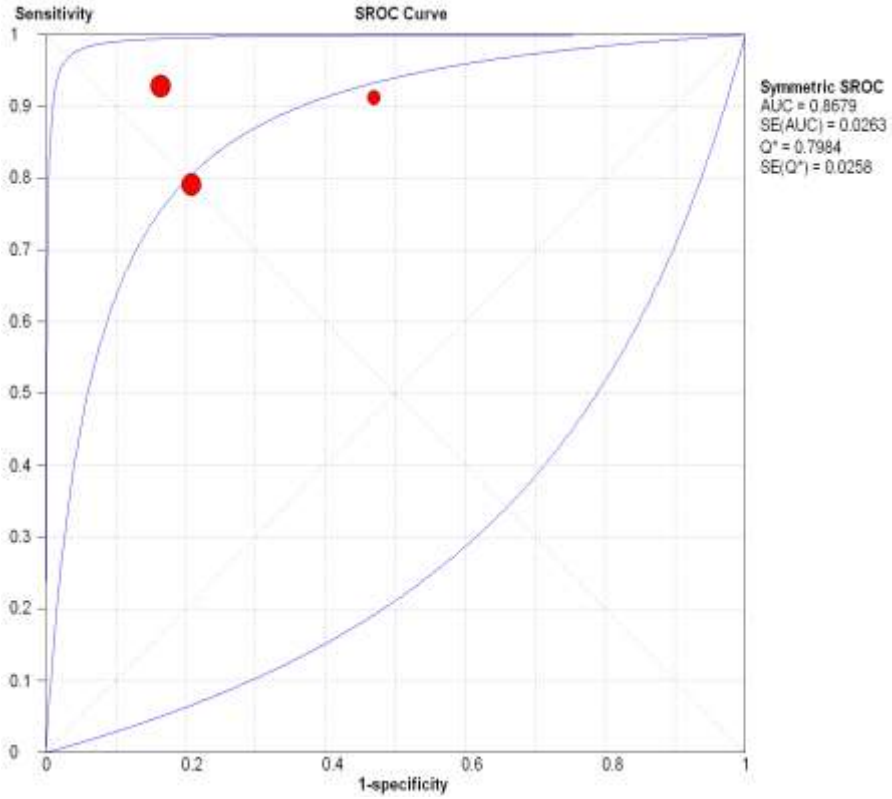


Figure 5.4.6 Summary ROC curve

Evidence summary Minolta JM-103

The EL II evidence on diagnostic accuracy of Minolta JM-103 shows variation in term babies. The correlation coefficients between the transcutaneous bilirubin readings and serum bilirubin levels ranged from a moderate positive 0.77 to a significantly positive 0.93. While three studies found evidence of underestimation of serum bilirubin by the device in term babies, the fourth study indicated overestimation which was much higher in babies with dark skin tones compared to those with light skin tones. The AROC was 0.87 but the summary ROC curve did not show a curvilinear pattern indicating heterogeneity in the study results. The pooled sensitivity and specificity were 85% and 80% with strong evidence of statistical heterogeneity for both results.

In preterm babies the correlation was positive with values of 0.79 in one study and ranging from 0.82 to 0.92 in the second study. The JM-103 consistently underestimated bilirubin levels by a mean of 19 ± 32 micromol/L..

GDG translation from evidence Minolta JM-103

Forehead or sternum measurement of transcutaneous bilirubin using the Minolta JM-103 is more accurate than visual assessment for the recognition of jaundice in term babies.

The evidence from two good quality studies showed a positive correlation between the JM-103 and serum bilirubin estimations. The GDG was concerned that the JM-103 consistently underestimated serum bilirubin by up to 50 micromol/L.

Results from one study (EL II) showed that the reliability of the JM-103 was lower when used on babies with dark skin tones when compared to those with light skin tones.

5.4.1.3 BiliChek

Description of included studies

Seven studies have been included in this section – three with EL I and four with EL II. The study population comprised term babies in one study, term and preterm babies in four studies, and preterm babies only in one study. One study included African babies. It was not possible to combine the studies in a meta-analysis as there were different study populations, different threshold values of transcutaneous bilirubin for calculating diagnostic accuracy, and different levels of laboratory serum bilirubin used as the reference standard. Hence these studies have been described in a narrative manner.

Review findings

The first study is a multi-centric European study[78] conducted in 6 hospitals across five countries – the UK, France, Germany, Italy and Switzerland. A total of 210 term and pre-term babies (35 from each centre) who underwent serum bilirubin measurements as part of normal care at these hospitals were recruited as the sample population. White babies made up 66% of the sample population and about 20% had a gestational age of 36 weeks or less. A single transcutaneous bilirubin measurement was made from the forehead and sternum of each baby using BiliChek 30 minutes before or after blood was drawn. The laboratory estimation of serum bilirubin in each of the participating centres was done using the laboratory's routine equipment. A portion of the blood sample was also sent to a central laboratory for bilirubin assay using HPLC-B without disclosure of the hospital laboratory results. There was a significant correlation between the forehead and sternal transcutaneous bilirubin measurements and laboratory serum bilirubin levels ($r = 0.87$ and 0.85 respectively, $p < 0.001$ for both). The correlation between the laboratory serum bilirubin and HPLC-B levels was also significant ($r = 0.93$, $p < 0.001$).

The difference between the mean serum bilirubin values and the mean transcutaneous bilirubin measurements was statistically insignificant at both the forehead (MD = 2.4 micromol/L, 95% CI -2.4 to 7.1 micromol/L) and the sternum (MD = -14.8 micromol/L, 95% CI -19.9 to 9.5). AROC curve was plotted to calculate the diagnostic accuracy of transcutaneous bilirubin measurements for predicting serum bilirubin determined by the HPLC-B method. At the threshold value of 187 micromol/L, transcutaneous bilirubin had a sensitivity of 93% and specificity of 73% in detecting serum bilirubin > 222 micromol/L. At a threshold of 240 micromol/L transcutaneous bilirubin had a sensitivity of 90% and specificity of 87% in detecting serum bilirubin levels > 290 micromol/L. transcutaneous bilirubin measurements showed similar diagnostic accuracy results (sensitivity and specificity) for detecting hyperbilirubinaemia (serum bilirubin values from HPCL-B method > 290 micromol/L) [EL Ib]

In the second observational study, from Malaysia[79], 345 healthy term babies from different ethnic backgrounds (Malays 63.8% Chinese 30.7% and Indians 5.5%) were studied to assess whether transcutaneous bilirubin measurement using BiliChek could accurately detect severe hyperbilirubinaemia. All babies requiring investigation for jaundice had forehead and sternal transcutaneous bilirubin levels measured within 30 minutes of venous blood being collected for serum bilirubin estimation. The laboratory technicians were blinded to the transcutaneous bilirubin readings. The prevalence of severe hyperbilirubinaemia (serum bilirubin > 300 micromol/L) in the sample population was 27.5% (95 of 345). The correlation between the laboratory serum bilirubin levels and transcutaneous bilirubin readings was strong and significant ($r = 0.80$ and 0.86 respectively for forehead and sternum respectively, $p < 0.001$). Minor variation was observed in correlation coefficients for the three ethnic groups, Malays, Chinese and Indians with the values ranging between 0.79 to 0.84 at the forehead and 0.86 to 0.94 at the sternum. When these data were segregated according to the timing of serum bilirubin and transcutaneous bilirubin, the correlation at less than 80 hours of age ($r = 0.85$) was better than that seen after 80 hours ($r = 0.71$) but 79% of the babies with severe hyperbilirubinaemia had their serum bilirubin estimation done after 80 hours of age.

Forehead transcutaneous bilirubin readings (threshold 250 micromol/L) had a sensitivity of 100% and specificity of 39% for detecting serum bilirubin levels > 300 micromol/L, while the values were 76% and 85% at a transcutaneous bilirubin threshold of 260 micromol/L. For

sternal transcutaneous bilirubin, the sensitivity and specificity at a threshold of 200 micromol/L were 100% and 34% while at a threshold of 280 micromol/L the values were 93% and 84% respectively. When the difference between serum bilirubin and transcutaneous bilirubin was plotted against the mean serum bilirubin and transcutaneous bilirubin measurements, the difference widened markedly from the line of agreement at the mean level of serum bilirubin and transcutaneous bilirubin above 250 micromol/L, especially when transcutaneous bilirubin was measured from the forehead. Moreover the areas under the curves for different serum bilirubin levels (≥ 250 micromol/L, ≥ 280 micromol/L and ≥ 300 micromol/L) were slightly but consistently larger for the sternum readings compared to the forehead readings.[EL I]

In a Danish study[48], the diagnostic accuracy of BiliChek was evaluated in both sick and healthy newborn babies. A total of 488 babies comprised the sample population – both preterm babies < 35 weeks and sick term and near-term babies in the NICU formed Group 1 (N = 261 with mean birthweight 2,521 grams) while Group 2 was made up of healthy term and near-term babies ≥ 35 weeks in the maternity ward (N = 227 with mean birthweight 3,362 grams). Exclusion criteria were well defined but blinding was not specified. Transcutaneous bilirubin was measured with BiliChek on the forehead, sternum, knee and foot, following which capillary blood was drawn for laboratory serum bilirubin estimation. In Group 1 babies, the correlation coefficients for serum bilirubin levels and transcutaneous bilirubin from the forehead and sternum were high (0.88 and 0.82), while they were 0.77 for the knee and only 0.51 for the foot. In Group 2, readings from the sternum showed the strongest correlation (0.90), while it was 0.87 for the forehead, 0.83 for the knee and 0.63 for the foot. Based on these results, the forehead was recommended as the preferred site for transcutaneous bilirubin measurement. Though exact data were not given for Bland-Altman analysis, figures from both groups showed that transcutaneous bilirubin from the forehead underestimates serum bilirubin levels and this underestimation increased as the serum bilirubin level increased. The diagnostic accuracy of transcutaneous bilirubin for detecting serum bilirubin levels, where phototherapy was indicated according to the Danish Pediatric Society guidelines (http://www.paediatri.dk/), was also determined. Using a screening threshold for transcutaneous bilirubin from the forehead as 70% of the serum bilirubin limit (300 micromol/L or 10% of bodyweight in grams for ill babies and 50 micromol/L higher for healthy babies), the sensitivity and specificity in Group 1 babies was 99% and 45%, and for Group 2 100% and 81% respectively [EL II]

The fourth study was conducted in the UK[49] in a regional teaching hospital and included all babies in the postnatal ward who were having blood taken for serum bilirubin estimation. A concurrent transcutaneous bilirubin reading (using BiliChek) was taken but the site was not specified. A total of 300 babies with gestational age ranging from 33 to 42 weeks were included in this study. Of these, 18.3% of them had serum bilirubin levels > 250 micromol/L. Significant correlation was seen between serum bilirubin levels and transcutaneous bilirubin readings ($r = 0.77$, $p < 0.001$). Though the BiliChek underestimated serum bilirubin levels by a small value (mean difference 10.7 micromol/L), the confidence intervals of the difference were wide ranging from -80 to +60 micromol/L. This discrepancy was not found to increase with rises in bilirubin levels. With a threshold value of > 195 micromol/L, transcutaneous bilirubin measurements using BiliChek could detect serum bilirubin levels > 250 micromol/L with a sensitivity of 91% and a specificity of 66% [EL II].

The fifth study was conducted in Italy[80] to evaluate BiliChek in preterm babies. The study population was made of 340 preterm babies with gestational age between 30 to 36 weeks admitted to the neonatal unit of a tertiary hospital. The mean birthweight of the sample was 2,145 ± 518 grams. The unit followed a policy of daily bilirubin monitoring for all preterm babies in the first 120 hours of life. After randomly selecting one of these observations, transcutaneous bilirubin was measured from the forehead about 10 minutes before drawing blood for serum bilirubin estimation. All transcutaneous bilirubin measurements were made by the same investigator, who was blinded to the serum bilirubin results. The correlation coefficient between the two measurements was 0.79 ($p < 0.01$). The BiliChek reading overestimated serum bilirubin level by more than 8.5 micromol/L in 61% of the sample (209/340), with a mean difference of 18.8 micromol/L. This difference was found to increase

at higher levels of bilirubin. The most effective transcutaneous bilirubin threshold values were 111 micromol/L to detect serum bilirubin levels > 171 micromol/L (sensitivity 100% and specificity 40%) and 171 micromol/L to detect serum bilirubin levels > 205 micromol/L (sensitivity 100% and specificity 72%) [EL Ib]

In the sixth study, from Nigeria[81], transcutaneous bilirubin measurements with BiliChek were correlated with serum bilirubin values in a group of African babies with varying degrees of skin pigmentation. The study was conducted at two hospitals; one in a rural setting and the other a tertiary teaching hospital. The study population comprised 127 term and preterm babies with jaundice. Transcutaneous bilirubin measurements were taken from the forehead simultaneously with blood sampling before phototherapy was started. Skin pigmentation was determined by visual observation and classified as light (54% babies), medium (36%) and dark (10%). Transcutaneous bilirubin measurements at the forehead correlated well with the serum bilirubin values ($r = 0.92$, $p<0.001$) when the data were combined from the two hospitals, and the mean difference was 8.5 ± 129.2 micromol/L. When the data were segregated according to serum bilirubin, correlation for serum bilirubin ≥ 205 micromol/L was better compared to serum bilirubin levels < 205 micromol/L ($r = 0.84$ vs. 0.67). At serum bilirubin levels ≥ 205 micromol/L, transcutaneous bilirubin measurements underestimated serum bilirubin with a mean difference of 21.4 micromol/L, but overestimated it when serum bilirubin levels were < 205 micromol/L (mean difference of 35.7 micromol/L). When the data were analyzed on the basis of skin pigmentation, transcutaneous bilirubin measurements correlated strongly with all three degrees of pigmentation. Though the mean difference between transcutaneous bilirubin and serum bilirubin readings was small (8.5 micromol/L), imprecision increased with increasing degree of pigmentation; 92 micromol/L for light, 133 micromol/L for medium, and 197 micromol/L for dark pigmentation. [EL II]

In the last study, from the USA[82], transcutaneous bilirubin measurements with BiliChek and the Vitros method. The study was conducted in a well-baby nursery at a general hospital. The study population comprised 177 term and preterm babies with suspected jaundice. Transcutaneous bilirubin measurements were taken from the forehead simultaneously with blood sampling. The median transcutaneous measurement was 209 micromol/L. The BiliChek overestimated diazo serum bilirubin by a mean of 34 micromol/L and Vitros serum bilirubin by a mean of 22 micromol/L. There was a moderately positive correlation between transcutaneous bilirubin and serum bilirubin values; diazo ($r2 = 0.65$) and Vitros ($r2 = 0.66$) when bias was accounted for. [EL II]

Evidence summary BiliChek

Evidence from good quality studies indicates that transcutaneous bilirubin measurement from the forehead using BiliChek correlates moderately well with serum bilirubin values in term and near-term babies. The correlation coefficient ranged from 0.80 to 0.87. In the study in healthy preterm babies it was 0.79 whereas in another study in preterm and sick term babies it was 0.88.

BiliChek was less accurate at bilirubin levels greater than 250 micromol/L. Results from two studies have reported an increase in the mean difference between serum bilirubin and BiliChek readings with a rise in bilirubin levels. One study found the BiliChek underestimated serum bilirubin in healthy term and near term babies while two studies reported overestimation in healthy term and preterm babies. Though there were differences in the populations studied, threshold cut-off values of transcutaneous bilirubin and the levels of laboratory serum bilirubin used as the reference test, the sensitivity of BiliChek to detect bilirubin levels was generally reported to be high, with variable results for the specificity. In the study on African babies, BiliChek readings showed a reasonable correlation with serum bilirubin values but the difference between transcutaneous bilirubin and serum bilirubin was greatest in babies with darker skin tones.

GDG translation from evidence BiliChek

High quality research suggests that forehead or sternum measurement of transcutaneous bilirubin by BiliChek is more accurate than visual inspection when used to assess the degree of jaundice in term and near-term babies with a range of skin tones.

Good quality studies of BiliChek measurement in preterm babies show a significantly positive correlation with serum bilirubin but there are no studies which report the use of the BiliChek in babies with gestational age less than 30 weeks. The GDG considered that, given the lack of evidence regarding babies of less than 30 weeks gestation, they could not recommend the use of the BiliChek in very preterm babies.

BiliChek is less accurate at higher levels of bilirubin and in babies with dark skin tones.

5.4.2 Cost-effectiveness evidence for transcutaneous bilirubinometers

Alternative testing strategies for hyperbilirubinaemia was identified by the GDG as a priority for an economic analysis. The results are summarised below; further details are available in Appendix B.

The GDG considered that there were two alternative testing strategies to "current practice" in the NHS. These two strategies were to either perform a serum bilirubin on all visually jaundiced babies or undertake a transcutaneous bilirubin measurement on all visually jaundiced babies, with a serum bilirubin measurement on those with transcutaneous bilirubinestimations above a certain threshold. They judged that under their recommended thresholds for treatment (a relatively high threshold) and further monitoring (a relatively low threshold) that either alternative would be equally effective at preventing cases of kernicterus. Therefore, a cost minimisation analysis was undertaken to compare these alternatives. There is insufficient clinical evidence to determine whether more intensive testing for hyperbilirubinaemia using one of these two strategies would be more cost-effective than "current practice", in which visual examination is often used to determine the severity of hyperbilirubinaemia with less than 10% of visually jaundiced babies having a serum bilirubin. However, there is very good evidence to show that visual examination is not reliable in assessing the degree of hyperbilirubinaemia in a jaundiced baby. Therefore, it seems likely that a more intensive testing strategy would overcome some of the limitations of visual examination leading to better and earlier detection of cases which would benefit from appropriate treatment. A threshold analysis was undertaken to estimates the number of kernicterus cases that would have to be averted in order for the more intensive testing strategies to be considered cost-effective.

The economic analysis suggested that, providing the testing strategy using transcutaneous bilirubin measurement could be delivered with less than 9,200 meters (without disposable tips) in England and Wales, it would be more cost-effective than a strategy where all visually jaundiced babies had a serum bilirubin. The threshold analysis suggested that a minimum of 1.52 kernicterus cases per annum would have to be avoided in order for more intensive testing to be considered cost-effective, but that a smaller number of averted cases could be cost-effective if less than 9,200 meters were required.

5.4.3 Overall GDG translation from evidence for transcutaneous bilirubinometers

Evidence shows that transcutaneous bilirubin measurements help with the assessment of the degree of jaundice and are more accurate than visual inspection. Good-quality indirect evidence shows that the BiliChek produces more accurate results than the Minolta JM-102 or JM-103 in babies with dark skin tones but there are currently no published studies directly comparing the BiliChek and the JM-103. The GDG understands that there are differences in the design of these devices but is unable to recommend a particular device.

Studies have used the forehead or sternum as the primary site for transcutaneous bilirubin measurement, and the results are comparable. The opinion of the GDG is that measurement over the sternum is more acceptable to parents and babies. Sternal measurement avoids the problem of failing to obtain a reading because the baby wrinkles his or her forehead when crying. Measurement using the forehead carries a potential risk of injuring the eye if the baby struggles.

The difference between transcutaneous bilirubin and serum bilirubin widens at levels above 250 micromol/L and as few babies with high levels were studied, transcutaneous bilirubin cannot be recommended at levels above 250 micromol/L. If a transcutaneous bilirubinometer records a bilirubin level above 250 micromol/L, a serum bilirubin level should be taken to

check accurately the bilirubin level. The GDG opinion is that transcutaneous bilirubin should not be used in very pre-term babies (GA < 34 weeks) because they are more vulnerable than term babies to kernicterus at relatively low levels of bilirubin and therefore need more accurate testing; and because the evidence for accuracy of transcutaneous bilirubinometers in this group is unclear. The GDG have made research recommendation for both the BiliCheck and JM-103 to be studies in these subgroups of babies with jaundice.

Based on the evidence reviewed in Section 5.1, the GDG are satisfied that visual inspection, by parents or clinical staff, is effective in ruling out jaundice but is unreliable in assessing the depth of jaundice. The GDG recognises that transcutaneous bilirubinometers are non-invasive and are more acceptable than blood sampling.The GDG considers that transcutaneous bilirubinometers should be used after 24 hours of age to avoid problems associated with taking and acting upon blood samples in the community. However if transcutaneous bilirubinometers are not available, serum bilirubin levels should be monitored and recorded.

The NICE guideline on "Postnatal care" recommends that if "jaundice develops in babies aged 24 hours and older, the intensity should be monitored and systematically recorded along with the baby's overall well-being with particular regard to hydration and alertness" (www.nice.org.uk/CG037). The GDG feel that any healthcare professional should be responsible for monitoring and recording the baby's bilirubin.

Current practice is to perform serum bilirubin on a small minority of jaundiced babies, and there are 5 - 7 cases of kernicterus each year in the UK. The GDG is of the opinion that current practice of assessing the depth of jaundice by visual inspection in the majority of babies is unacceptable in view of the evidence which shows that this is inaccurate. The GDG are of the opinion that bilirubin measurement within 6 hours is required for all jaundiced babies. Options include serum bilirubin testing in all term babies who are jaundiced, or transcutaneous bilirubin in those of > 34 weeks followed by serum bilirubin in appropriate subgroups. Depending of the number of bilirubinometers needed, the latter strategy is a more cost-effective option than serum bilirubin in all visibly jaundiced babies (See Appendix B and section 5.4.2) In addition, transcutaneous bilirubin measurement is a less invasive procedure than blood sampling and thus is more acceptable to parents and clinical staff.

Recommendations – Recognition

Measuring the bilirubin level in babies with jaundice

When measuring the bilirubin level

- use a transcutaneous bilirubinometer in term and near term babies more than 24 hours of age
- 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 check the result by measuring the serum bilirubin
- always use serum bilirubin measurement to determine the bilirubin level in babies with jaundice in the first 24 hours of life
- always use serum bilirubin measurement to determine the bilirubin level in preterm babies less than 34 weeks gestational age
- always use serum bilirubin in babies receiving phototherapy.
- do not use an icterometer.

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

Recognition

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

Why this is important

Evidence: The accuracy of transcutaneous bilirubinometers has been adequately demonstrated in term babies below treatment levels (bilirubin < 250 micromol/L). New research is needed to compare the accuracy of different device, BiliChek and Minolta JM-103 in different populations including i) gestational age under 37 weeks, ii) dark skin tones, iii) high levels of bilirubin and iv) hyperbilirubinaemia during, and after phototherapy. Population: Term babies in the first 28 days of life. Subgroups to include pre-term and babies with dark skin tones. Exposure: BiliChek and Minolta JM-103 readings of bilirubin levels. Comparison: Bilirubin levels assessed using serum (blood) tests. Outcome: Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value), parental anxiety, satisfaction, and cost effectiveness. Time stamp: Sept 2009

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6 Formal assessment

Introduction

Most babies with an elevated serum bilirubin level do not have underlying disease, and the jaundice resolves by two weeks of age. However, an important minority have a diagnosis which requires specific treatment. Babies who have haemolysis (rapid breakdown of red cells) because of antibodies or G6PD deficiency can have rapidly rising bilirubin levels which are difficult to control even with phototherapy. The correct diagnosis of ABO blood group incompatibility has implications for future pregnancies, and G6PD deficiency can affect other family members. In babies with prolonged jaundice, a late diagnosis of biliary atresia significantly reduces the chance of successful surgery and increases the chance of a liver transplant being required. For all these reasons further investigation has to be considered in some cases.

Current practice regarding the level of investigation which is carried out in babies who are jaundiced varies enormously, particularly with regard to concern about bacterial sepsis and the use of antibiotics. The GDG considered that it was important to examine the evidence in order to determine the appropriate investigations which should be performed, and in which groups (mild, moderate and severe hyperbilirubinaemia, and early and prolonged jaundice).

Clinical question
Q4. What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia?

i) What are the elements of a formal assessment in a baby with neonatal hyperbilirubinaemia?

a) Clinical examination
b) Total and split bilirubin
c) Blood tests – blood grouping, G6PD levels, haematocrit,
d) Urine tests
e) Biochemical tests (bilirubin/albumin ratio, other relevant tests)

ii) What is the clinical and cost effectiveness of the tests carried out during formal assessment?

In order to identify possible causes of neonatal jaundice according to the severity of hyperbilirubinaemia, it was decided to include only those studies that met the following pre-defined selection criteria:

- Studies with well defined serum bilirubin levels as cut-off for entry into the study
- Studies with no exclusion criteria
- Studies examining incidence rates of both blood group incompatibility and G-6-PD deficiency levels.
- Incidence rates of infections and idiopathic jaundice were also analysed if reported.

Finally, we examined the use of the additional tests such as tests for conjugated and unconjugated hyperbilirubinaemia, medical comorbidity, prolonged jaundice and the bilirubin/albumin (B/A) ratio. The calculation of the B/A ratio has long been suggested as a "proxy" for free bilirubin, because if albumin levels are low then there is more unbound unconjugated free bilirubin in the circulation, and it is free bilirubin which crosses the blood brain barrier. Although there is a substantial literature on the B/A ratio it is not often used in

clinical practice. The GDG are aware of an ongoing RCT in the Netherlands which is specifically directed at evaluating the use of the B/A ratio as an adjunct to serum bilirubin levels in the management of jaundice, but the work is ongoing and no results are as yet available.

Hyperbilirubinaemia:

Identified studies were subdivided into three groups as follows:

- A group with an entry level of serum bilirubin >154 micromol/L but no mean serum bilirubin for the entire sample (used here as a proxy for 'mild' hyperbilirubinaemia)
- A group including studies where either the serum bilirubin threshold for inclusion or the mean serum bilirubin of the entire sample was between 255 and 399 micromol/L. (used here as a proxy for 'moderate' hyperbilirubinaemia)
- A group including studies where the serum bilirubin threshold for inclusion was > 400 micromol/L, the mean serum bilirubin of the entire sample was greater than 400 micromol/L or studies where exchange transfusions were required. (used here as a proxy for 'severe' hyperbilirubinaemia)

Kernicterus

Identified studies included babies who met recognised criteria for kernicterus including the following clinical features:

- Poor feeding
- Lethargy
- High-pitched cry
- Increased tone
- Opisthotonos
- Seizures
- Sensorineural hearing loss,
- Motor delay, extrapyramidal disturbance
- Gaze palsy
- Dental dysplasia

Description of included studies

Overall 33 articles contributed to this analysis and some have been included in more than one group*. All studies were of EL III. Fourteen were case-series and three were cohort studies. Chart reviews, surveys and case-control studies accounted for two studies each. The median sample size was 109 (range 21 – 3,099). For population-based studies the incidence of jaundice by live births was recorded.

Serum bilirubin >154 micromol/L

Nine studies with 10,204 participants contributed data to this analysis (Table 6.1). Three studies each were carried out in Nigeria and India and one apiece in Australia, Pakistan and China. The entry levels ranged from bilirubin levels between >154 micromol/L to >205 micromol/L. Mean serum bilirubin levels were not reported in any study. Jaundice at this level affected 10.4% of all live births in the three population-based studies included in this analysis. Where reported the age of onset of jaundice ranged from 0 – 10 days. Preterm babies were included in three studies and accounted for between 3.6 % and 36.3% of the study sample. Breastfeeding rates and the mean gestational age were not reported in any study. Only one study reported mean birthweight which was 2.73 ± 0.74 kgs. Males accounted for 57.9% of cases in the three studies that reported gender.

Serum bilirubin between 255 and 399 micromol/L

Twelve studies with 2,333 participants contributed data to this analysis (Table 6.2). Two studies each were carried out in Nigeria and Singapore and one apiece in India, Israel, Papua New Guinea, Iran, Saudi Arabia, Taiwan, Turkey and the United Arab Emirates. Bilirubin levels

* If a study was included in more than one category sample demographics are only provided for the first category.

at entry ranged from >170 micromol/L to >306 micromol/L. Jaundice at this level affected 2.2% of all live births in the five population-based studies included in this analysis. The percentage of preterm babies (reported in five studies) ranged between 0% and 18.6% and the mean serum bilirubin levels (also reported in five studies) ranged between 310 micromol/L to 374 micromol/L. Where reported the age of onset ranged from 0 – 15 days, and breastfeeding rates ranged from 63% to 100%. In one study the mean gestational age was 39.3 ± 1.2 weeks and not reported in the other 11 studies. The mean birthweight ranged from 3,082 ± 530 grams to 3,206 ± 340 grams in two studies and was not reported in 10. Males accounted for 52.2% of cases of moderate jaundice in the seven studies that reported on gender.

Serum bilirubin > 400 micromol/L or requiring exchange transfusion

Seventeen studies with 1,997 participants contributed data to this analysis (Table 6.3). There were three good quality national surveillance studies from Canada, Denmark and the UK, while of the rest; two studies each were carried out in India, Nigeria and Turkey and one apiece in Australia, China, Ghana, Greece, Iran, Pakistan, Papua New Guinea and Singapore. Bilirubin levels at entry ranged from >425 micromol/L to >510 micromol/L. Subjects in studies with lower entry level of serum bilirubin but who received exchange transfusions were also included in this analysis. Five studies reported mean serum bilirubin levels ranging from 471 micromol/L to 595 micromol/L. Hyperbilirubinaemia at these levels affected 0.02% of all live births in the three population-based studies included in this analysis. Seven studies reported the proportion of preterm babies and these babies accounted for between 0% and 19.9% in the studies. Where reported the age of onset of jaundice ranged from 0 – 60 days, breastfeeding rates ranged from 81.4% to 100%, mean gestational age ranged from 38.2 weeks to 38.6 weeks and mean birthweight ranged from 2,943 grams to 3,560 grams. Mean birthweight was not reported in four studies. Males accounted for 63.1% of cases of severe jaundice in the seven studies that reported on gender.

Kernicterus

Ten studies with 467 participants contributed data to this analysis (Table 6.4). The studies were carried out in China, Ghana, Singapore, Turkey, the UK and the USA. One population based study reported that kernicterus affected 0.001% of all live births in a UK based sample. No demographic details are available as the data on kernicterus are a subset of the complete sample not all of whom had kernicterus*.

6.1 Blood group incompatibility

Review findings

The pooled prevalence rates of blood-incompatibility increased as serum bilirubin levels rose. This was identified as a cause of hyperbilirubinaemia in 16.9% of cases at serum bilirubin <254 micromol/L, 23.9% at serum bilirubin between 255 micromol/L and 399 micromol/L and 33.7% serum bilirubin >400 micromol/L. Blood group incompatibility was also implicated in 27.8% of cases of kernicterus.

A sensitivity analysis of these prevalence rates (Figure 6.1) shows the varying importance of blood group incompatibility in different regions of the world. In Africa and Asia it accounted for over 20% of cases from serum bilirubin <254 micromol/L to kernicterus. In studies form the Middle East it was found in 21.9% cases of cases of serum bilirubin between 255 and 399 micromol/L, in 29.1% of cases of exchange transfusion or serum bilirubin > 400 micromol/L and in 27.8% of cases of kernicterus. In Europe/North America blood group incompatibility was implicated in 32.1% of cases of serum bilirubin >400 micromol/L or exchange transfusions and 18.9% of kernicterus cases.

* If a study was included in more than one category sample demographics are only provided for the first category.

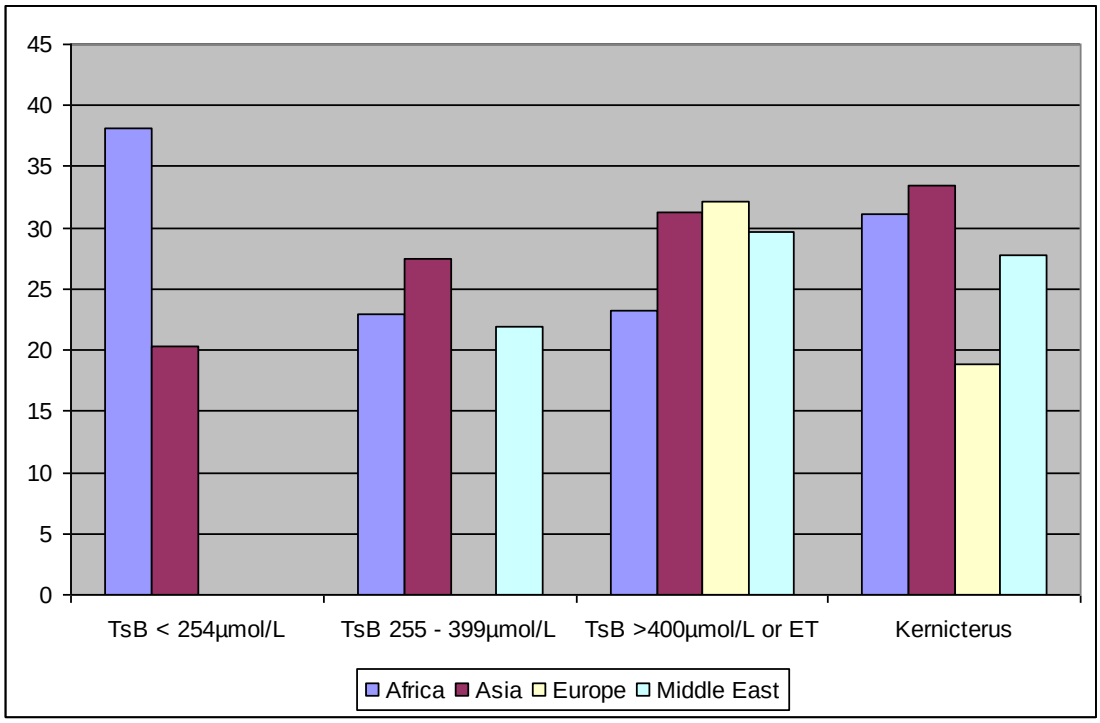


Figure 6.1 Prevalence of blood group incompatibility related to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases (on the Y axis)

6.2 G-6-PD deficiency

Review findings

The pooled prevalence rates of G-6-PD deficiency increased as serum bilirubin levels rose. This was identified as a cause of hyperbilirubinaemia in 6.8% of cases of serum bilirubin <254 micromol/L, 11.8% at serum bilirubin between 255 micromol/L and 399 micromol/L and 16.5% serum bilirubin >400 micromol/L. G-6-PD deficiency was also implicated in 30.6% of cases of kernicterus.

A sensitivity analysis of these prevalence rates (Figure 6.2) shows the varying importance of G-6-PD deficiency in different world regions. In Africa it accounted for over 35.0% of cases at each level of serum bilirubin and in cases of kernicterus. In Asia the prevalence rates rose from 8.8% at serum bilirubin <254 micromol/L, 9.3% at serum bilirubin between 255 and 399 micromol/L, 19.6% of cases of exchange transfusion or serum bilirubin > 400 micromol/L reached a peak at 35.4% of kernicterus cases.

Likewise in the Middle East the prevalence of G6PD deficiency rose from 8.0% in cases with serum bilirubin between 255 and 399 micromol/L to 27.8% in cases of kernicterus. In Europe and North America it was implicated in 5.5% of babies with serum bilirubin > 400 micromol/L or receiving exchange transfusions and 20.9% of kernicterus cases.

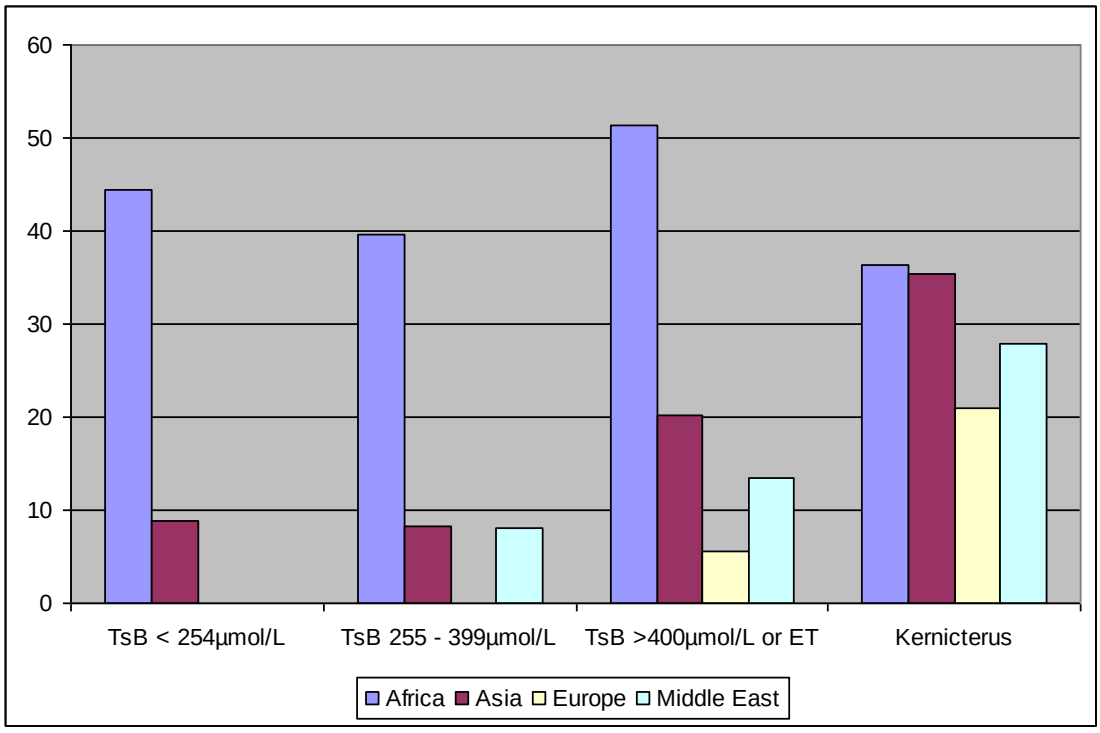


Figure 6.2 Prevalence of G6PD deficiency related to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases (on the Y axis)

6.3 Infection

Review findings

The pooled prevalence rates of infection (as defined in each study – see evidence table) varied as serum bilirubin levels rose. This was identified as a cause of hyperbilirubinaemia in 12.4% of cases at serum bilirubin <254 micromol/L, 9.7% at serum bilirubin between 255

micromol/L and 399 micromol/L and 8.9% at serum bilirubin >400 micromol/L. Infection was also implicated in 15.4% of cases of kernicterus.

A sensitivity analysis of these prevalence rates (Figure 6.3) shows the varying importance of infection in different world regions. In Africa infection was associated with over 13.9% of all cases of hyperbilirubinaemia or kernicterus.

In Asia the prevalence rates ranged from 9.7% and 31.2% of all cases of hyperbilirubinaemia. In the Middle East infection was found in 6.9% of cases of serum bilirubin between 255 and 399 micromol/L and 50.0% of cases of kernicterus. In Europe and North America infection was implicated in 1.9% of babies with serum bilirubin >400 micromol/L or receiving exchange transfusions and in 14.3% of kernicterus cases.

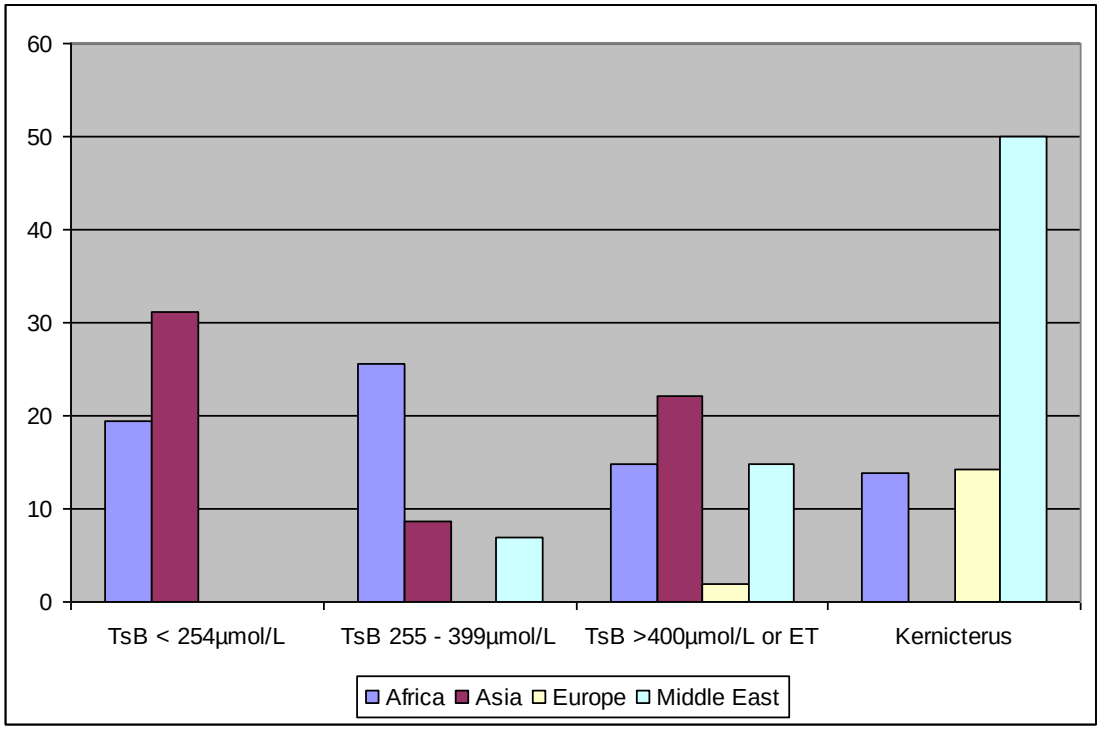


Figure 6.3 Prevalence of infection related to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases (on the Y axis)

6.4 No known cause

Review findings

Unsurprisingly no cause for jaundice was found in significant numbers of babies at all levels of serum bilirubin. No cause was identified in 9.0% of babies who had serum bilirubin <254 micromol/L, 28.8% at serum bilirubin between 255 micromol/L and 399 micromol/L and 31.2% serum bilirubin >400 micromol/L. No cause could be found for the hyperbilirubinaemia in 31.2% of cases of kernicterus.

A sensitivity analysis of these prevalence rates (Figure 6.4) shows the varying importance of idiopathic hyperbilirubinaemia in different world regions. In Africa no known cause was found in over 9.0% of cases from serum bilirubin <254 micromol/L to kernicterus. In Asia no cause could be found for 27% of cases with serum bilirubin between 255 micromol/ and 399 micromol/ and 29.9% of cases or exchange transfusion or serum bilirubin > 400 micromol/L. In the Middle East no cause was found for 62.3% of cases of serum bilirubin over 400 micromol/L and 16.7% of cases of kernicterus. In Europe and North America 27.3% of babies with serum bilirubin over 400 micromol/ and 33.3% of cases of kernicterus had no cause identified.

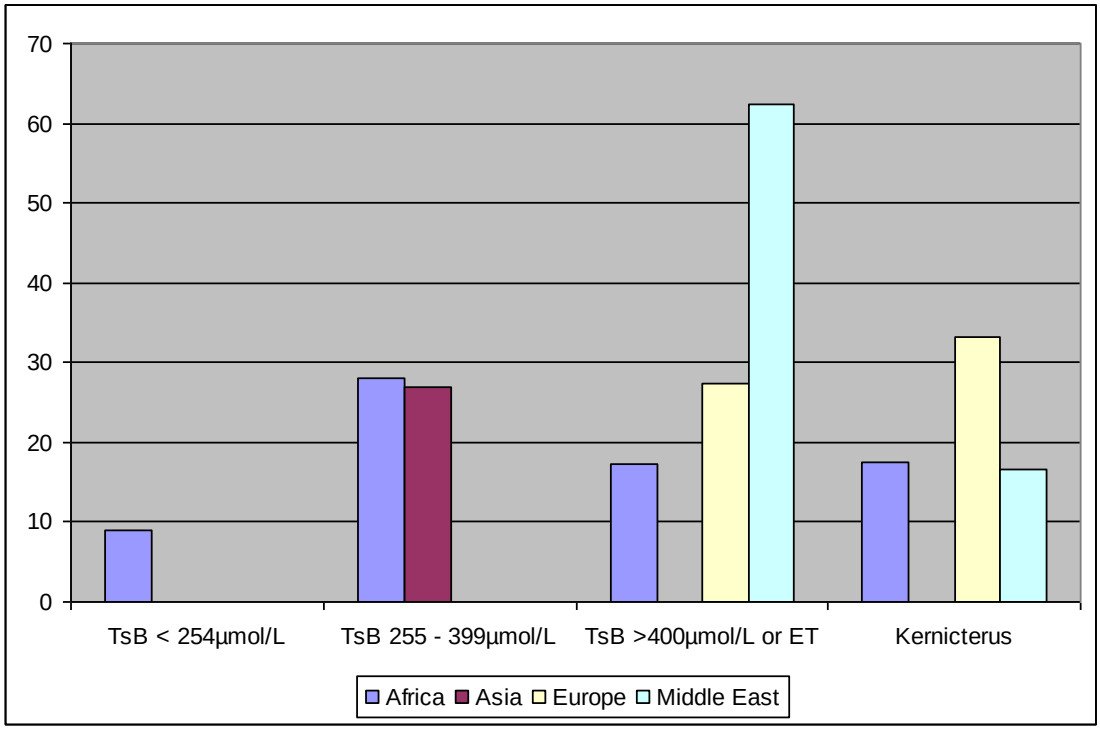


Figure 6.4 Prevalence of 'no cause identified' in relation to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases

Overall Evidence summary

This meta-analysis indicates that blood group incompatibility or G-6-PD deficiency are the most commonly associated conditions in babies with hyperbilirubinaemia over 255 micromol/L. Infection was less commonly found at this serum bilirubin level but was more often found in cases of kernicterus, and in many cases no cause was ever found.

Further examination of the data demonstrates that among jaundiced babies in Europe and North America blood group-incompatibility was the most prevalent underlying factor leading to higher bilirubin levels (> 400 micromol/L), whereas G-6-PD deficiency was more common in kernicterus cases.

G-6-PD deficiency is the most common associated condition in cases of jaundice of any severity among African babies while blood group incompatibility was the second most common factor in this group. Amongst jaundiced babies in Asia both blood group incompatibility and G-6-PD deficiency were the two most common causes and they were identified more frequently in babies with more severe hyperbilirubinaemia. Data from studies in the Middle-East were too sparse to allow any meaningful sensitivity analysis.

Overall GDG translation from evidence

Only poor quality evidence (EL2- and EL3) was available to inform our recommendations regarding the formal assessment of babies with hyperbilirubinaemia. The evidence supports current clinical practice, which includes investigations targeted at detecting haemolysis due to blood group incompatibility and G-6-PD deficiency in appropriate ethnic groups.

The evidence shows that blood group incompatibility remains an important cause of hyperbilirubinaemia and kernicterus in Europe and worldwide. Although the evidence did not support the routine use of DAT in healthy babies this finding emphasizes the conclusions reached in the chapter on prediction (see section 4.5) namely that a positive DAT in a baby born to a mother who did not receive prophylactic anti-D immunoglobulin during pregnancy should be taken into account when considering the cause of jaundice. Any information about the presence of maternal blood group antibodies should be transferred from the mother's notes to those of the baby.

Sepsis was an important co-morbidity in some reported series. No co-morbidity was identified in a significant minority of the babies in the included studies.

Recommendations – Formal assessment

In addition to a clinical examination, carry out all of the following tests in babies with hyperbilirubinaemia requiring treatment (see treatment thresholds in table 1 and graphs A-F):

- 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).

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).

6.5 Bilirubin / Albumin ratio

Review findings

The usefulness of the bilirubin/albumin (B/A) ratio in predicting bilirubin-induced neurotoxicity in preterm babies (<32 weeks) with unconjugated hyperbilirubinaemia was examined in a systematic review[83]. Studies were included if the B/A ratio was measured and outcome data on neurotoxicity or neurodevelopmental outcome was reported. Six studies were included. One study reported a trend suggesting that the B/A ratio was better than serum bilirubin in predicting abnormal auditory brainstem response (ABR) maturation ($p = 0.19$ vs $p = 0.98$) while a second reported that higher B/A ratios were present in babies with abnormal ABR who subsequently developed hearing loss. One of the included studies reported on IQ at six years and found that IQ decreased at higher B/A ratios ($r = -0.12$, $p = 0.06$). A study of autopsies in 398 babies identified 27 (6.8%) with kernicterus. These 27 babies were compared with 103 autopsied babies matched for birthweight and gestational age. There was no difference in mean serum bilirubin between the kernicteric and non-kernicteric babies. Serum albumin and the reserve albumin binding capacity were lower in the kernicteric babies but where B/A ratios could be calculated there was no difference. The final included study found that the bilirubin-binding capacity expressed as the molar B/A ratio was lower in kernicteric than non-kernicteric babies ($p < 0.05$). [EL I]

A case series in India[84] reported the correlation between the B/A ratio and free bilirubin. The study included 53 babies with hyperbilirubinaemia with a mean gestational age of 37.9 ± 2.3 weeks and mean birthweight of 2780 ± 620 grams. The reported mean serum bilirubin as 227 ± 80 micromol/L, mean free bilirubin 8.7 ± 5.6 nmol/l and mean albumin levels were 3.6 ± 0.7 g/dl. The mean B/A ratio was 3.7 and the correlation between free bilirubin and B/A ratio was 0.74 ($p < 0.001$). [EL II]

A Canadian case series[85] examined the relationship between albumin levels and free bilirubin. A total of 55 plasma samples from 46 jaundiced babies were used. Diagnoses included prematurity, birth asphyxia, respiratory distress syndrome and idiopathic hyperbilirubinaemia. The mean gestation age was 36 ± 4 weeks and mean birthweight was2453 ± 813 grams. No other demographic details were reported. There was a correlation between free bilirubin and the bilirubin/albumin molar ratio ($r = 0.75$, $p < 0.001$) [EL III]

6.6 Relationship between circulating free bilirubin and unconjugated bilirubin.

Review findings

A case series from Brazil[86] examined the correlation between free bilirubin and unconjugated bilirubin in 43 term babies with non-haemolytic hyperbilirubinaemia. Inclusion criteria were birth weight >2500 grams, negative DAT, gestational age 37 to 41 weeks, postnatal age < 7 days, and negative maternal history and serology for syphilis The babies had no history of perinatal hypoxia, had Apgar > 8 at 1 and 5 minutes, did not receive any substances competing for albumin binding sites and had not received phototherapy, exchange transfusions or human albumin. Over half of the sample 25 (58.1%) were male but no other demographic data were reported. The correlation between free bilirubin and indirect bilirubin was 0.69 ($p<0.01$). [ELIII]

6.7 Medical co-morbidity identified by measuring conjugated bilirubin, routine haematology or urinalysis

Review findings

A retrospective case series in the USA[87] looked at the usefulness of measuring conjugated bilirubin in jaundiced term babies. Preterm babies were excluded. Testing rates were different in both units in one serum bilirubin and conjugated bilirubin were measured in 55% and 53% of the term babies and in the second unit in 16% and 5% respectively. Abnormal results were defined as the top 5% of conjugated bilirubin measurements in each unit so in the first unit an abnormal score was > 39 micromol/L while in the second it was >17 micromol/L. Of 149 babies with high conjugated bilirubin levels 40 (26.8%) had associated conditions but identifying conjugated hyperbilirubinaemia contributed to the diagnosis in only four of these. Over half, 78 (52.3%), of the cases with high conjugated bilirubin were unexplained while 24 (16.1%) were laboratory errors. Associated diagnoses included isoimmunisation in 19 (12.7%) babies, sepsis or pneumonia in 5 (3.6%), congestive heart failure in 5 (3.6%), multiple anomalies in 2 (1.3%), pyloric stenosis in 2 (1.3%), extreme growth restriction (possible rubella) in 1 (0.7%), hypothyroidism in 1 (0.7%), choledochal cyst in 1 (0.7%). [EL III]

A retrospective case series in the USA[88] looked at the usefulness of laboratory tests in babies with hyperbilirubinaemia. Only babies (n = 447) with a birthweight of > 2,500 grams were included. The mean birthweight of 3,440 ± 485 grams were included. No other demographic details were reported. Routine tests included total and conjugated bilirubin, blood type, complete blood count, differential cell count, reticulocyte count, platelet count, red blood cell morphologic exam, a urinalysis. No cause was identified in 214 (47.8%) cases of hyperbilirubinaemia. A possible cause of hyperbilirubinaemia was identified only from patient history, physical exam or routine haematocrit (at 4 hours) in 145 (32.4%) cases. 13 (2.9%) of cases had other causes related to hyperbilirubinaemia which were not identified by the routine tests. 75 (16.8%) of cases were diagnosed from the routine tests. These included isoimmunization alone in 58 (12.9%) cases and isoimmunization accompanied by prematurity, bruising, cephalohaematoma, bacterial infection, viral infection and maternal diabetes in 17 (3.8%) of cases. [EL III]

Overall Evidence Summary

A number of poor quality studies and one good quality review were identified. The good quality review identified 6 studies that showed a link between the bilirubin/albumin ratio and various indices of bilirubin encephalopathy (abnormal ABR, IQ at six years). Two poor quality studies showed a moderately positive correlation between free bilirubin and both the bilirubin/albumin ratio and the bilirubin/albumin molar ratio $r = 0.74$ and $r = 0.75$ respectively. There was also a moderately positive correlation between unconjugated bilirubin and free bilirubin ($r = 0.69$).

Similarly a couple of studies have been carried out to determine the yield from additional tests, including direct bilirubin, to help in the investigation of early jaundice or prolonged jaundice. The value of these additional tests was variable, and they were often non-contributory.

Overall GDG translation to recommendations

The evidence does not support changing current clinical practice in the UK, which does not routinely include the calculation of the B/A ratio in determining treatment thresholds for jaundice. Further, expert advice received by the GDG is that most commonly used laboratory methods overestimate albumin, especially at low concentrations. External quality assurance data from October 2009 (www.birminghamquality.org.uk) shows that the affected methods are used by virtually all NHS laboratories. The GDG are aware of an ongoing RCT in the Netherlands which is examining the use of the B/A ratio alongside serum bilirubin in jaundiced babies as an indicator for treatment with phototherapy.

Poor quality evidence did not show a clinically useful correlation between unconjugated bilirubin and free bilirubin. Previous advice advocated subtracting direct bilirubin from the total serum bilirubin when deciding on management in babies with hyperbilirubinaemia. The GDG agree with the AAP that this practice should cease, and total bilirubin levels should be used to guide management. The GDG are aware of rare cases of kernicterus with high conjugated bilirubin levels, and there is a theoretical risk that conjugated bilirubin can elevate free bilirubin levels by displacing unconjugated bilirubin from the binding sites. Specialist advice should be sought for the exceptional cases in which the conjugated bilirubin is more than 50% of the total.

The GDG consider that total serum bilirubin should be used to guide the management of jaundiced babies less than 14 days old.

Recommendations

Do not use the albumin/bilirubin ratio.

Do not subtract conjugated bilirubin from total serum bilirubin when making decisions about the management of hyperbilirubinaemia. See management thresholds in table 1 and graphs A-F below

6.8 Prolonged jaundice

Review findings

A UK case series[89] examined causes of prolonged jaundice, defined as jaundice persisting beyond day 14. The mean gestational age of the 154 included babies was 39 weeks, mean birthweight was 3,200 grams and mean age at referral was 16 days. Of the group, 96 (62.3%) were male and 89 (57.8%) were white, 36 (23.4%) were black and 20, (13.0%) were Asian. The vast majority (142 (92.2%)) were breastfed and the remainder either bottle-fed or had mixed feeds. Overall, initial assessment resulted in 9 (5.8%) babies being referred on for further investigation. Clinical examination identified one case of hepatoblastoma, and ultimately led to the detection of trisomy 9p. Abnormal results for liver function tests identified one baby with giant cell hepatitis. Three cases of G-6-PD deficiency and two cases of urinary tract infection were identified. [EL III]

A case series from Turkey[90] examined causes of prolonged jaundice in term and near term babies. Of 381 babies with hyperbilirubinaemia, 31 (8.1%) had prolonged jaundice and 26 were included in study. The mean gestational age was 38 weeks, mean birthweight was 3194 grams, mean age at presentation was 19 days and 15 (57.7%) of the group were male. The mean serum bilirubin at presentation was 246 micromol/L. One baby had conjugated hyperbilirubinaemia and was referred for exclusion of biliary atresia. Seven babies (26.9%)

had blood group incompatibility and 4 (15.4%) had inadequate caloric intake. The remaining 14 (53.8%) had "breastmilk" jaundice. [EL III]

Causes of conjugated hyperbilirubinaemia were also reported in another Turkish study[91]. A retrospective review of 42 affected babies. The mean gestational age was 37 weeks and no other demographic details were reported. The mean age at presentation was 20 days. The mean total serum bilirubin was 292 micromol/L, and mean conjugated bilirubin was 130 micromol/L. The causes of the conjugated hyperbilirubinaemia included culture-proven sepsis 15 (35.7%), perinatal hypoxia-ischaemia 7 (16.7%), blood group incompatibility 5 (11.9%), trisomy 21: 3 (7.1%), TPN-associated cholestasis 3 (7.1%), neonatal hepatitis 2 (4.8%), metabolic liver disease 1 (2.4%), biliary atresia 1 (2.4%) and portal venous thrombosis 1 (2.4%). No cause was identified in 4 (9.5%) cases. [EL III]

Evidence summary

First-line investigations for prolonged jaundice resulted in 9 (5.8%) babies being referred on for further investigation in a UK- based study. A Turkish study resulted in one baby (3.8%) being referred for tertiary investigation while 14 (53.8%) considered to have "breastmilk" jaundice. In a second Turkish study, associated pathology was identified in 38 of 42 (90%) babies with conjugated hyperbilirubinaemia.

GDG translation from evidence

In term babies, jaundice at or beyond day 14 is defined as 'prolonged jaundice'. In these babies a full clinical examination is crucial, and key investigations include measurement of total and conjugated bilirubin, urine culture and testing for G-6-PD deficiency (if appropriate).

The GDG are aware that many neonatal units use jaundice persisting at or beyond day 21 as the definition of prolonged jaundice in preterm babies. There was no evidence available for review on this aspect of prolonged jaundice, and hence the GDG saw no reason to change clinical practice in this respect.

The importance of hypothyroidism as a cause of neonatal jaundice should be appreciated and clinicians should check that babies with prolonged jaundice have undergone routine newborn bloodspot screening. Infection, liver disease (eg biliary atresia and neonatal hepatitis) are important underlying causes of prolonged jaundice and should be considered if conjugated hyperbilirubinaemia is identified. Pale stools and dark urine staining the nappy are a well recognised and important clue to possible liver disease. The GDG are aware of the evidence demonstrating better outcomes for babies with biliary atresia who are offered early surgery and hence stress the urgency of seeking specialist advice when a high level of conjugated bilirubin is found.

Recommendations – Prolonged jaundice

In term babies with jaundice lasting more than more than 14 days and more than 21 days in preterm babies (prolonged jaundice):

- look for pale chalky stools and/or dark urine which stains the nappy
- measure the conjugated bilirubin
- refer babies with a conjugated bilirubin greater than 25 micromol/litre for expert investigation

Carry out the following investigation in babies with prolonged jaundice (that is, persisting more than 14 days in term babies and more than 21 days in preterm babies):

- visual inspection of stool and urine
- total and conjugated bilirubin
- full blood count
- 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.)
- urine culture
- ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed.

In babies with high levels of conjugated bilirubin (more than 25 micromol/litre), arrange urgent referral to a specialist centre, because this may indicate serious liver disease.

Table 6.1 serum bilirubin less than 255 micromol/L related to disorders found

Country	Criteria	Preterm	Age	BF	Blood group incompatibility			G-6-PD deficiency			Infection			Idiopathic / No known cause		
		%	days	%	n	N	%	n	N	%	n	N	%	n	N	%
Nigeria[92]	>170		0 - 10		180	424	42.5	229	424	54	60	424	14.1	39	424	9.2
Nigeria[93]	>170		0 - 10		11	40	27.5	13	40	32.5	34	40	85	3	40	7.5
Nigeria[94]	>205	25.6			43	150	28.7	109	327	33.3	38	217	17.5			
India[95]	>170				30	100	30	4	100	4						
India[96]	>205	14			9	50	18	2	50	4	7	50	14			
India[97]	>205	16.7			102	454	24.5	23	454	5.1						
Pakistan[98]	PT	13			113	869	13	20	869	2.3	165	869	19			
Australia[99]	>154	36.3			794	6129	12.9	51	6129	0.8	198	6129	3.2			
China[100]	>170	3.6	0 - 10		414	1811	22.9	241	1811	13.4	680	1811	37.5			

Table 6.2 Serum bilirubin between 255 micromol/L and 399 micromol/L

Country	Criteria	Preterm	Age	BF	Blood group incompatibility			G-6-PD deficiency			Infection			Idiopathic / No known cause		
		%	days	%	n	N	%	n	N	%	n	N	%	n	N	%
India[101]	>255	18.5	0 - 15	63	24	92	26.1	4	92	4.3	18	92	19.6			
Nigeria[102]	>170				24	102	23.5	41	102	40.2	57	102	55.9			
Israel[103]	>306	0	0 - 10	95.2	0	21	0	2	21	9.5	0	21	0			
Nigeria[104]	>255	16	0 - 7		28	125	22.4	49	125	39.2	1	125	0.8	35	125	28
Papua New Guinea[105]	>255	10		100	12	50	24	11	50	22	8	50	16	19	50	38
Singapore[106]	>255				78	270	28.9	18	270	6.7						
Singapore[107]	>221	6.6			43	181	23.8	4	181	2.2						
Taiwan[108]	>255		0 - 10		62	196	31.6	43	196	21.9	10	196	5.1	53	196	27
Turkey[109]	359				220	624	35.3	24	624	3.8	36	624	5.7			
Iran[110]	ICD			100	22	376	5.8	8	376	2.1	59	376	15.7			
UAE[111]	Chart	26	0 - 6		23	85	27	8	85	9.4						
Saudi Arabia[112]	>255				23	211	10.9	64	211	30.3	4	411	1.9			

Table 6.3 Serum bilirubin> 400 micromol/L or exchange transfusion

Country	Criteria	Preterm	Age	BF	Blood group incompatibility			G-6-PD deficiency			Infection			Idiopathic / No known cause		
		%	days	%	n	N	%	n	N	%	n	N	%	n	N	%
China[100]	ET	3.6	0 - 10		157	581	27	130	581	22.4						
Singapore[106]	ET				18	46	39.1	2	46	4.3	8	46	17.4	6	46	13
India[97]	ET				39	66	59.1	11	66	16.7						
India[113]	ET				21	141	14.9	24	141	17.2	34	141	24.1	50	141	35.4
Pakistan[98]	ET				11	27	40.1	2	27	7.4	6	27	22.2			
Papua New Guinea[105]	ET	10		100	4	11	36.4	3	11	27.3	2	11	18.2	2	11	18.2
Australia[99]	ET				166	248	66.9	2	248	0.8	2	248	0.8			
Ghana[114]	>340	0	0 - 8		15	35	42.9	13	35	37.1				10	35	28.6
Nigeria[104]	ET	16	0 - 7		16	53	30.2	21	53	39.6	0	53	0	11	53	20.7
Nigeria[115]	>204				15	109	13.8	67	109	61.5	24	109	22	13	109	11.9
UK[19]	>510		0 - 31	87.7	39	106	36.8	5	106	4.7	4	106	3.8	29	106	27.3
Turkey[116]	>425	0			8	21	38.1	4	21	19.5				10	21	47.5
Turkey[117]	>428		0 - 30	100	14	93	15.1	2	39	5.1	7	93	7.5	61	93	65.6
Greece[118]	ET				35	75	46.7	14	75	18.7						
Iran[110]	ET			100	2	14	14.3	0	14	0	9	14	64.3			
Denmark[119]	>450	8.8	0 - 28	100	54	113	47.8	1	113	0.9						
Canada[120]	>425		0 - 60	81.4	60	258	23.2	20	258	7.75	3	258	1.2			

Table 6.4 Kernicterus

Country	Criteria	Preterm	Age	BF	Blood group incompatibility			G-6-PD deficiency			Infection			Idiopathic / No known cause		
		%	days	%	n	N	%	n	N	%	n	N	%	n	N	%
China[100]	K				51	156	32.7	58	156	37.2						
UK[19]	K				4	14	28.6	3	14	21.4	2	14	14.3	1	14	7.1
Nigeria[121]	BE				35	115	30.4	40	115	34.8	16	115	13.9			
Ghana[114]	K				6	17	35.3	8	17	47				3	17	17.6
USA[122]	K				1	14	7.1	3	14	21.4	2	14	14.3	6	14	42.8
USA[22]	K				24	125	19.2	26	125	20.8				44	125	35.2
Singapore[107]	K				4	8	50	0	8	0						
Greece[118]	K				1	6	16.7	3	6	50						
Turkey[117]	K				1	6	16.7	1	6	16.7	3	6	50	1	6	16.7
Turkey[109]	K				3	6	50	1	6	16.7						

7 Treatment

Introduction

Clinical question

i) How effective is phototherapy?

ii) What is the best modality of giving phototherapy (clinical & cost-effectiveness)?
- Conventional phototherapy (single, double or multiple phototherapy)
- Sunlight
- Fibreoptic phototherapy (BiliBlankets, Bilibeds and other products)

iii) What are the criteria/indications for starting and stopping phototherapy in babies with neonatal hyperbilirubinaemia?

iv) What is the correct procedure when administering phototherapy (with specific reference to method of feeding/types of feed, incubator or bassinet care, the effect of intermittent vs. constant phototherapy on maternal-infant bonding, and parental anxiety)?

Clinical question

i) How effective is exchange transfusion?

ii) What is the best method (single volume vs. double volume exchange)?

iii) What are the criteria/indications for carrying out an exchange transfusion?

Clinical question

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
- Complementary/alternative medicines (Chinese herbal remedies like Yin-chin)

As there is a large evidence base for phototherapy the literature search was restricted to RCT's and meta-analyses. Altogether 472 records were identified by searches. These were screened and 140 hard-copy articles were requested. 75 studies included information about the effect of phototherapy in combination with other treatments or were prophylaxis studies and were excluded at this stage. From the remaining studies, 42 randomized controlled trials were included and 23 were excluded (20 were quasi-randomized or not randomised, one was a commentary, one had incomplete data and one was a duplicate publication). No RCT's dealing with sunlight or environmental light were found.

7.1 Phototherapy

To evaluate the evidence more clearly, conventional phototherapy was compared initially to no treatment, then with multiple phototherapy and finally with newer forms of phototherapy including fibreoptic and light emitting diode (LED) phototherapy. Different aspects of phototherapy, such as choice of colour, whether given continuously or intermittently, and

positioning of the baby, were also examined. Meta-analysis was performed to calculate the effectiveness of phototherapy using the programme RevMan 5 (http://www.cc-ims.net/revman). Where possible a distinction was made between term and pre-term babies and evidence was evaluated accordingly.

7.1.1 Phototherapy in term / normal birthweight babies

19 of the included studies contributed to the following comparisons:

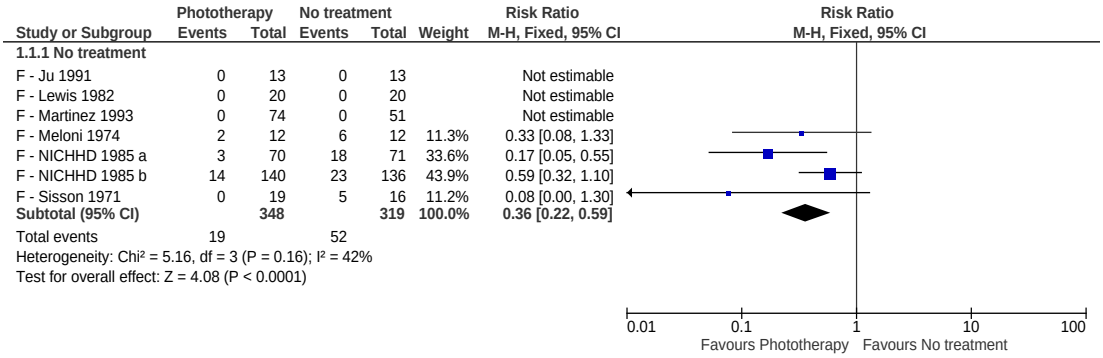
- Conventional phototherapy versus usual care/no treatment (7 studies from 6 articles),
- Conventional phototherapy versus multiple phototherapy (4 studies),
- Conventional phototherapy versus fibreoptic phototherapy (6 studies)
- Conventional phototherapy versus LED phototherapy (2 studies).

Conventional phototherapy versus no treatment

Seven studies [123-128] with 667 participants were included in this comparison. Three of the studies were carried out in the USA and one each in Italy, Taiwan and the UK. The evidence level of the included studies ranged from EL1- to EL1^{++}. Three studies specified the method of randomisation used as a random numbers table, one study used a computer-generated sequence and one used a coin-toss method. The remaining two studies did not report the method used. Two studies reported using sealed envelopes as allocation concealment.

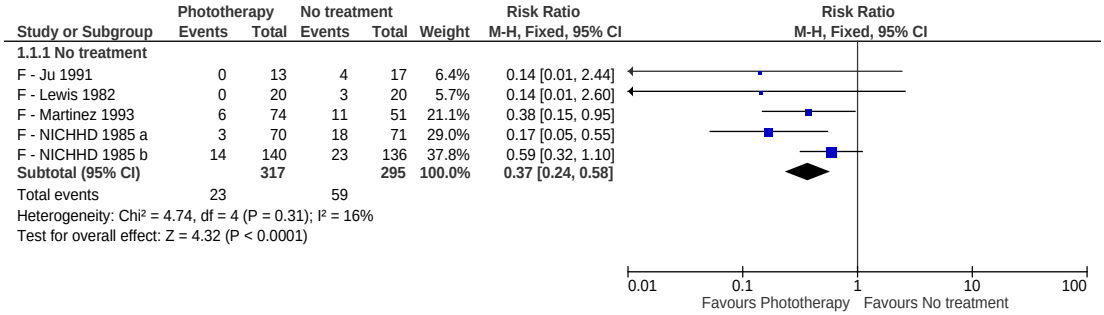
Where reported the mean and standard deviation for gestational age of the study participants ranged from 34.8 ± 2.7 weeks to 39.2 ± 0.9 weeks, mean birthweight ranged from 2,155 ± 632 grams to 3,404 ± 361grams, mean age at entry to study ranged from 48.1 ± 14.7 hours to 97.2 ± 22.4 hours and mean baseline serum bilirubin levels ranged from 174 ± 40 micromol/L to 306 ± 12 micromol/L. In the studies which reported gender, 377 participants (52%) were male. Seven studies included only term babies while one dealt with preterm babies.

Significantly fewer exchange transfusions were carried out in babies treated with conventional phototherapy (Risk Ratio (RR) 0.36 (95% CI: 0.22 to 0.59)). Heterogeneity was within acceptable limits (I^2 = 42%). The number needed to treat with phototherapy to prevent one exchange transfusion was 10.



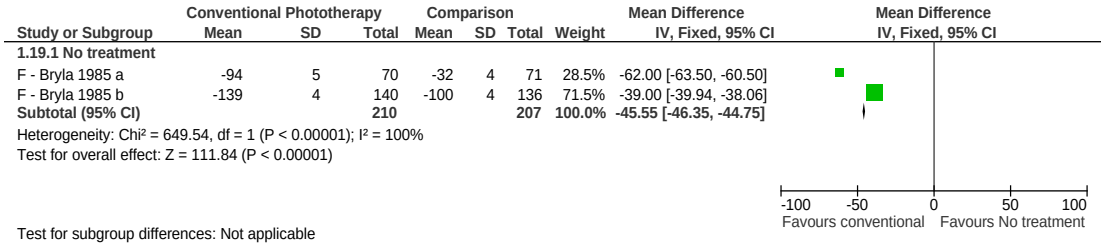
Forest plot 7.1.1.1 Conventional versus No treatment - Number of exchange transfusions

Five studies examined treatment failure as an outcome. This was defined as either two successive rises in serum bilirubin after initiation of phototherapy, serum bilirubin rising above pre-defined serum bilirubin levels or the need for exchange transfusion. The RR was (RR = 0.37 (95% CI: 0.24 to 0.58) respectively. Heterogeneity was within acceptable limits (I^2 = 16%).



Forest plot 7.1.1.2 Conventional versus No treatment - Number of Treatment failures

Though only two studies contributed data there was a significantly greater decrease in the mean serum bilirubin levels in the conventional phototherapy group compared to the no treatment group. Mean difference (MD) = -45.55 micromol/L (95% CI: -46.35 to -44.75). There was significant heterogeneity (I^2 = 100%).



Forest plot 7.1.1.3 Conventional versus No treatment – Mean decrease in serum bilirubin

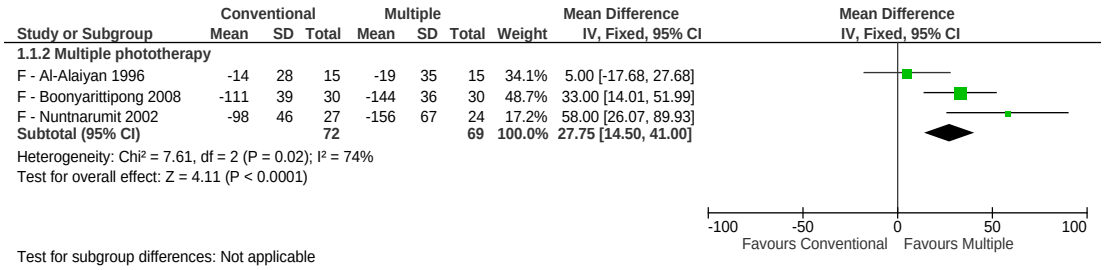
Conventional phototherapy versus multiple phototherapy

Four studies[129-132] with 328 participants were included but not all subjects were used in this comparison as some studies had additional treatment arms examining other types of phototherapy. Two of the studies were from Thailand and one apiece from Saudi Arabia and Singapore. The evidence level of the included studies ranged from EL1- to EL1+. One study specified the method of randomisation used as the lottery method while the remaining three studies did not report the method used. One study reported using sealed envelopes as allocation concealment.

The mean gestational age of the study participants ranged from 37.9 ± 2.08 weeks to 38.7 ± 1.29 weeks, the mean birthweight ranged from 2921 ± 696 grams to 3130 ± 311 grams, the mean age at entry to the study ranged from 37.9 ± 24.1 hours to 96.9 ± 30.9 hours (not reported in one study) and the mean baseline serum bilirubin levels ranged from 185 ± 56 micromol/L to 316 ± 47 micromol/L. In all, 185 (56.4%) of participants were male.

There were no cases of exchange transfusion or treatment failures and only three cases of rebound jaundice, two in the conventional phototherapy group and one in the multiple phototherapy group, but this difference was not significant. There was no significant difference between the groups in terms of mean duration of phototherapy.

Three studies compared changes in serum bilirubin with each intervention. The mean decrease in serum bilirubin was significantly greater in the multiple phototherapy group MD = 27.75 micromol/L (95% CI: 14.50 to 41.00). Heterogeneity was significant (I2 = 74%).



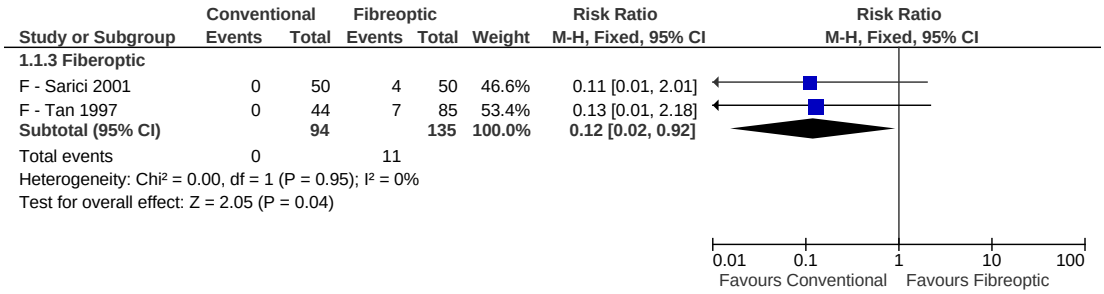
Forest plot 7.1.1.4 Conventional versus Multiple – Mean decrease in serum bilirubin

Conventional phototherapy versus fibreoptic phototherapy

Six studies[129;132-136] with 426 participants were included in this comparison. Two of the studies were from the USA and one apiece from Italy, Saudi Arabia, Singapore and Turkey. The included studies ranged from EL1- to EL1+. Three studies specified the method of randomisation used as the lottery method, computer-generated or sequential and the remaining three studies did not report the method used. Two studies reported using sealed envelopes as allocation concealment while in one study the nurses who allocated the babies to the groups were blind to the serum bilirubin levels.

When reported the mean gestational age ranged from 37.9 ± 2.1 weeks to 39.6 ± 1.6 weeks, mean birthweight from 2921 ± 696 grams to 3380 ± 359 grams, mean age at entry to study ranged between 37.9 ± 24.1 hours to 105.4 ± 42.8 hours (not reported in 2 studies) and mean baseline serum bilirubin levels ranged from 185 ± 56 micromol/L to 308 ± 47 micromol/L. In the studies which reported gender, 190 participants (55.4%) were male.

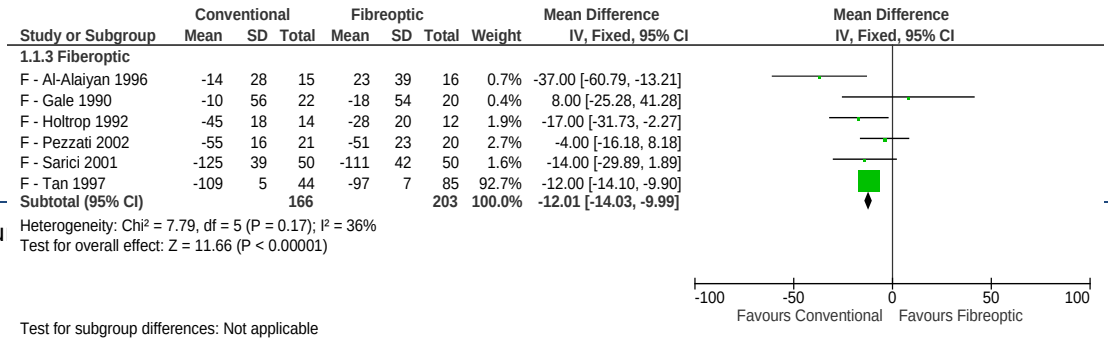
No exchange transfusions were needed with either intervention. Two studies reported on treatment failures, defined in one study as having two successive rises in serum bilirubin after initiation of phototherapy, but not defined in the second. Babies who received fibreoptic phototherapy were more likely to be considered as treatment failures. RR = 0.12 (95% CI: 0.02 to 0.92). Heterogeneity was non-existent (I^2 = 0%).



Forest plot 7.1.1.5 Conventional versus Fibreoptic – Treatment failure

Three studies reported on rebound jaundice which was defined a serum bilirubin returning to pre-phototherapy levels. Babies who received fibreoptic phototherapy had fewer cases of rebound jaundice but this was non-significant.

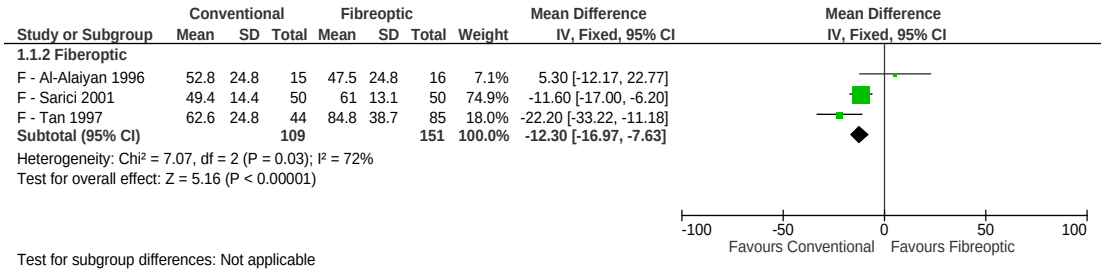
All six studies reported mean change in serum bilirubin. Babies in the conventional phototherapy group had a greater decrease in serum bilirubin than babies in the fibreoptic group. MD = -12.01 micromol/L (95% CI: -14.03 to -9.99). Heterogeneity was within



acceptable limits (I2 = 36%).

Forest plot 7.1.1.6 Conventional versus Fibreoptic – Mean decrease in serum bilirubin

Three studies reported the mean duration of phototherapy. Babies receiving conventional phototherapy spent a significantly less time undergoing phototherapy than babies receiving fibreoptic phototherapy. MD = -12.30 hours (95% CI -16.97 to -7.63) but heterogeneity was a factor (I^2 = 72%).



Forest plot 7.1.1.7 Conventional versus Fibreoptic – Mean duration of phototherapy

Conventional phototherapy versus LED phototherapy

Two studies from Israel[137;138] with 183 participants were included in this comparison. The evidence level of both studies was EL1+. Both used computer-generated sequences as the method of randomisation but neither reported on allocation concealment.

The mean gestational age in one study was 39.5 ± 1.5 weeks but was not reported in the second though a gestational age >37 weeks was an inclusion criteria. The mean age in one study was 53.9 ± 37.8 hours and was not reported in the second. Gender and mean birthweight were not reported in either study. The mean baseline serum bilirubin level was 251 ± 74 micromol/L in one study and 251 ± 77 micromol/L in the second.

There were no reported cases of exchange transfusion, treatment failures or rebound jaundice in either study. Both studies reported the mean decrease in serum bilirubin; this did not differ significantly between the groups (MD = -4.29 micromol/L (95% CI: -18.95 to 10.36) with no heterogeneity (I2 = 0%). Likewise there was no significant difference in terms of mean duration of phototherapy. MD = 0.64 hours (95% CI: -4.97 to 6.26) with no heterogeneity (I^2 = 0%).

Evidence summary in term/normal weight babies

No studies examining sunlight or environmental light for the treatment of hyperbilirubinaemia were identified.

The pooled results of meta-analysis show that in hyperbilirubinaemia, conventional phototherapy is more effective than no treatment. Although there were variations in the initial serum bilirubin level at which treatment was initiated, conventional phototherapy was found statistically to significantly decrease the risk of exchange transfusion and treatment failure. Treatment failure was defined as either two successive rises in serum bilirubin after initiation of phototherapy, serum bilirubin rising above pre-defined serum bilirubin levels or the need for exchange transfusion. There was also a significantly greater decrease in the mean serum bilirubin levels with conventional phototherapy compared to no treatment.

A statistically significant decrease in treatment failure was reported in babies who received conventional phototherapy compared to those receiving fibreoptic phototherapy. Similar results were seen for mean decreases in serum bilirubin, with results favouring conventional phototherapy. Conventional phototherapy was significantly more effective than fibreoptic phototherapy in term babies.

Compared with fibreoptic phototherapy, treatment failure was significantly less common in babies receiving conventional phototherapy. Similarly conventional phototherapy was associated with significantly greater mean reduction in serum bilirubin than fibreoptic phototherapy. Specifically, conventional was significantly more effective than fibreoptic phototherapy in term babies.

There was a trend towards a greater decrease in serum bilirubin levels among the group treated with conventional phototherapy when compared to LED phototherapy but this was not significant, and there was no difference between the two types of phototherapy in terms of the mean duration of phototherapy.

GDG translation from evidence in term/normal weight babies

A formal cost-effectiveness analysis of the different modalities of phototherapy was not undertaken because the GDG did not believe these represented realistic treatment alternatives. No evidence of sunlight was reviewed so the GDG cannot recommend sunlight as a treatment option for hyperbilirubinaemia. Fibreoptic phototherapy, with greater treatment failure, was not deemed a suitable treatment for term babies. Whilst the evidence suggests that multiple phototherapy is more effective than conventional phototherapy, advances in technology has rendered this characterisation less useful, because modern phototherapy units are more powerful than those tested in the trials examined. The effectiveness of multiple phototherapy is a indicator of the desirability to expose as much an area of skin as possible to the lights. Multiple phototherapy is accompanied by more fluid balance problems and it is currently believed that this needs to be continuous. The GDG felt that further research was needed on LED phototherapy before they could be in a position to recommend it, although their clinical experience so far is that it is effective.

Conventional modes of phototherapy when used and maintained according to the manufacturer's instructions have a low adverse side effects profile and are effective as first-line medical treatment for hyperbilirubinaemia in term babies. Other modes of phototherapy are as effective as conventional phototherapy with the exception of fibreoptic phototherapy which is less effective than conventional phototherapy in term babies, and leads to more treatment failures. Monitoring the effect of treatment is essential because in spite of phototherapy some babies may require further medical interventions.

Evidence demonstrates that multiple phototherapy is more effective than conventional phototherapy. However, conventional phototherapy works in most cases and, in order to support breast feeding, the GDG consider that multiple phototherapy should be reserved for the treatment of jaundice that does not respond to conventional treatment (no reduction in serum bilirubin 6 hours after initiation of treatment or serum bilirubin that continues to rise) or who require a rapid reduction in serum bilirubin levels.

Recommendations – Type of phototherapy to use in term babies

Do not use sunlight as phototherapy for hyperbilirubinaemia.

Use conventional blue light phototherapy as first-line treatment for hyperbilirubinaemia in term babies.

Do not use fibreoptic phototherapy as first-line treatment for hyperbilirubinaemia in term babies.

Ensure all equipment is maintained and used according to the manufacturers' guidelines.

For recommendations on multiple phototherapy in term babies see 7.1.2 below

Research recommendations – Phototherapy in term babies

What is the clinical and cost-effectiveness of:

- LED phototherapy compared to conventional phototherapy in term and preterm babies with hyperbilirubinaemia?

Why this is important.

Existing research has shown that while there is no difference between LED phototherapy and conventional phototherapy, LED phototherapy may be easier to use in clinical setting by reducing over-heating and the potential need for additional fluids. New randomized controlled trials are needed to examine LED phototherapy. Population: Term and pre-term babies in the first 28 days of life. Interventions: LED phototherapy compared with fiberoptic phototherapy or conventional phototherapy. Outcome: Effectiveness in terms of the mean decrease in bilirubin levels and the mean duration of phototherapy. Extra outcomes should include adverse effects, parental bonding and parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

- fibreoptic phototherapy using large pads compared to conventional phototherapy in term babies with hyperbilirubinaemia?

Why this is important.

Existing research has demonstrated the effectiveness of fiberoptic phototherapy in pre-term babies but not in term babies. This is due to that fact that existing fiberoptic pads are small and cannot ensure adequate skin coverage in larger babies. New devices using larger pads may be effective in term babies. New randomized controlled trials are needed to examine fiberoptic phototherapy which uses larger pads. Population: Term babies with hyperbilirubinaemia in the first 28 days of life. Interventions: Fiberoptic phototherapy with larger pads compared with conventional phototherapy. Outcome: Effectiveness in terms of mean decrease in bilirubin levels and mean duration of phototherapy. Extra outcomes should include adverse effects, parental bonding and parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

7.1.2 Phototherapy in preterm / low birthweight babies

17 of the included studies contributed to the following comparisons:

- Early phototherapy versus usual care/no treatment (7 studies)
- Conventional phototherapy versus multiple phototherapy (2 studies)
- Conventional phototherapy versus fibreoptic phototherapy (6 studies)
- Conventional phototherapy versus LED phototherapy (2 studies)

Early phototherapy versus no treatment

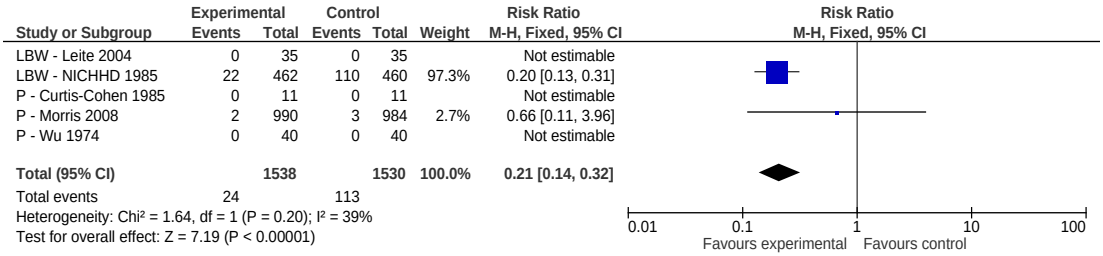
Seven studies[123;139-144] with 1,238 participants were included in this comparison. Early phototherapy is used for lowering maximum bilirubin levels in babies with low birth weight (less than 1500 grams) and in preterm babies. Early phototherapy is initiated before serum bilirubin reaches the normal phototherapy threshold.

Six of the studies were from the USA and one from Brazil. Babies were included either on the basis of gestational age or birthweight. The evidence level of the included studies ranged from EL1- to EL1++. One study specified the method of randomisation used as a random-numbers table and one reported using randomised cards while the remaining four studies did not report the method used. One study used sealed envelopes for allocation concealment.

When reported the mean and standard deviation for gestational age of the study participants ranged from 26.0 ± 2.0 weeks to 34.2 ± 3.8 weeks (not reported in 3 studies), mean birthweight ranged from 777 ± 134 grams to 1860 ± 344 grams (not reported in 2 studies), mean age at entry to study was 24.2 ± 8.0 hours reported in one study. In two studies phototherapy was initiated within 24 hours of birth; the mean baseline serum bilirubin levels was 97 ± 33 micromol/L in the one study which reported. In the studies which reported gender, 1,179 participants (51.5%) were male.

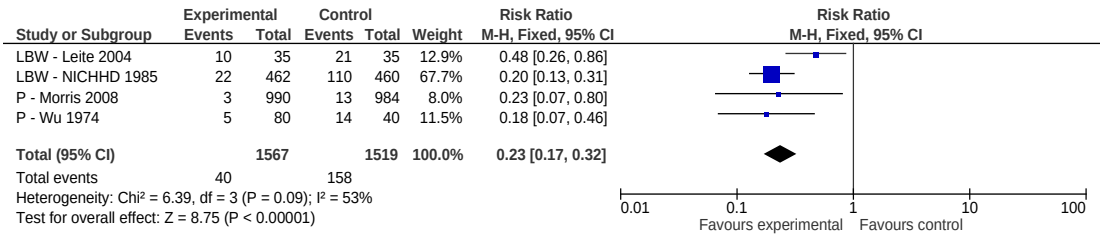
Early phototherapy was initiated at varying serum bilirubin levels (eg 85.5 micromol/L) or within 24 ± 12 hours of birth in low-birthweight samples. One study also used postnatal age with phototherapy being initiated at 85 micromol/L for the first week of life and at 120 micromol/L in the second week of life. In three studies babies in the control groups received phototherapy if their serum bilirubin levels reached an a priori cut-off of serum bilirubin.

There were significantly fewer exchange transfusions and treatment failures in babies treated with early phototherapy RR = 0.21 (95% CI: 0.14 to 0.32) in the five studies which reported on these outcomes. Most of the exchange transfusions were carried out in one study in which exchange transfusions were conducted at relatively low levels of serum bilirubin based on birthweight and risk profile.[123] The number needed to treat with early phototherapy to prevent one exchange transfusion was 16.



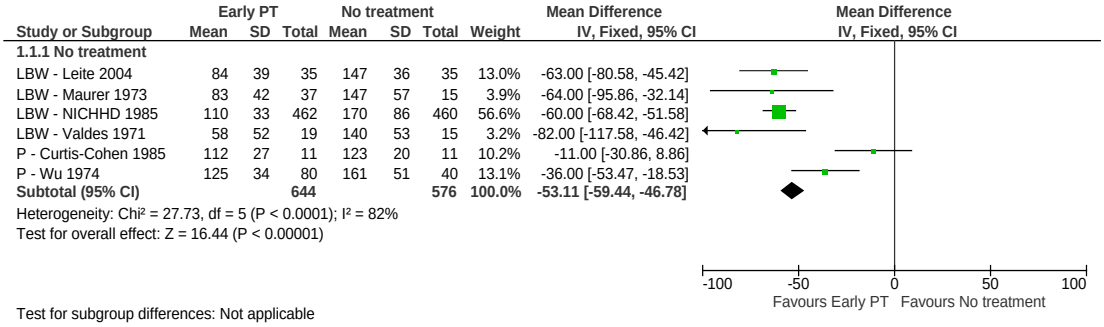
Forest plot 7.1.2.1 Early phototherapy versus No treatment - Number of exchange transfusions

Four studies examined treatment failure as an outcome. Treatment failure was defined as serum bilirubin rising above a pre-defined level or the need for exchange transfusion. RR = 0.23 (95% CI: 0.17 to 0.32). Heterogeneity was a factor (I^2 = 53%)



Forest plot 7.1.2.2 Early phototherapy versus No treatment - Number of Treatment failures

The mean peak in serum bilirubin was significantly lower among babies who received early phototherapy. MD = -53.11 micromol/L (95% CI: -59.44 to -46.78) but heterogeneity was high (I^2 = 84%).



Forest plot 7.1.2.3 Early phototherapy versus No treatment – Mean peak serum bilirubin

Conventional phototherapy versus multiple phototherapy

Two studies[145;146] of EL1+, with 206 participants were included in this comparison. One study apiece was from Italy and the USA. One study specified the method of randomisation used as a computer-generated sequence and the other study used sealed envelopes for allocation concealment.

The mean gestational age of the study samples ranged from 27.9 ± 1.4 weeks to 30.4 ± 2.7 weeks, the mean birthweight ranged from 1019 ± 283 grams to 1518 ± 419 grams, the mean age at entry to the study ranged from 38.3 ± 7.1 hours to 58 ± 25.8 hours and the mean baseline serum bilirubin levels ranged from 109 ± 5 micromol/L to 168 ± 49 micromol/L. In all, 107 (51.9%) of participants were male.

There were no significant differences between the groups in terms of the number of exchange transfusions, number of treatment failures or frequency of rebound jaundice.

As both studies used different populations, (pre-term and very pre-term) and different time-points for measuring the change in serum bilirubin it was not possible to pool the results. One study measured serum bilirubin at 18 hours after initiation of phototherapy and this showed no significant difference between conventional phototherapy and multiple phototherapy. The second study which measured change in serum bilirubin over 72 hours found a statistically significant difference in favour of multiple phototherapy. MD = 11.00 micromol/L (95% CI: 9.01 to 12.99)

Conventional phototherapy versus fibreoptic phototherapy

Six studies[146-151], of EL1+, with 398 participants were included in this comparison. Four studies were carried out in Italy and one apiece in Australia and the Netherlands. The evidence level of all included studies was EL1+. One study specified the method of randomisation used as the lottery method while the remaining four studies used sealed envelopes.

When reported the mean gestational age ranged from 27.9 ± 1.4 weeks to 34.4 ± 1.2 weeks, mean birthweight from 1019 ± 283 grams to 2600 ± 382 grams, mean age at entry to study ranged was between 26.5 ± 15.0 hours to 63.2 ± 17.8 hours and mean baseline serum bilirubin levels ranged from 94 ± 36 micromol/L to 241 ± 9 micromol/L. In the studies which reported gender, 162 (54.1%) of the population of the studies which reported gender were male.

There was no significant difference in the number of exchange transfusions carried out; five babies who received conventional phototherapy and seven babies who received fibreoptic phototherapy required exchange transfusions. There were no significant differences for treatment failure (defined as requiring double phototherapy or reaching a pre-defined serum bilirubin level) between conventional and fibreoptic groups. No study reported cases of rebound jaundice.

Three studies contributed data on the mean decrease in serum bilirubin; there was no significant difference between the groups. MD = -1.17 micromol/L (95% CI: -3.87 to 1.53).

Heterogeneity was non- existent at I2 = 0%. Four studies contributed data on the mean duration of phototherapy and there was a significant difference between the groups in favour of fibreoptic phototherapy. MD = 2.63 hours (95% CI: 0.69 to 4.58). Heterogeneity was non- existent at I^2 = 0%.

Conventional phototherapy versus LED phototherapy

Two studies[152;153] with 119 participants were included in this comparison. One study was carried out in Brazil and the second in Italy. The evidence level in one study was EL1- and in the second EL1+. Neither study reported on the randomisation method nor one study reported using sealed envelopes for allocation concealment.

Where reported the mean gestational age ranged from 30.7 ± 2.0 weeks to 33.6 ± 1.9 weeks, the mean age at time of entry to the study ranged from 64.4 ± 15.2 hours to 68.1 ± 25.5 hours, the mean birthweight ranged from 1192 ± 238 grams to 1998 ± 541 grams and the mean baseline serum bilirubin levels ranged from 180 ± 38 micromol/L to 200 ± 16 micromol/L. One study reported gender and 58 participants (65.9%) were male.

There were no reported cases of exchange transfusions or treatment failures in either group. There were fewer cases of rebound jaundice in the conventional phototherapy group (8 vs. 12) but this difference was not significant.

Phototherapy in both studies was terminated once a pre-defined serum bilirubin level was reached so it was not possible to calculate the mean decrease in serum bilirubin. Babies in the LED phototherapy had a significantly shorter duration of phototherapy. MD = 9.15 hours (95% CI: 3.53 to 14.77) but heterogeneity was high (I^2 = 90%).

Evidence summary for preterm / low birthweight babies

The pooled results of meta-analysis indicate that phototherapy is effective in the treatment of hyperbilirubinaemia in pre-term and low-birthweight babies.

Babies who received early phototherapy had a statistically significant lower mean peak in serum bilirubin level Early phototherapy was also found statistically to significantly decrease the risk of exchange transfusion and treatment failure when compared to no treatment. However in the study which contributed most to this analysis the exchange transfusion thresholds were very cautious and would not be used in current clinical practice in the UK.

Multiple phototherapy did not show any clinical difference on any outcome when compared to conventional phototherapy.

There was no significant difference in the number of exchange transfusions or treatment failures in studies comparing fibreoptic and conventional phototherapy. Fibreoptic phototherapy, however, was significantly better than conventional therapy in terms of duration of treatment.

LED phototherapy was shown to shorten significantly the duration of treatment compared to conventional phototherapy in preterm babies. Conversely there was a trend towards a greater decrease in serum bilirubin levels among the group treated with conventional phototherapy but this was not significant.

GDG translation from evidence for preterm / low birthweight babies

All modes of phototherapy when used and maintained according to the manufacturer's instructions are safe and effective as first-line medical treatment of hyperbilirubinaemia in pre-term babies.

The evidence supporting the use of early phototherapy in preterm babies is limited by the relatively low thresholds for exchange transfusion used in one study which contributed most to the analysis and does not reflect current clinical practice in the UK. Early initiation of phototherapy in preterm babies is effective in reducing the duration of phototherapy and reducing peak bilirubin levels. The GDG is of the opinion that this evidence supports the choice of relatively low threshold levels for starting phototherapy in preterm babies based on the fomula given in Section 7.1.8.

GDG experience is that fibreoptic devices are more acceptable to parents and nursing staff for a number of reasons including less glare than from overhead lamps, the parents can hold and feed the baby and no eye protection is needed. However fibreoptic phototherapy was less effective than conventional phototherapy in term babies. Monitoring the effect of treatment is essential because in spite of phototherapy some babies require further medical interventions.

Recommendation – Phototherapy in preterm babies

Use either fibreoptic phototherapy or conventional blue light phototherapy as first-line treatment for hyperbilirubinaemia in preterm babies.

See section 7.1.3 for more information on bulb colour

Recommendation – multiple phototherapy in term and pre term babies

Use continuous multiple phototherapy to treat hyperbilirubinaemia in term and preterm babies who:

- have a bilirubin level that fails to respond to conventional phototherapy (that is, the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting conventional phototherapy)
- have rapidly rising serum bilirubin levels (more than 8.5 micromol/litre/hour)
- have serum bilirubin at a level for which exchange transfusion is indicated (see table 1 and graphs A-F).

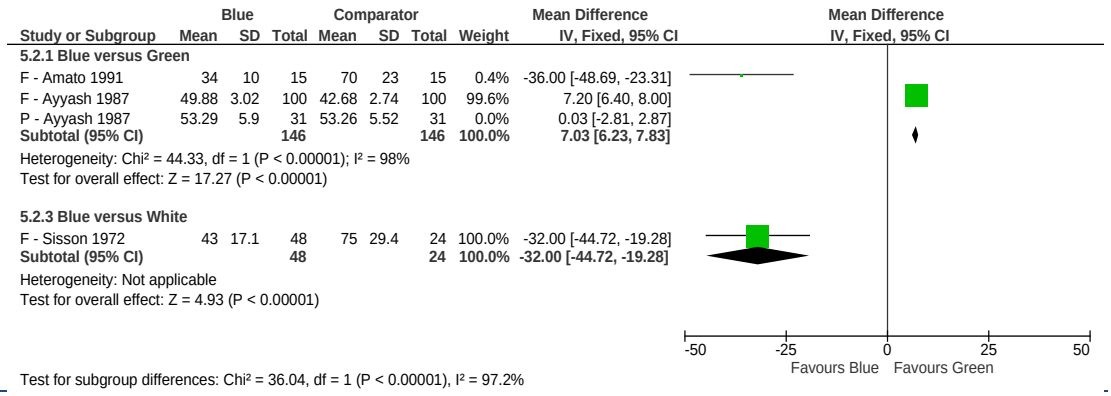
See section 7.1.1 for more information on types of phototherpy of term babies

7.1.3 Bulb colour for conventional phototherapy

Six studies[154-159] with 674 participants were included in this comparison. Two of the studies were from Denmark and one apiece from Greece, Italy, Switzerland and the USA. The included studies ranged from EL1- to EL1+. Two studies specified the method of randomisation one used a random numbers table and another used a computer-generated sequence while one study used sealed envelopes for allocation concealment.

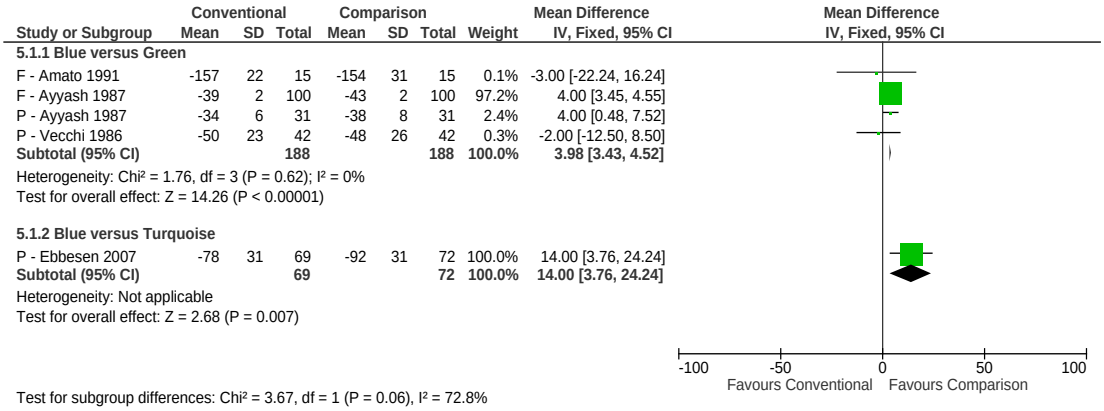
Three studies each dealt with term and pre-term babies and as there were no significant differences in outcome these were analysed together. When reported the mean gestational age ranged from 33.8 ± 2.49 weeks to 39.0 ± 1.03 weeks, the mean age at entry to study ranged from 70.5 ± 23.1 hours to 101.8 ± 4.32 hours, the mean birthweight ranged from 1,930 grams to 3,395 ± 547 grams and the mean baseline serum bilirubin levels ranged from 190 micromol/L to 292 ± 35 micromol/L. In all, 142 participants (55.5%) were male.

Regarding duration of treatment green phototherapy was significantly shorter than with blue phototherapy MD = 7.03 hours (95% CI 6.23 to 7.83), which in turn was significantly shorter than with white phototherapy MD = -32.0 hours (95% CI -44.72 to -19.28).



Forest plot 7.1.3.1 Blue versus green versus white – Mean Duration of treatment

There was a significantly greater decrease in serum bilirubin levels among babies treated with green phototherapy (MD = 3.98 micromol/L (95% CI: 3.43 to 4.52)), both in term and preterm babies. Turquoise phototherapy also resulted in a significantly greater decrease in serum bilirubin levels MD = 14.00 micromol/L (95% CI: 3.76 to 24.24).



Forest plot 7.1.3.1 Blue versus green versus turquoise – Mean decrease in serum bilirubin

Evidence summary Bulb colour for conventional phototherapy

Comparison between different types of coloured lights used for phototherapy reveals that green light phototherapy is significantly better than blue light phototherapy in reducing the duration of treatment and reducing the mean serum bilirubin levels. Results from one trial indicates that turquoise light phototherapy is better than blue light for the same two outcomes

GDG translation from evidence Bulb colour for conventional phototherapy

The GDG recognises that the colour of the phototherapy lamps is important and that green light is the most effective in reducing serum bilirubin. It is not, however, well tolerated by clinical staff. Phototherapy units that combine white with blue light are "easier on the eyes" and are better tolerated by clinical staff. These may also be more acceptable to parents.

Recommendations

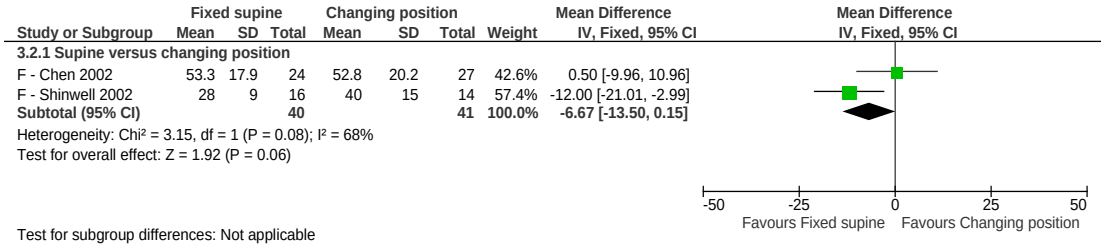
See section 7.1.1 and 7.1.2 for recommendation on bulb colour for conventional phototherapy

7.1.4 Fixed position versus changing positions

Three studies[160-162] with 131 participants were included in this comparison but not all studies contributed data to each analysis. One study apiece was from Iran, Israel and Taiwan. The included studies ranged from EL1- to EL1+. No study reported the method of randomisation though two studies used sealed envelopes for allocation concealment.

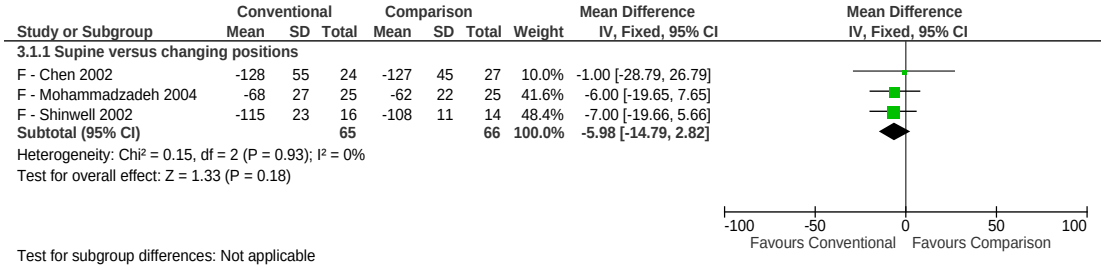
All three studies included only term babies. When reported the mean gestational age ranged from 38.1 ± 1.0 weeks to 38.2 ± 1.14 weeks, the mean age at study entry ranged from 104.2 ± 48.5 hours to 143.4 ± 48.5 hours, the mean birthweight ranged from 3,137 ± 384 grams to 3,500 ± 478 grams and the mean baseline serum bilirubin levels ranged from 320 ± 17 micromol/L to 321 ± 39 micromol/L. In all, 27 participants, (33.3%) of participants were male.

There was a non-significant trend in favour of a fixed supine position as regards the mean duration of treatment, MD = -6.67 hours (95% CI -13.50 to 0.15).



Forest plot 7.1.4.1 Fixed supine position versus changing positions – Mean duration of treatment

A similar trend was also reported for mean change in serum bilirubin. MD = -5.98 micromol/L (95% CI: -14.79 to 2.82).



Forest plot 7.1.4.2 Fixed supine position versus changing positions – Mean decrease in serum bilirubin

Evidence summary

There was a non-significant trend in favour of a fixed supine position for mean duration of treatment and mean decrease in serum bilirubin in reviewed studies.

GDG translation from evidence

The GDG accepts that, in term babies, the position of the baby during phototherapy has no significant influence duration of phototherapy or mean change in serum bilirubin. No studies in preterm babies were identified. To ensure consistent advice regarding the risk of sudden infant death syndrome, babies should be placed in a supine position. (see also sections 7.1.1 and 7.1.9)

Recommendations – Fixed position versus changing position and environment

During phototherapy:

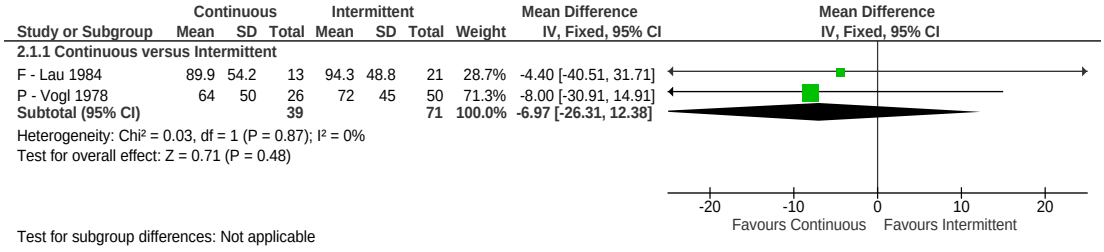
- place the baby in a supine position unless other clinical conditions prevent this
- ensure treatment is applied to the maximum area of skin
- monitor the babies temperature and ensure the baby is kept in an environment that will minimise energy expenditure (thermoneutral environment)
- support parents and carers and encourage them to interact with the baby.

7.1.5 Continuous versus intermittent phototherapy

Two studies [163;164] (N = 110) contributed to this analysis each comparing continuous phototherapy to different intermittent regimens. One study was from Hong Kong and one from the USA. The evidence level of both studies was EL1-. Neither study reported the method of randomisation or allocation concealment.

Data from the various intermittent regimens were combined. The mean gestational age ranged from 34.7 ± 2.0 weeks to 39.9 ± 1.5 weeks, the mean age at entry to study was 56.8 ± 10.8 hours in one study and not reported in the second, the mean birthweight ranged from 1,836 ± 299 grams to 3,229 ± 394 grams and the mean baseline serum bilirubin levels ranged from 150 ± 19 micromol/L to 198 ± 25 micromol/L. Gender was not reported. One study each dealt with term and pre-term babies.

There was a non-significant difference between the two groups in favour of continuous phototherapy, MD = -6.97 hours (95% CI -26.31 to 12.38).



Forest plot 7.1.5.1 Continuous versus intermittent phototherapy – Mean duration of treatment

Evidence summary

Two RCT's, one in term babies and one in preterm babies, examined continuous phototherapy versus intermittent phototherapy with phototherapy being initiated at low serum bilirubin levels. No significant difference was found for any of the reported outcomes. No studies have examined intermittent phototherapy at moderate or high levels of serum bilirubin so we were unable to examine any evidence on the effectiveness of intermittent phototherapy at moderate or high serum bilirubin levels.

GDG translation from evidence

The GDG notes that there was no difference between continuous or intermittent phototherapy on either the duration of phototherapy or the mean change in serum bilirubin when initiated at low serum bilirubin levels.

Interrupting phototherapy at low bilirubin levels does not hinder the baby's treatment. The GDG supports brief interruptions of phototherapy treatment to facilitate breastfeeding and cuddles. These interruptions can be could be used by health care professionals to support parents and carers and encourage them to interact with the baby. This may help to reduce the anxiety and stress for both parents and babies caused by phototherapy.

The GDG notes that there is no evidence to support the safe use of intermittent phototherapy at moderate or high levels of serum bilirubin.

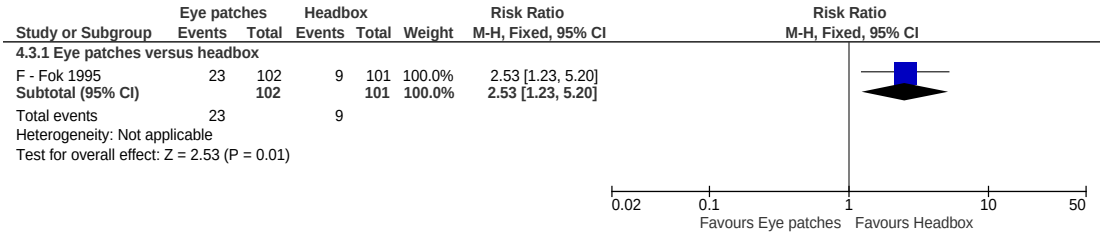
The GDG concluded that multiple phototherapy should be continuous and that other types of phototherapy can be interrupted (see also section 7.1.1 and 7.1.2 above)

7.1.6 Eye coverings

Two studies, reported in three publications[165-167] with 241 participants were eligible for this comparison but only one (comparing eye patches to a tinted head box) contributed outcome data. One study was from Hong Kong and the other from Italy. The evidence level of one study was EL1+ as a computer-generated sequence was used to allocate babies into the two groups. The second study was rated EL1- as neither the method of randomisation or allocation concealment.

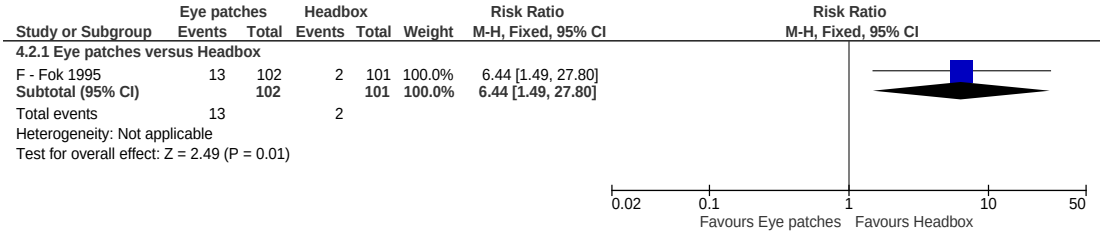
The mean gestational age from this study was 38.6 ± 2.56 weeks, the mean age at entry to study was 89.5 ± 27.6 hours, the mean birthweight was 3,087 ± 611 grams and the mean baseline serum bilirubin levels was 258 ± 27 micromol/L. In all, 106 participants (52.2%) were male.

There were significantly fewer cases of purulent eye discharge among the head box group compared to the eye patches group RR = 2.53 (95% CI 1.23 to 5.20).



Forest plot 7.1.6.1 Eye patches versus Headbox – Purulent eye discharge

And similarly there were fewer features of conjunctivitis among the Head box group RR = 6.44 (95% CI 1.49 to 27.80).



Forest plot 7.1.6.2 Eye patches versus Headbox – Features of conjunctivitis

Evidence summary

One RCT reported fewer cases of purulent eye discharge and conjunctivitis among babies nursed in a head box while receiving phototherapy compared to those using eye patches

GDG translation from evidence

While headboxes led to fewer eye problems in one study the GDG feels that if appropriate eye protection and care are given, either eye patches or headboxes can be used when conventional phototherapy is being used with term babies. During multiple phototherapy tinted headboxes are not recommended because the head constitutes a significant proportion of the baby's skin surface, which needs to be exposed to phototherapy for it to be effective.

There were no studies of headboxes in preterm babies and the GDG concludes that unless the preterm baby is being treated with fibreoptic phototherapy appropriate eye protection and eye care should be given, and tinted headboxes should not be used.

Recommendations – Eye coverings that should be used during conventional phototherapy

Use eye protection and give routine eye care to the baby during phototherapy.

Use tinted headboxes as an alternative to eye protection in term babies undergoing conventional phototherapy.

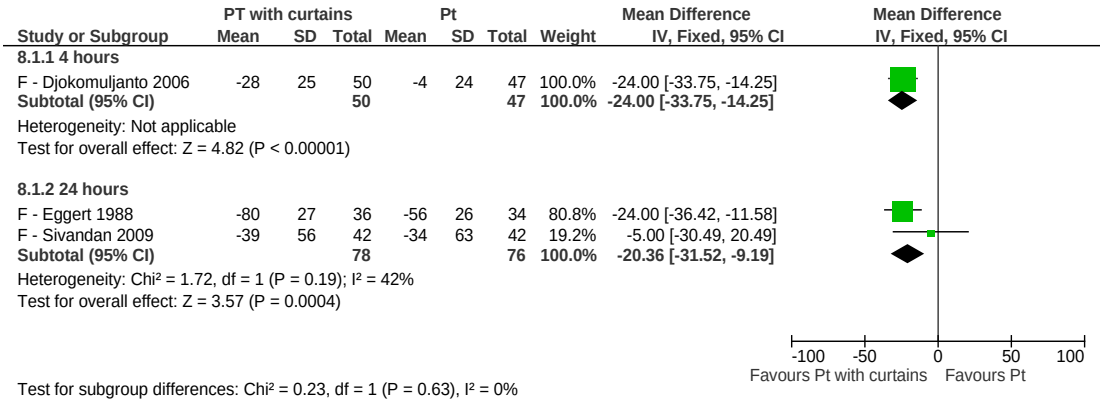
7.1.7 White curtains

Three RCT's[168-170] (N = 283) were eligible for this comparison. One study apiece was from Germany, India and Malaysia. One study was rated EL1+ as block randomisation was used and investigators were blind to the allocation, the second EL1+ as sealed opaque envelopes

were used as allocation concealment while the third study did not report on either the randomisation method or the allocation concealment so was rated EL1-. In one study the four outer walls of the incubator were draped in white cloth while in the other two a white cloth was hung from both sides of the phototherapy unit.

The mean gestation age of study participants was reported in one study as 37.5 ± 1.3 weeks and in another the median age was 40 weeks. Mean birthweight was reported in one study as 2,856 ± 345 grams and not reported in the other two studies. The mean age at entry to study arranged from 69 ± 36 hours to 105 ± 35 hours and was not reported in one study. The mean serum bilirubin ranged from 243 ± 28 micromol/L to 280 ± 39 micromol/L. In all, 165 participants (58.3%) were male.

As different time-points (4 hours and 24 hours) were used to measure the primary outcome of change in serum bilirubin concentration it was not appropriate to combine the results. However all studies showed a significantly greater decrease in serum bilirubin at the different time-points for babies in the curtained groups. At 4 hours the mean difference was -24.00 (95% CI: -33.75 to -14.25) and at 24 hours the mean difference was -20.36 (95% CI: -31.52 to -9.19)



Forest plot 7.1.7.1 White curtains – Mean change in serum bilirubin

One study reported that white curtains made no significant difference to the mean duration of phototherapy[170] Another study, using Cox proportional hazards regression analysis, reported that the median duration of phototherapy was significantly shorter (22 hours) in the phototherapy with curtains group compared with the control[168]

Evidence summary

Three studies reported that using white curtains on the side of the incubator or draped from the overhead unit led to a greater decrease in serum bilirubin levels at both 4 and 24 hours. One study report a significant decrease in the duration of phototherapy when white curtain were used while a second study reported no difference in duration of phototherapy.

GDG translation from evidence

The GDG accepts that the use of white curtains as an adjunct to phototherapy can aid serum bilirubin reduction but, because their use compromises the ability to observe the baby, the GDG does not recommend their use.

Recommendations – White curtains

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

7.1.8 What are the criteria/indications for starting and stopping phototherapy in babies with neonatal hyperbilirubinaemia?

Evidence summary

No evidence was identified

GDG translation from evidence

As no evidence was identified the GDG reached consensus on when phototherapy should be initiated and discontinued in both term and pre-term babies.

The consensus view (see Table 1 below) was that in term babies commencing phototherapy at a level of 350 micromol/L was safe provided the level was monitored with repeat testing at 6-hourly intervals. This would mean that even if the bilirubin level rose quickly it was very unlikely to exceed a dangerous level at the time of the next estimate, and there would therefore be adequate to permit the introduction of other appropriate therapy (e.g., multiple phototherapy, IVIG or exchange transfusion) if necessary. It was agreed by the GDG that using a lower threshold for phototherapy would increase the use of phototherapy unnecessarily. The GDG also accepted threshold levels for preterm infants that were in keeping with current practice in the UK. This employs a formaula based on gestational age in weeks multiplied by 10 minus 100 micromol/ for phototherapy and gestational age in weeks multiplied by 10 for an exchange transfusion.

Finally the RCT's of phototherapy (reviewed in sections 7.1.1 and 7.1.2), which could be considered to be 'best practice', predominantly assessed serum bilirubin levels every 6 – 12 hours to monitor treatment progress. The GDG decision to use 6 hourly intervals for repeat bilirubin testing was driven by the need to detect rapidly raising bilirubin (> 8.5 micromol/L/hour) which may be an indicator of haemolysis.

The GDG considered 50 micromol/L below the phototherapy threshold to be a reasonable level at which to stop phototherapy. This would avoid the need to keep babies under phototherapy longer than necessary.

Recommendations – Bilirubin thresholds for phototherapy

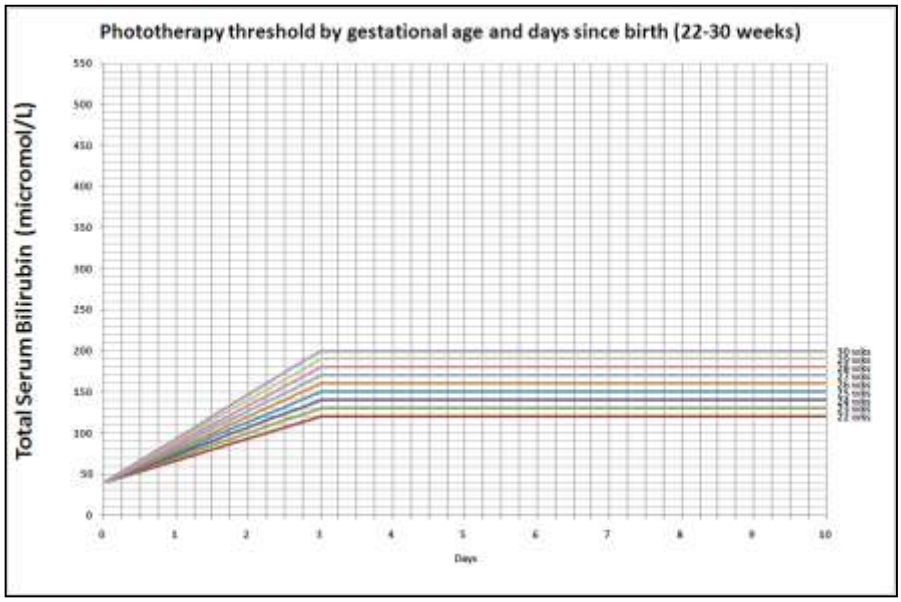
Use serum bilirubin measurement to determine the management of hyperbilirubinaemia in all babies (see table 1 below and graphs A-F).

Table 1 Consensus based serum bilirubin thresholds for management of babies ≥ 38 weeks gestational age

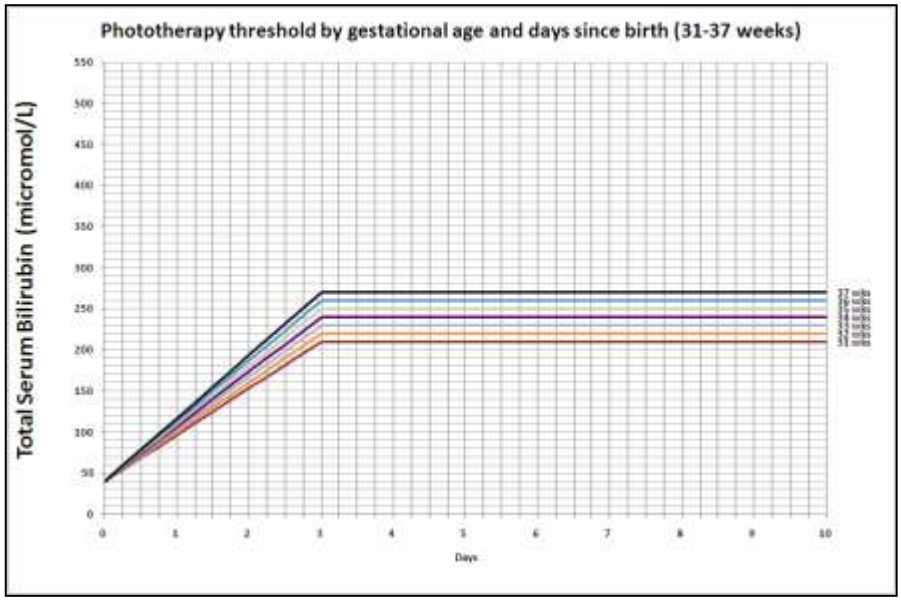
Age (hours)	**Serum Bilirubin measurement** (micromol/litre)			
0			> 100	> 100
6	> 100	> 112	> 125	> 150
12	> 100	> 125	> 150	> 200
18	> 100	> 137	> 175	> 250
24	> 100	> 150	> 200	> 300
30	> 112	> 162	> 212	> 350
36	> 125	> 175	> 225	> 400
42	> 137	> 187	> 237	> 450
48	> 150	> 200	> 250	> 450
54	> 162	> 212	> 262	> 450
60	> 175	> 225	> 275	> 450
66	> 187	> 237	> 287	> 450
72	> 200	> 250	> 300	> 450
78		> 262	> 312	> 450
84		> 275	> 325	> 450
90		> 287	> 337	> 450
96+		> 300	> 350	> 450
Action	↓	↓	↓	↓
	Repeat transcutaneous bilirubin/serum bilirubin (6–12 hours)	**Consider phototherapy (repeat transcutaneous bilirubin/serum bilirubin in 6 hours)**	**Start phototherapy**	**Perform an exchange transfusion**

Do not subtract conjugated bilirubin from total serum bilirubin when making decisions about the management of hyperbilirubinaemia (see section 6.6 and 6.7 above).

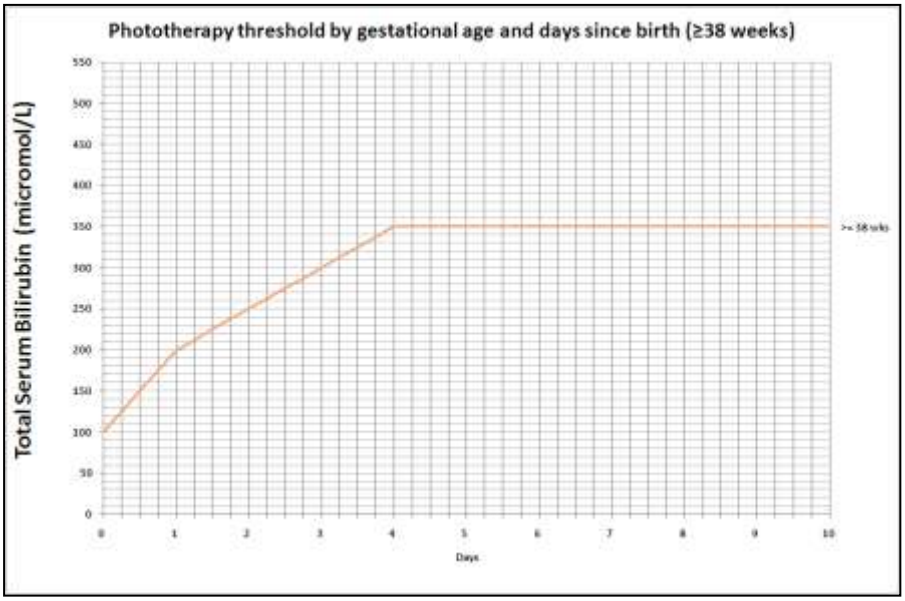
Graph A



Graph B



Graph C



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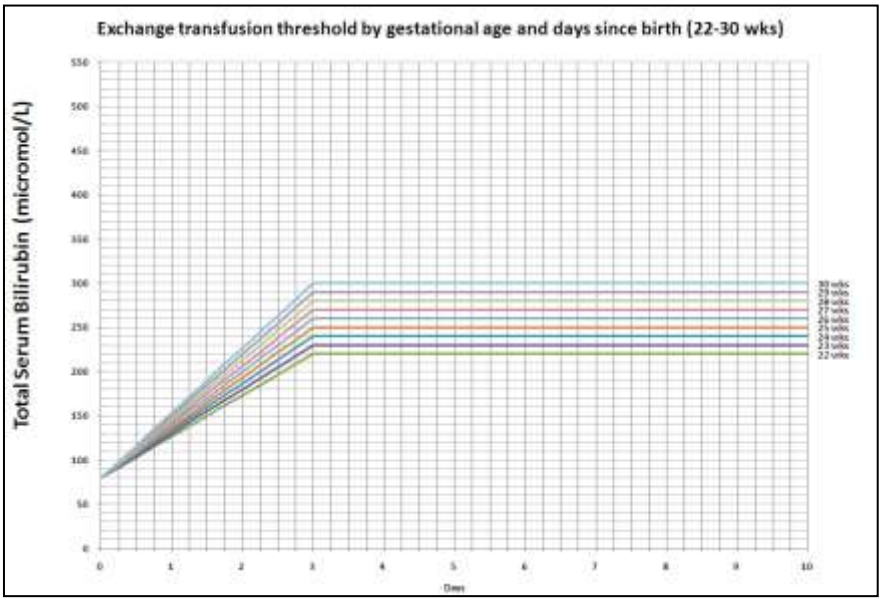
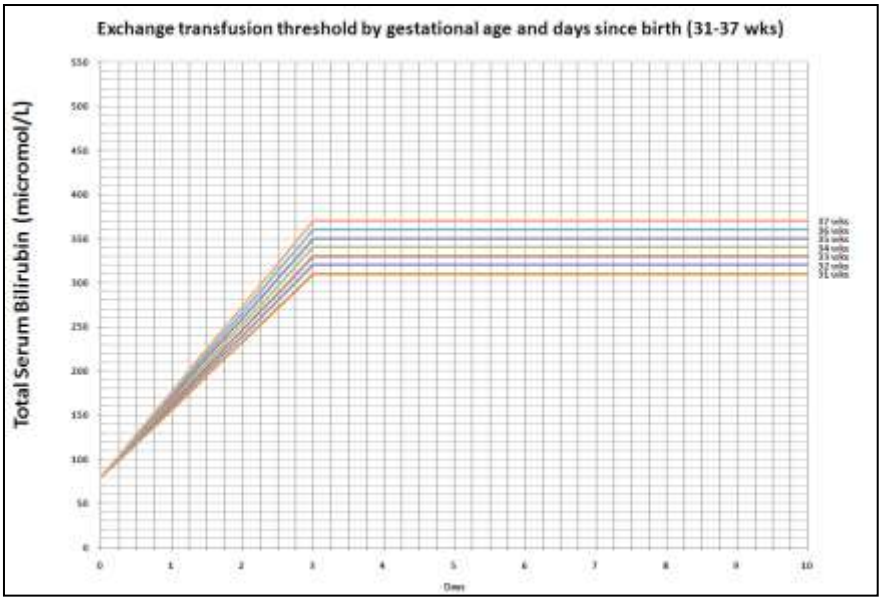
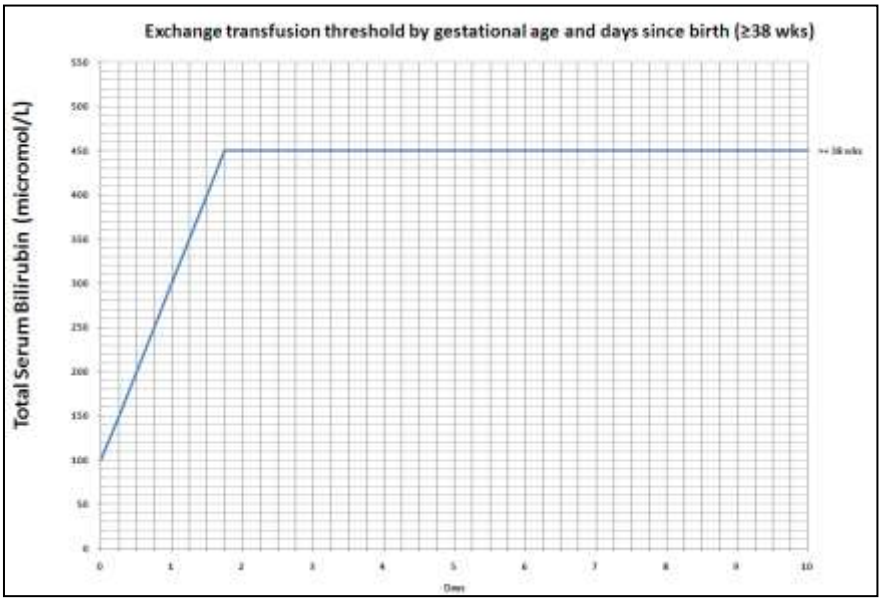
Graph D



Graph E



Graph F



Recommendations – Bilirubin thresholds for starting phototherapy

Use serum bilirubin measurement and treatment thresholds when considering the use of phototherapy (see Table 1 and graphs A-F)

In babies with a gestational age of 38 weeks or more whose bilirubin is in the 'repeat transcutaneous bilirubin/serum bilirubin' category (table 1) repeat transcutaneous bilirubin/serum bilirubin in 6–12 hours.

In babies with a gestational age of 38 weeks or more whose serum bilirubin is in the 'consider phototherapy' category (table 1) repeat serum bilirubin in 6 hours regardless of whether or not phototherapy has subsequently been started.

Do not use phototherapy in babies whose bilirubin does not exceed the phototherapy threshold levels (see table 1 and graphs A-F).

During phototherapy

If treatment has been started, use serum bilirubin measurement for all subsequent assessments until the baby has been discharged from the care of the maternity or neonatal service.

During conventional 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.

Stopping phototherapy

Stop phototherapy once serum bilirubin has fallen to a level at least 50 micromol/litre below the appropriate phototherapy threshold (see table 1 and graphs A-F).

7.1.9 Should incubators or bassinettes be used?

Evidence summary

No evidence was identified

GDG translation from evidence

As no evidence was identified the GDG cannot recommend either for the treatment of hyperbilirubinaemia and considers that clinical considerations and availability should determine whether incubators or bassinettes are used to nurse babies who require phototherapy. Babies should be nursed in a thermo-neutral environment, in other words in surroundings of an ambient temperature which minimizes their energy expenditure on keeping warm or cool.

Recommendations

Use incubators or bassinettes according to clinical need and availability.

7.1.10 Satisfaction with treatment

Evidence summary

No RCT's examining this question has been identified.

7.1.11 Side effects of phototherapy

Several concerns have been raised about the immediate and long-term potential adverse effects of phototherapy for neonatal hyperbilirubinaemia.

DNA damage

A review of in vivo studies[171] demonstrated that phototherapy had DNA-modifying properties which could induce genetic and carcinogenic effects [EL1+]. A second study from Turkey[172] examined the effects on DNA in 33 term babies who receive phototherapy for jaundice compared with 14 healthy controls with jaundice who did not received phototherapy. There were no significant differences between the groups at entry. The mean gestational age was 39.3 ± 0.9 weeks, mean birthweight was 3021 ± 450 grams and the mean age at entry was 113 ± 46 hours. 29 (61.7%) of the sample were male. Phototherapy was applied using a standard Air Shields unit with four 18W blue-fluorescent tubes and two 18W white fluorescent tubes. The light range was between 480-520 nm and the irradiance was 12 microW/cm2/nm. DNA was collected and analysed according to standard practice. Images of 100 randomly selected cells were analysed visually. Each image was classified according to the intensity of fluorescence in the comet tail (caused if a damaged cell is exposed to an electric current, the cell fragments get drawn out into a comet tail) and given a value of 0, 1, 2, 3, 4 (from undamaged (class 0) to maximally damaged (class 4)) so that the total score of a slide could be between 0 and 400 arbitrary units. The mean DNA-damage scores were significantly different between the groups; 58.4 ± 3.2 for the phototherapy group and 23.1 ± 4.9 for the control group. [EL 2-]

A second study, from Turkey[173], also examined the effects on DNA in 46 term babies who received phototherapy (23 each received conventional and intensive phototherapy) for jaundice compared with 19 healthy controls with jaundice who did not received phototherapy. The gestational age ranged from 38 – 41 weeks and age at entry was between 3 and 10 days. Not other demographic details were reported. Phototherapy was applied using a standard Bilicrystal unit with either six 20W white fluorescent tubes placed 45cm above the baby or for intensive phototherapy twelve 20W white fluorescent tubes placed 20cm above the baby. The irradiance was 12-16 microW/cm2/nm for conventional phototherapy and 30-34 microW/cm2/nm for intensive phototherapy. DNA was collected and analysed according to standard practice. Images of 100 randomly selected cells were analysed visually. Each image was classified using the same methods as the previous study. The mean DNA-damage scores were significantly different between the groups, 32 ± 9 for the intensive phototherapy group, 28 ± 9 for the conventional phototherapy group and 21 ± 10 for the control group ($p < 0.001$). [EL 2-]

Malignant melanoma

A matched case-control study[174] from Sweden retrospectively examined the risk of developing malignant melanoma after treatment with phototherapy for neonatal jaundice. The hospital records of 30 adolescents with malignant melanoma were compared with the records of 120 controls matched for date of birth, hospital and gender. No significant risk of developing childhood malignant melanoma after phototherapy of babies with hyperbilirubinaemia was found. [EL2-]

A second study[175] examined data from an RCT of photoprotection educational programs in for 8-9 year old children in France. From a total of 828 children participating, 180 (22%) had been exposed to neonatal blue-light phototherapy. A melanocytic naevus count was conducted by a nurse who was unaware of the childrens' history of exposure to phototherapy. Naevus size on exposed body parts (arms and back) was recorded as <2mm, 2-5mm or >5mm. Children who had received phototherapy showed no significant difference in naevus counts than those who had not. [EL1+]

A small case-control study from France[176] assessed the role of blue-light phototherapy used to treat hyperbilirubinaemia on naevus acquisition in children aged 8-9 years old. A total of 58 children were included, of whom 18 (31%) had received phototherapy. The children were examined by a dermatologist and naevus size was recorded as <2mm, 2-5mm or >5mm. Univariate analysis indicated that the number of naevi > 2 mm was higher in the exposed

group (3.5 ± 3.05 for exposed children versus 1.45 ± 1.99 for unexposed children). After stratification for classic clinical risk factors (age, skin types I and II, medium coloured or light skin, fair hair and light eye colour) the association between phototherapy exposure and naevus size 2mm or larger was significant (p = 0.003). [EL2-]

Trans-epidermal water loss (TEWL)

A case control study from Thailand[177] examined TEWL during phototherapy in term babies. A group of 40 babies with non-haemolytic hyperbilirubinaemia was compared with 40 healthy controls. The mean gestational age was 39.0 ± 1.2 weeks and mean birthweight was 3166 ± 435 grams. The mean serum bilirubin of the babies receiving phototherapy was 248 ± 15 micromol/L. In all, 44 (55.0%) of the sample were male. Babies received conventional phototherapy in an open crib. TEWL increased by 16.7% after 6 hours of phototherapy. This was significantly higher than the rate of loss in control babies not requiring phototherapy. [EL2-]

Another case series, from Israel[178] examined TEWL during phototherapy in pre-term babies. The study included 31 babies, of whom 15 (48.4%) were males, with a mean gestational age of 31.2 weeks and mean birthweight of 1447 grams were included. Babies with respiratory distress, sepsis and those requiring ventilatory support were excluded. Babies were nursed naked except for eye patches in incubators and received conventional phototherapy (Air Shields Micro-Lite). The mean increase in TEWL was 26.4%. [EL3]

A second case series from the Netherlands[179], examined TEWL in preterm babies during phototherapy with halogen lamps. This study included 18 babies with a mean gestational age of 30.6 ± 1.6 weeks and a mean birthweight of 1412 ± 256 grams who received phototherapy for non-haemolytic hyperbilirubinaemia. Babies with metabolic disorders and serious skin lesions were excluded Phototherapy was applied using a single-quartz lamp (Ohmeda Bililight) positioned 55cm above the baby with an irradiance of 12.5microW/cm2/nm. There was an increase of 21.3% in TEWL after 1 hour of phototherapy with halogen lamps. [EL3]

An RCT[180] in Thailand evaluated the effect of application of a clear topical ointment on TEWL in preterm babies receiving phototherapy. In this study, 40 babies – 22 (55.0%) males - with a mean gestational age of 33.1 ± 2.6 weeks, mean birthweight of 1443 ± 196 grams and mean serum bilirubin of 171 ± 39 micromol/L were randomised to receive phototherapy and topical ointment or phototherapy alone. The ointment was a 1:1 mixture of Vaseline and liquid paraffin. After 5 hours, mean TEWL decreased by 13.8% in the group that received ointment but increased by 14.1 % in the control group. There was no significant difference between the groups in pre- and post-phototherapy serum bilirubin levels. [EL1-]

Heart rate variability

A controlled before and after study from Israel[181] examined the effects of phototherapy on cardiovascular function. Thirty term babies with Apgar > 7 at 1 minutes and >8 at 5 minutes who required phototherapy for jaundice were included. Babies with haemolysis, G-6-PD deficiency, fever, maternal use of narcotic analgesics during labour or ruptured membranes > 18 hours were excluded. The mean gestational age was 39.1 ± 1.5 weeks and mean birthweight was 3116 ± 392 grams. The mean age at entry to study was: 53 ± 31 hours and mean serum bilirubin was 238 ± 43 micromol/L. Sixteen participants (53.3%) were male. While there were no significant changes in heart rate during phototherapy, significant changes in heart rate variability were observed. mean SD1 measurements before and during phototherapy were 12 ± 8ms and 8 ± 4 ms respectively (p< 0.02); mean SD2 measurements were 33 ± 16 ms and 22 ± 10 ms respectively (p < 0.01); mean SDDN measurements were 30 ± 14 ms and 18 ± 7 ms respectively (p < 0.01), and mean RMSSD measurements were 18 ± 12 ms and 11 ± 6 ms (p < 0.02). [EL 3]

Vasodilator effects

An RCT[182] carried out in Turkey compared close phototherapy (15 cm above the baby) and remote phototherapy (30 – 45 cm above the baby) in 61 term and 37 pre-term babies. The mean gestational age of the term babies was 38.7 ± 1.2 weeks and the mean birthweight was 3361 ± 449 grams while for pre-term babies, the mean gestational age and mean

birthweight were 33.5 ± 2.8 weeks and 2088 ± 604 grams respectively. No significant differences were found in body temperature, heart rate and blood pressure, serum nitric oxide (NO) levels, or vascular endothelial growth factor (VEGF) levels in babies receiving close or distant phototherapy. [EL1-].

Patent ductus arteriosus

An RCT[183] from the USA evaluated the use of foil shields placed over the chest of preterm babies (N = 74) receiving phototherapy to prevent patent ductus arteriosus. The mean gestational age of the population was 29.3 weeks and mean birthweight was 1,035 grams. The mean duration of phototherapy was 8.3 days for the shield group and 8.5 days for the no shield group. Use of the foil shield was associated with a significantly lower frequency of patent ductus arteriosus ($p < 0.009$) but with a non-significant trend to increased later mortality (up to 167 days) with ten versus four deaths ($p = 0.056$). The majority of deaths due to complication of prematurity or sepsis and not relate to curse of therapy in the first 4 weeks [EL 1-].

Evidence summary

Studies of mixed quality reported that trans-epidermal water loss increased significantly (by up to 25%) in babies receiving conventional phototherapy. An RCT [EL 1-] of close and distant phototherapy found no significant differences in clinical variables, including body temperature, heart rate and blood pressure during phototherapy. Three studies, one EL1+ and two EL2-, examined the association between of history of exposure to phototherapy and later naevus acquisition in primary school children. No significant association was identified. One small study reported a significant link after stratification for risk factors. One study reported that phototherapy was associated with DNA damage. However there is no evidence that this effect on DNA at a microscopic level can lead to long term adverse effects in phototherapy-treated babies.

GDG translation from evidence

Good clinical practice should ensure that babies are kept hydrated while undergoing phototherapy. Hydration can be assessed by changes in body weight, and observation of wet and dirty nappies. The evidence suggests that neither fluorescent nor LED lights contribute significantly to increased transepidermal water loss, whereas haologen lights do increase such water losses. Conventional phototherapy should be interrupted to facilitate breastfeeding, and mothers should be offered lactation support. Breast feeding mothers should be taught how to express their milk if their baby needs additional fluids, and encouraged to express frequently if their baby requires continuous phototherapy.

When multiple phototherapy is required phototherapy should be continuous. Most babies requiring continuous phototherapy can continue to receive milk feeds. Long term concerns about adverse effects of phototherapy (see section 7.1.11), serve as a reminder that phototherapy is a powerful tool and should not be used without specific indications.

No evidence was found to suggest that preterm babies or other vulnerable groups of babies are at increased risk of adverse effects from phototherapy.

Recommendations

Monitor hydration by daily weighing and assessing wet nappies.

During conventional phototherapy:

- using clinical judgement encourage breaks (of up to 30 minutes) for breastfeeding, nappy changing and cuddles as long as the bilirubin levels are not significantly elevated
- continue lactation/feeding support
- do not give additional fluids or feeds routinely.

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

During multiple phototherapy:

- monitor hydration by daily weighing and assessing wet nappies
- do not interrupt phototherapy for feeding but continue administering intravenous/oral feeds
- continue lactation/feeding support so that breastfeeding can start again when treatment stops.

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

7.1.12 Discharge and monitoring

Clinical question

How to monitor a baby with jaundice?

i) 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?

When to discharge a baby treated for hyperbilirubinaemia? What follow-up is required?

i) What is the appropriate criterion for discharge of babies treated for neonatal hyperbilirubinaemia?

ii) What is the appropriate timing/frequency of follow-up?

As there was overlap between these questions one search was carried out for all questions. Primary screening of 418 titles and abstracts from the database searches led to the retrieval of 17 full-text papers. Of these 15 were excluded as they were overviews of the management of hyperbilirubinaemia (N = 5), synopses of guidelines or position statements (N = 5), examining the effect of early post-natal discharge on hyperbilirubinaemia (N = 2), reporting or evaluating electronic patient bilirubin management software (N = 2) or a letter (N = 1). Two papers, a RCT of different serum bilirubin levels as criteria for stopping phototherapy and an uncontrolled clinical study of an a priori serum bilirubin level to indicate rebound jaundice, were included. Existing national guidelines from Canada, Israel and the USA were also checked for recommendations on discharge and monitoring

Review findings

An RCT from Israel[184] compared stopping phototherapy at two different levels, one 17 micromol/L and the second 51 micromol/L below the threshold for phototherapy. The study included 52 term babies (gestational age > 36 weeks) with birthweight >2500 grams who were eligible for phototherapy for neonatal hyperbilirubinaemia. The mean gestational age of the sample was 38.7 ± 1.6 weeks, mean birthweight was 3302 ± 453 grams and mean serum bilirubin at entry was 252 ± 36 micromol/L. 25 (48.1%) were male. Computer-generated block randomisation was used and the sequence was concealed until allocation was completed. Parents were blinded to treatment allocation. There was no significant difference between the groups in either duration of phototherapy or in the number of babies requiring a second course of phototherapy. [EL 1++]

An uncontrolled clinical study from Israel[185] examined the occurrence of post-phototherapy rebound. A group of 226 term and near-term babies treated with phototherapy had serum bilirubin measured 12-36 (mean 24) hours after stopping phototherapy. Babies received phototherapy according to the 2004 AAP guideline. The mean gestational age of the sample was 39 ± 2 weeks, mean birthweight was 3204 ± 445 grams, mean age at onset was 62.2 ± 38.3 hours. The mean bilirubin at initiation of phototherapy was 260 ± 55 micromol/L. In all, 134 participants (59.3%) were male. Serum bilirubin was routinely measured every 12 hours or more often if clinically indicated. Phototherapy was discontinued at when serum bilirubin had fallen to 205 micromol/L, or once serum bilirubin stabilized and fell below the 75th centile on the hour specific nomogram. Rebound jaundice was defined as serum bilirubin > 256 micromol/L measured between 12 and 36 hours after stopping phototherapy. Phototherapy was recommenced at the clinician's discretion but usually not at serum bilirubin levels below 256 micromol/L. In all, 30 (13.3%) babies had rebound jaundice, with serum bilirubin > 256 micromol/L. Of these, 22 were re-treated with phototherapy up to a mean of 42 ± 26 hours after phototherapy had been discontinued. A greater number of babies rebounded among those in whom phototherapy was initiated < 72 hours (26 of 154, 16.9%) compared to those in whom phototherapy was initiated > 72 hours (4 of 74, 5.4%). [EL3]

Existing guidelines vary in their recommendations on discharge and monitoring of babies with hyperbilirubinaemia. The Canadian Pediatric Society recommends that serum bilirubin should be monitored 6 – 12 hours after the start of phototherapy and checked 24 – 48 after discontinuation of phototherapy but do not specify when phototherapy should be discontinued.[186]

The AAP recommends that for term and near-term babies (GA > 35 weeks) serum bilirubin should be repeated every 2-3 hours (to coincide with feedings) until levels fall, at which point serum bilirubin can be repeated every 8-12 hours. Phototherapy may be discontinued at serum bilirubin <222 – 239 micromol/L and measuring serum bilirubin 24 hours after stopping to check for rebound jaundice is optional.[11]

The Israel Neonatal Society guidelines recommend that for term and near-term babies (Gestational age > 35 weeks) serum bilirubin measurement should be repeated at least twice daily depending on clinical judgement. Phototherapy should be discontinued at 205 – 222 micromol/L. In high-risk babies serum bilirubin should be measured 12-24 hours post-discontinuation of phototherapy.[187]

Evidence Summary

Two studies from Israel show that establishing a priori serum bilirubin levels for discontinuation of phototherapy and of rebound jaundice did not make a difference to clinical practice. The RCT of high and low threshold levels provided equal number of rebound jaundice cases and did not lead to significant reduction in duration of phototherapy. While the uncontrolled study identified 30 cases of rebound jaundice (serum bilirubin > 256 micromol/L), only 22 of these were considered by the clinician to need a second course of phototherapy.

Existing guidelines vary in their recommendations on how frequently to monitor serum bilirubin, when to discontinue phototherapy and how often to monitor for rebound jaundice.

GDG translation from evidence

The evidence base was not adequate to inform the GDG regarding recommendations for monitoring of jaundice after discontinuation of phototherapy and checking for rebound. One good quality study looked at discontinuation of phototherapy but used the Bhutani nomogram and was not relevant to UK practice.

The RCT's reviewed in 7.1.1 and 7.1.2 generally adopted the practice of discontinuing phototherapy once the bilirubin levels below the threshold value on two successive measurements. The GDG reached a consensus opinion. Consideration was given to the potential for rapidly rising bilirubin in the presence of haemolysis, and the interval between testing was determined with this in mind. Expert advice is that a threshold of 6 hours

between tests allows safe differentiation between sequential results in order to measure a true rate of increase.

The GDG recommend a serum bilirubin level be taken 12 – 18 hours after stopping phototherapy to check for rebound jaundice, because of their decision (see Section 7.1.8) to stop phototherapy once bilirubin levels at least 50 micromol/l below the age-appropriate threshold ware reached. This provides for a 'safety net' for measurement errors and to identify the occasional baby with increased bilirubin production even after apparently successful phototherapy.

Recommendation – Stopping phototherapy

Check for rebound of hyperbilirubinaemia with a repeat serum bilirubin measurement between 12 and 18 hours after stopping phototherapy – babies do not necessarily have to remain in hospital for this to be done

7.1.13 Additional fluids / feeds during phototherapy

Clinical question

Is it beneficial to give additional fluids (cup feeds, fluids) during treatment with phototherapy?

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)
- Parenteral feeds

1831 references were identified by the electronic searches (were not restricted by study methodology) though the majority were excluded on the basis of title and abstract. The main reasons for exclusion at this stage were either that the reference dealt with a non-interventional study or that feeding was not the intervention being examined but was mentioned in passing.

Of the 20 references that were requested as hard copy articles, 4 were included and 16 were excluded for the following reasons; babies were not jaundiced (N = 6), not randomized (N = 5), no clear intervention (N = 4), comparison of phototherapy with interruption of breastfeeding (N = 1), and the comparison of hospital routines which included feeding (N = 1).

The included studies were divided into two groups; one group dealing with fluids or feeds given in combination with phototherapy and the other dealing with additional fluids or feeds as interventions to minimise the rise in serum bilirubin and reduce the need for phototherapy.

Description of included studies

Four RCT's dealt with additional fluids or feeds alongside phototherapy for the treatment of hyperbilirubinaemia. Two studies used computer-generated or block randomisation and two studies used sealed envelopes to conceal allocation. Where reported the mean birthweight of the samples ranged from 2936 ± 473 grams to 3404 ± 361 grams. The mean gestational age was 37.6 ± 0.9 weeks to 39.4 ± 0.9 weeks, mean age at entry to the study was between 95 ± 17.7 hours and 139 ± 47 hours while the mean serum bilirubin levels ranged from 254 ± 22 micromol/L to 377 ± 66 micromol/L. Of the combined sample, 269 participants (57.4%) were male.

Review findings

The first RCT, from India[188], compared giving extra fluids to babies undergoing phototherapy with a control group receiving standard hydration. Babies in the 'extra fluids' group received intravenous fluid supplementation with 1/5 normal saline in 5% dextrose for a period of 8

hours before phototherapy. Standard care consisted of conventional phototherapy combined with 30mL/kg/day of extra oral feeds (expressed breast milk or formula) until phototherapy was discontinued. Subjects were randomised in stratified blocks according to serum bilirubin levels at entry to the study. Sealed envelopes were used to conceal the allocation. Significantly fewer exchange transfusions were needed among babies randomised to receive extra fluids (Risk Ratio 3.3 (95% CI 1.51, 7.35)). The 'extra fluids' group also showed a significantly greater mean? Reduction in serum bilirubin (26 micromol/L (95% CI; 10.60, 41.40) over 24 hours and a shorter duration of phototherapy (mean difference 21 hours (95% CI; 9.45, 32.55)). [EL 1++]

The second RCT, from Malaysia[189], also examined the supplementation of phototherapy and enteral feeds with intravenous fluids. All babies received daily maintenance fluids at 90 mL/kg on day 2, 120 mL/kg on day 3 and 150 mL/kg from day 4 onwards. They were also given an additional 10% of their respective total daily fluid requirement to compensate for fluid loss during phototherapy. The enteral feeds group was given 8 divided feeds at 3-hour intervals. Breast-fed babies were fed on demand. In addition the breast-fed babies were given half the volume of formula feeds that formula fed babies received. In the intravenous group babies were given half of their daily fluid requirement as eight divided feeds at 3-hour intervals. The remaining half of their daily fluid requirement was given as continuous intravenous 1/5 normal saline and 5% dextrose infusion. Blinding was not reported but subjects were stratified by serum bilirubin level, hydration status and usual type of feed before randomisation. Sealed envelopes were used to conceal the allocation. Fewer babies in the un-supplemented group needed an exchange transfusion but this difference was not significant. There was a greater decrease in serum bilirubin in the babies given supplemental intravenous fluids, but again this difference was not significant. [EL 1+]

An RCT carried out in Argentina[127] compared conventional phototherapy combined with either breastfeeding (usual care) or with formula feeds. No information was given on the contents of the formula feeds. Blinding was not reported though subjects were randomised using a computer-generated sequence of numbers. There was no significant difference between the two groups in mean decrease in serum bilirubin over the 48 hours of phototherapy. [EL1+]

The final RCT, from Thailand[190], compared the effect on serum bilirubin of different types of formula feeds in combination with phototherapy. The formula feed, 'Enfamil', was compared with a lactose-free formula 'Prosobee'. These feeds have compatable energy, carbohydrate, fat and mineral content; Prosobee has a slightly higher protein content that Enfamil. Babies were fed with 3 ounces of formula 8 times a day over 72 hours of conventional phototherapy. Blinding and randomisation methods were not reported. There was no significant difference between the types of formula in of mean decrease in serum bilirubin during phototherapy. [EL 1-]

Evidence summary

Evidence from good quality RCTs [EL 1+ or EL 1++] on the effectiveness of the addition of intravenous fluids to phototherapy shows contrasting results. One study shows that fewer babies given additional IV fluids during phototherapy needed exchange transfusion, show greater reduction in mean serum bilirubin, and need shorter duration of phototherapy compared to babies given only enteral feeds. The second study did not confirm these findings.

In one RCT of EL I- formula feeds was no more effective than breast feeding in reducing serum bilirubin during phototherapy. In another study, lactose-containing formula was no more effective than lactose-free formula during phototherapy.

No studies examining additional fluids in pre-term babies receiving phototherapy were identified.

GDG translation from evidence

Additional fluids given to term babies receiving phototherapy shorten the duration of treatment and reduce the number of exchange transfusions required. However the GDG

considers that the automatic prescription of additional fluids when phototherapy is initiated is not warranted as this can hinder successful breastfeeding. The NICE guideline on 'Postnatal care' recommends that "breastfed babies should not be routinely supplemented with formula, water or dextrose water for the treatment of jaundice". (www.nice.org.uk/CG037) All the studies examined were performed before modern LED phototherapy devices were developed, devices which are claimed to reduce fluid losses. The GDG's opinion is that the need for additional fluids during phototherapy should be considered on an individual clinical basis.If additional fluids are indicated, the GDG supports maternal expressed breast milk as the additional fluid of choice.

Recommendations

see section 7.1.11 for recommendations

7.2 Exchange transfusion

Clinical question

i) How effective is exchange transfusion?
ii) What is the best method (single volume vs. double volume exchange)?
iii) What are the criteria/indications for carrying out an exchange transfusion?

Following electronic searches, 103 records were identified and 17 hard copy articles were requested. Following expert advice, five more hard copy articles were ordered. Of these 12 were included and 10 excluded for the following reasons: no jaundice-related outcomes specified (N = 3), exchange transfusion not the primary subject (N = 2), commentary (N = 1), correspondence (N = 1), conference abstract (N = 1), study included non-jaundiced babies (N = 1), and duplicate publication (N = 1). Initially only RCTs were to be included, but due to the paucity of data on adverse effects reported in these studies the scope was expanded to include lower quality studies that reported adverse effects.

7.2.1 Double volume exchange transfusion (DVET)

In the six RCTs double volume exchange transfusion (DVET) was compared with alternative treatment strategies. Exchange transfusion was generally performed using the umbilical vein and acid citrate dextrose (ACD) or citrate phosphate dextrose (CPD) blood less than 2 or 5 days old. The volume of blood used was 75 - 170ml/kg body weight. Exchange transfusions were initiated at varying serum bilirubin levels, the lowest being 256.5 micromol/L in preterm babies and 307.8 micromol/L in term babies. In one RCT, exchange transfusions were carried out within 9 hours of birth in babies with haemolytic disease of the newborn.

DVET versus no treatment

The first RCT[191] carried out in the USA compared exchange transfusion with no treatment in 100 babies with indirect serum bilirubin >307.8 micromol/L. Babies were less than 1 week old. Demographic details and method of randomisation were not reported though sealed envelopes were used to conceal allocation to intervention groups. There were three deaths in each group, none attributable to exchange transfusion. One baby in control group had kernicterus confirmed by autopsy. Seven of the exchange transfusion group had an abnormal neurological examination at 12-24 months compared to six in the control group. [EL 1+]

DVET versus simple transfusion

This RCT[192;193] compared exchange transfusion with simple top-up transfusion in 137 babies with haemolytic disease of the newborn. All transfusions were carried out within 9 hours of birth. Sample demographics and method of randomisation were not reported, though sealed envelopes were used to conceal allocation to intervention groups [see above]. There were significantly fewer deaths in the exchange transfusion group (RR = 0.26 (95% CI 0.11, 0.60)) and also significantly fewer cases of kernicterus (RR = 0.38 (95% CI 0.17, 0.87)). [EL 1+]

DVET versus single volume exchange transfusion

This RCT[194], carried out in Switzerland, compared DVET with SVET in the management of ABO haemolytic disease. Twenty babies were included, of whom 15 (75%) were male. The mean gestational age of the sample was 39.5 ± 1.0 weeks, mean birthweight was 3305 ± 392 grams, mean age at entry to study was 17.9 ± 6.13 hrs and the mean serum bilirubin was 207 ± 45 micromol/L. A random numbers table was used to allocate babies to the groups but allocation concealment was not reported. Both interventions were initiated according to the modified Polacek curve as described by Cockington[195];. There was no significant difference between SVET and DVET in mean reduction of serum bilirubin, mean duration of adjunctive phototherapy and level of rebound hyperbilirubinaemia. There were no cases of kernicterus or reported adverse effects in either group. [EL 1-]

Exchange transfusion versus phototherapy

An RCT[196,] carried out in Singapore, compared DVET with phototherapy for the management of non-haemolytic hyperbilirubinaemia. In all, 52 babies were included of whom 28 (53.8%) were male. The mean gestational age of the sample was 37.0 ± 2.78 weeks, mean birthweight was 2501 ± 576 grams, mean age at entry to study was 84 ± 12 hrs and mean serum bilirubin was 297 ± 25 micromol/L. Both interventions were initiated at serum bilirubin > 256.5 micromol/L in pre-term babies and > 307.8 micromol/L in term babies. Neither the method of randomisation or allocation concealment was reported but there were no significant differences between the groups on any baseline variable. There was a significantly greater reduction in mean serum bilirubin 24 hours after initiation of treatment in the phototherapy group (MD = 51 micromol/L (95% CI 39.70, 62.30)). In the exchange transfusion group there was an initial fall in serum bilirubin levels at 6 hours but this was rapidly followed by rebound hyperbilirubinaemia. There were more treatment failures in the exchange transfusion group, with 8 babies requiring repeat exchange transfusion while no babies in the phototherapy group required additional treatment. The Risk ratio (RR) of treatment failure was significant at 17.00 (95% CI 1.03, 280.07). There were no cases of kernicterus in either group. [EL 1-]

7.2.2 Different types of exchange transfusion

The fifth RCT[197,] carried out in Canada, compared conventional DVET with albumin enriched DVET. A total of 42 babies were included, of whom 25 (59.5%) were male, and 27 (64.3%) had Rh or ABO incompatibility. The mean gestational age of the sample was 36.0 ± 0.7 weeks, mean birthweight was 2455 ± 153 grams and mean serum bilirubin was 263 ± 82 micromol/L. Neither the method of randomisation or allocation concealment was reported but there were no significant differences between the groups on any baseline variable. There was no significant difference between DVET and albumin enriched DVET in mean reduction of serum bilirubin, mean duration of adjunctive phototherapy and the degree of rebound hyperbilirubinaemia. There were no cases of kernicterus or reported adverse effects in either group [EL 1-].

The sixth RCT[198], carried out in the USA, compared DVET with exchange transfusion with frozen erythrocytes diluted in plasma. The sample was divided into low birthweight (<2500grams) and appropriate birthweight (>2500) grams groups [either ≤2500 or ≥ 2500], and subjects within each group were randomly allocated to either treatment. Neither allocation concealment nor the method of randomisation was reported but there were no significant differences between the groups on any baseline variable. In the low birthweight group the mean gestational age of the sample was 32.6 ± 3.2 weeks, mean birthweight was 1,670 ± 434 grams and mean serum bilirubin was 304 ± 48 micromol/L while in the appropriate birthweight group the mean gestational age of the sample was 39.1 ± 1.8 weeks, mean birthweight was 3,234 ± 494 grams and mean serum bilirubin was 328 ± 25 micromol/L There was no significant difference between DVET and frozen erythrocytes in mean reduction of serum bilirubin, the number of treatment failures or deaths. There were no cases of kernicterus or reported adverse effects in either group. [EL 1-]

7.2.3 Side effects of Double volume exchange transfusion

A non-randomised controlled study from India[199] examined the role of calcium in exchange transfusion by alternately allocating subjects to either DVET or to DVET with 1 ml of 10% calcium gluconate IV for every 100ml of CPD blood exchanged. Sample demographics were not reported. No jaundice related outcome data were presented but one baby who received calcium had a cardiac arrest. The authors concluded that the administration of calcium had no role in exchange transfusion. [EL2+]

A study from India[200], using historical controls, compared exchange transfusion through peripheral vessels, either brachial or radial artery, with exchange via the umbilical vein. Of 198 babies who underwent exchange transfusion, 90 were exchanged through peripheral vessels, using the brachial or radial artery on one side and a good peripheral or antecubital vein on the other side. No major complications were observed, although two babies who received exchange transfusions through the radial artery suffered from transient blanching of the hand. The perceived advantage of peripheral exchange transfusions was that feeding could be continued while the procedure was taking place. [EL III]

Another retrospective chart review from the USA[201], examined the adverse effects of exchange transfusion over a 10 year period. Babies <30 days old who had received at least one exchange transfusion for hyperbilirubinaemia were included. In all, 55 babies underwent a total of 66 exchange transfusions. The mean gestational age of the sample was 35 ± 4 weeks and mean birthweight was 2388 ± 973 grams. 30 (54.5%) of the sample were male. The mean serum bilirubin was 307.8 ± 136.8 micromol/L. An adverse event was attributed if it occurred with 7 days of exchange transfusion. One baby died and another suffered seizures. The most common adverse effects were thrombocytopaenia (N = 22), hypocalcaemia (N = 19), catheter malfunction (N = 6), hypotension (N = 5), venous thrombosis (N = 2), hypokalaemia (N = 2) and hypoglycaemia (N = 2). One baby each suffered from bradycardia, acute renal failure and omphalitis. [EL III-]

A third retrospective chart review in the USA[202], reported the adverse effects of exchange transfusion over a 15 year period. The sample (N = 106) was divided into two groups, those with hyperbilirubinaemia (N = 81) and those with co-morbid medical problems (N = 25). The mean gestational age was 36.6 ± 3.6 weeks and mean body weight was 2846 ± 806 grams. The 106 babies included had a total of 140 exchange transfusions. Repeat exchange transfusions were more commonly needed among those with co-morbid medical problems. Three babies died of causes probably attributable to exchange transfusion, while four suffered permanent serious sequelae (defined as serious complications that resulted in permanent bodily alterations) and four suffered serious prolonged complications (defined as symptomatic patients with serious problems whose problems eventually resolved). The most common adverse effects were related to hypocalcaemia (1 death and 26 requiring treatment) and thrombocytopaenia (2 deaths and 15 requiring treatment) 12 babies experienced had catheter malfunctions (due to clotting) requiring a replacement catheter and/or discontinuation of treatment. [EL III-]

The National Institute of Child Health and Human Development (NICHHD) study in the USA[123], which compared phototherapy with no treatment used exchange transfusion as an outcome. The morbidity and mortality associated with exchange transfusions was also examined in the 190 subjects who received 331 exchange transfusions. The serum bilirubin levels at which exchange transfusions were indicated ranged from 171 micromol/L for high-risk low-birthweight babies to 342 micromol/L for babies with birthweight > 2500 grams. The mean reduction in serum bilirubin was 139 ± 30 micromol/L. Adverse effects related to exchange transfusions were transient bradycardia in 8 babies (4.2%) - 6 after receiving calcium, transient cyanosis in 3 (1.6%), transient vasospasm in 2 (1.0%), vasospasm with thrombosis in 2 (1.0%) and apnoea and/or bradycardia requiring treatment in 7 babies(3.7%). Three babies died within 24 hours (one within six hours) of exchange transfusion. [EL III-}

Evidence summary for exchange transfusion

Most of the included RCT's were of poor quality, had small sample sizes and were conducted more than 30 years ago. In one trial with EL 1-, no difference was observed in the mortality or

incidence of kernicterus between babies given DVET and those not given any treatment, although this study did not specify the demographic characteristics or the criteria for diagnosing kernicterus. Results from the second trial with EL 1+ suggest that compared to simple transfusion, DVET leads to fewer deaths and less kernicterus in the treatment of haemolytic disease of the newborn. Another trial with EL 1- compared phototherapy with DVET for the treatment of non-haemolytic hyperbilirubinaemia and showed better results with phototherapy. However DVET was carried out as a single procedure and was not followed by phototherapy, as is the current clinical practice. The other trials showed no significant differences between DVET and SVET, albumin-enriched exchange transfusions or transfusion using frozen erythrocytes diluted in plasma for the treatment of hyperbilirubinaemia.

Evidence on the adverse effects of exchange transfusions was collated from non-comparative studies. The most common adverse effects were thrombocytopaenia, hypocalcaemia, catheter malfunction, hypotension, venous thrombosis, hypokalaemia and hypoglycaemia.

GDG translation from evidence for exchange transfusion

The GDG considered the potential adverse side effects of double volume exchange transfusions when carried out by experienced health care professionals and concluded that this procedure is relatively safe and effective for babies with or at risk of severe hyperbilirubinaemia or babies who fail to respond to phototherapy.

The GDG noted that a single study reported no difference between single volume exchange transfusion and double volume exchange transfusion but considered this single study to be insufficient evidence to change current clinical practice. The clinical rationale for using double volume rather single volume is to reduce the likelihood of needing repeat transfusion.

No added benefit was found for albumin priming or for giving calcium with the exchange transfusion so the GDG considered that in the abscence of evidence to support these practice they should not be recommended.

Blood used for exchange transfusions should comply with the current guidance from the British Committee for Standard in Haematology (www.bcshguidelines.com).

As stated on page 70 (section 3.2, translation) the GDG saw no reason to alter current clinical practice, which is to perform an exchange transfusion in babies with signs of acute bilirubin encephalopathy (which include opisthotonos and retrocollis). Babies with signs attributable to acute bilirubin encephalopathy require exchange transfusion even if their bilirubin levels are controlled by phototherapy.

Recommendations – Exchange transfusion

Use serum bilirubin measurement and the treatment thresholds when considering the use of an exchange transfusion (see table 1 and graphs A-F)

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 helpful in treating 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.

Use a double-volume exchange transfusion to treat babies:

- whose serum bilirubin level (using the threshold levels in table 1 or Graphs A-F) indicate its necessity
- with hyperbilirubinaemia that fails to respond to phototherapy
- with clinical features and signs of acute bilirubin encephalopathy.

During exchange transfusion do not :

- perform a single-volume exchange
- use albumin priming
- routinely administer intravenous calcium.

7.3 Other treatments

Clinical question

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
- Complementary/alternative medicines (Chinese herbal remedies like Yin-chin)

Review findings

Following electronic searches, restricted to controlled trials and reviews, 167 records were identified and 22 hard copy articles were requested. These were supplemented by relevant articles identified by earlier searches for the phototherapy review. A total of 61 hardcopy articles were obtained. For some interventions no RCT's were identified so other study types were used in these analyses.

7.3.1 Clofibrate

Clofibrate is a fibric acid derivative which acts as a lipid regulating drug. In neonatal hyperbilirubinaemia its presumed mode of action is by increasing bilirubin conjugation and excretion.

From the six articles obtained one was excluded as the trial was not randomised. Five RCT's carried out in Iran[203-207]examined clofibrate combined with phototherapy against phototherapy alone for the treatment of non-haemolytic hyperbilirubinaemia. The evidence level of the included studies ranged from EL1- to EL1++. Two studies reported using random numbers tables and one used a computer-generated sequence as the method of

randomisation while one study used sealed envelopes to conceal the allocation to treatment groups.

In four studies clofibrate was administered in a single oral dose of 100mg/kg while in the fifth study it was given in either a low dose of 25mg/kg or a moderate dose of 50mg/kg. This study reported results after the first 24 hours of treatment while the other RCT's reported up to 96 hours of treatment. This study was subjected to a sensitivity analysis to ascertain the robustness of the results in terms of dose/duration of study.

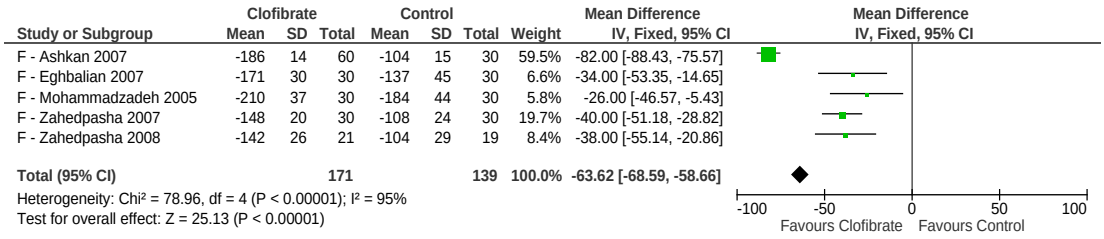
All the studies were carried out in term babies. Where reported the mean gestational age ranged from 38.7 ± 0.9 weeks to 38.8 ± 1.6 weeks, mean birthweight from 2542 ± 547 grams to 3259 ± 481 grams, mean age at entry to study from 123 ± 55 hours to 216 ± 94.8 hours and the mean serum bilirubin was between 301 ± 23.4 micromol/L and 395 ± 58 micromol/L. 145 (53.7%) of the sample were male.

Results - Dichotomous outcomes

None of the studies reported on either the number of exchange transfusions needed or the adverse effect profile of clofibrate.

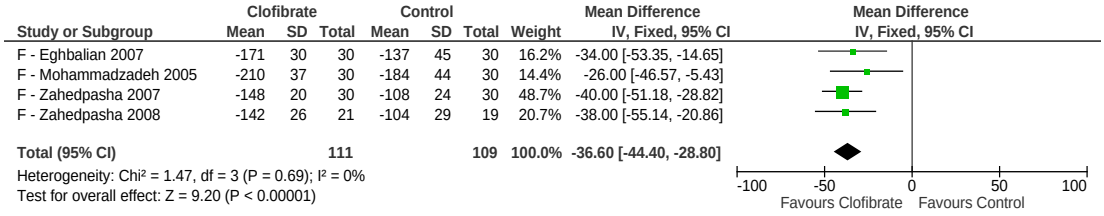
Results - Continuous outcomes

All five studies (N = 310) contributed to the analysis on the mean decrease in serum bilirubin. There was a significantly greater decrease in serum bilirubin among those treated with clofibrate, mean difference (MD) = -63.62 micromol/L (95% CI: -68.59, -58.66). Heterogeneity was very high at I^2 = 95%.



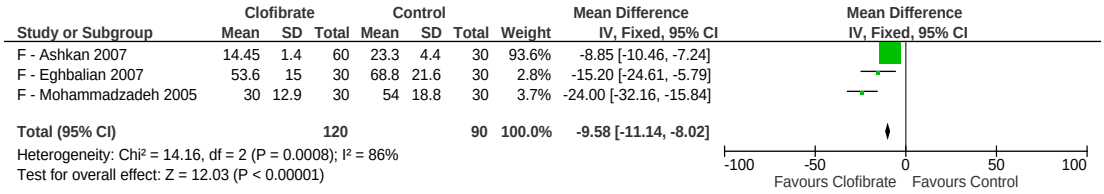
Forest plot 7.3.1.1 Clofibrate - Mean decrease in serum bilirubin – all studies

The post-hoc sensitivity analysis excluding the low/moderate dose study showed a MD of -36.60 micromol/L (95% CI: -44.40, -28.80) and heterogeneity was non-existent at I^2 = 0%.



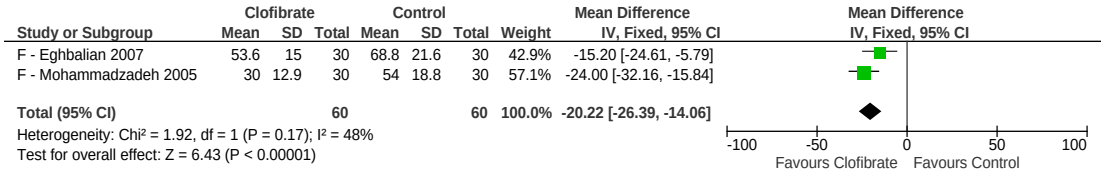
Forest plot 7.3.1.2 Clofibrate - Mean decrease in serum bilirubin – sensitivity analysis

Three studies (N = 210) contributed data on duration of phototherapy, Babies who received clofibrate required a significantly shorter time under phototherapy MD = -9.58 hours (95% CI: -11.14, -8.02). There was a high level of heterogeneity (I^2 = 86%).



Forest plot 7.3.1.3 Clofibrate - Mean duration of phototherapy – all studies

The post-hoc sensitivity analysis excluding the low/moderate dose study showed a MD of -20.22 hours (95% CI: -26.39, -14.06) with I^2 still relatively high at 48%.



Forest plot 7.3.1.4 Clofibrate - Mean duration of phototherapy – sensitivity analysis

7.3.2 Intravenous Immunoglobulin (IVIG)

IVIG acts by preventing the destruction of sensitized erythrocytes. IVIG contains pooled IgG immunoglobulins extracted from the plasma of over one thousand blood donors. The Department of Health has recently updated their guidance on the use of IVIG (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085235)

Eleven articles were obtained, including reports of five RCTs [208-212] carried out in Argentina, Germany, Iran, Saudi Arabia and Turkey comparing IVIG in combination with phototherapy with phototherapy alone for the treatment of haemolytic jaundice. Six articles were excluded for the following reasons: not randomised (N = 2), compared different dosages of IVIG (N = 1), examined IVIG as prophylaxis to prevent the need for phototherapy (N = 1), non-English language (N = 1) and conference abstract (N = 1).

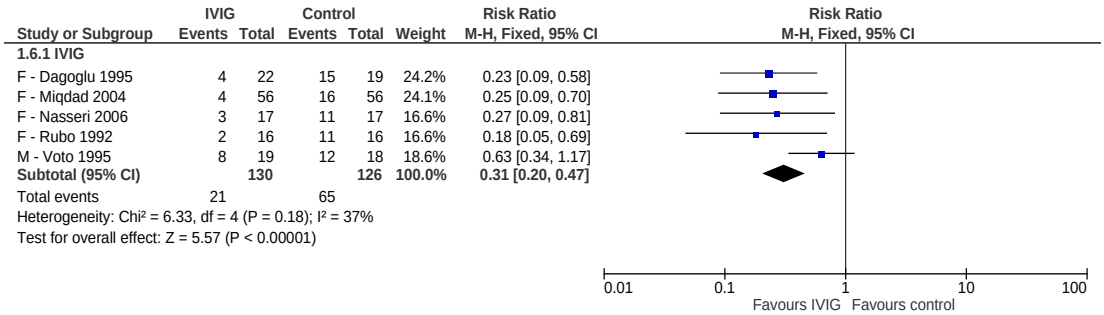
One study reported using random numbers to allocate the babies into the treatment groups and using sealed envelopes to conceal the treatment allocation so was rated EL1++. None of the other studies reported the method of randomisation or allocation concealment so were rated EL1-. IVIG was administered as a single dose (500mg/kg) over 2 hours in one study, as a single dose (500mg/kg) over 4 hours in the second, as a single dose (500mg/kg) as soon as possible after birth in the third study and as three doses (500mg/kg each) over 4 hours every 12 hours in the fourth study and as 800mg/kg/day for three days in the final study.

One study included both term and pre-term babies while the other four included only term babies. Three of the studies included only babies with rhesus haemolytic disease, one included only babies with ABO haemolytic disease and the fifth included babies with either rhesus or ABO haemolytic disease and presented the results for both groups. Where reported the mean birthweight ranged from 2683 ± 292 grams to 2834 ± 569 grams in two studies and was not reported in the other two studies, the mean age at entry to study was 20.2 ± 9.5 hours in one study and not reported in the remainder, the mean serum bilirubin was 254 ± 57 micromol/L in one study and was not reported in the other three and the mean gestational age was between 36.1 ± 2 weeks and 38 weeks in three studies and another included only term babies. In the three studies which reported on gender, 109 participants (58.3%) were male

Results - Dichotomous outcomes

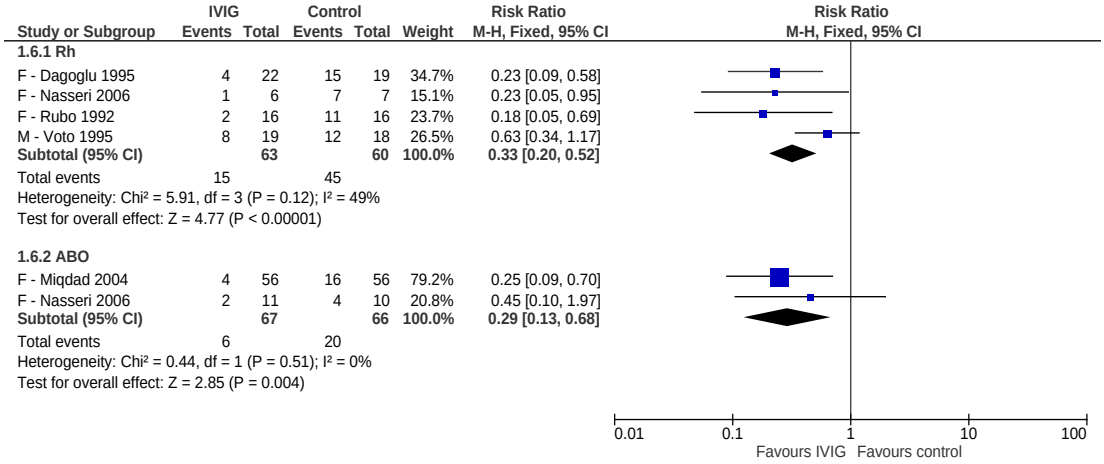
Indications for exchange transfusion in the studies included: serum bilirubin ≥ 340 micromol/L (two studies); serum bilirubin ≥ 307.8 micromol/L in babies over 2,000 grams;

serum bilirubin above the Polacek criteria 213;214 and serum bilirubin rising by 8.5 or 17.1 micromol/L per hour. Babies randomised to receive IVIG needed significantly fewer exchange transfusions than controls (RR = 0.31 (95% CI: 0.20, 0.47)). Heterogeneity was not significant at I^2 = 37%.



Forest plot 7.3.2.1 IVIG – Number of exchange transfusions needed

A post-hoc sensitivity analysis examined the effect of IVIG in rhesus haemolytic disease and ABO haemolytic disease.



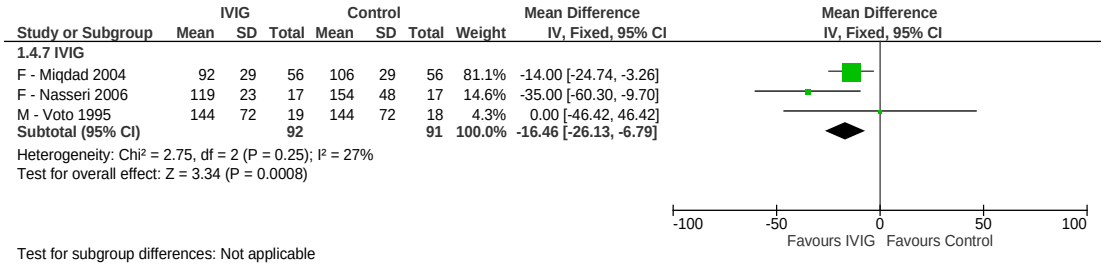
Forest plot 7.3.2.2 IVIG – Number of exchange transfusions needed – sensitivity analysis

The RR was similar in both rhesus and ABO haemolytic disease, RR = 0.33 (95% CI: 0.20, 0.52) and RR = 0.29 (95% CI: 0.13, 0.68) respectively. However the number needed to treat (NNT) with IVIG to prevent one exchange transfusion differed in each category of haemolytic disease. For rhesus disease the NNT was 2 while in ABO disease the NNT was five.

The included studies did not report on the adverse effect profile of IVIG.

Results - Continuous outcomes

Only three studies reported the duration of adjunctive phototherapy. This was significantly shorter in babies receiving IVIG (MD = -16.46 hours (95% CI:-26.13, -6.79)). Heterogeneity was significant factor at 1^2 = 27%.



Forest plot 7.3.2.3 IVIG – Mean duration of phototherapy

7.3.3 Riboflavin

From the four articles obtained, one was excluded as the study reported was not randomised. Three RCT's [215-217] from Hungary, Turkey and the USA compared riboflavin in combination with phototherapy with phototherapy alone for the treatment of hyperbilirubinaemia. One study used random numbers to allocate treatment but did not report on allocation concealment, so was rated EL1+. Neither of the other two studies reported either randomisation method or allocation concealment so were rated EL1-.

Where reported, the mean birthweight ranged from 3230 ± 502 grams to 3338 ± 425 grams, mean age at entry to study from 50.2 ± 27.2 hours to 71.3 ± 24.1 hours and mean serum bilirubin was 358 ± 71 micromol/L (one study). In one study which reported gender, 12 participants (50.0%) were male. The mean gestational age was not reported.

Results - Dichotomous outcomes

None of the studies reported on either the number of exchange transfusions needed or the adverse effect profile of riboflavin.

Results - Continuous outcomes

In one RCT from the USA, riboflavin (sodium phosphate 1.5mg/kg every 12 hours) was given for 6 hours prior to phototherapy for the treatment of non-haemolytic hyperbilirubinaemia in term babies. Riboflavin was discontinued after 24 hours of phototherapy. In babies randomised to riboflavin there was a non-significant mean reduction in serum bilirubin after 24 hours (MD = -17.00 (95% CI: -35.81, 1.81)). [EL1+]

In the second RCT, from Turkey, riboflavin was given as a single oral dose of 3mg/kg within 30 minutes of starting phototherapy in the treatment of term babies with non-haemolytic hyperbilirubinaemia. Babies receiving riboflavin showed a significant reduction in mean serum bilirubin after 24 hours (MD = -30.00 (95% CI: -49.20, -10.80)). There was no significant difference regarding mean duration of phototherapy. [EL1-]

The third RCT, from Hungary, evaluated riboflavin given as an intravenous dose of 10mg/kg for the treatment of haemolytic hyperbilirubinaemia in term babies being prepared for exchange transfusion. Bilirubin concentrations fell in the riboflavin group and rose in the control group resulting in a significantly greater difference between the groups in serum bilirubin after 3 hours (MD = -119.00 micromol/L (95% CI: -154.62, -83.38)). [EL1-].

7.3.4 Metalloporphyrins

Five articles were obtained and all were excluded as they examined metalloporphyrins as prophylaxis for hyperbilirubinaemia.

7.3.5 Albumin infusions

Three articles were obtained and two were excluded for the following reasons; compared two preparations of human serum albumin (N = 1), non-randomised controlled trial (N = 1). The other study has been included in the section on exchange transfusions. There was no significant difference between DVET and albumin enriched DVET in terms of mean reduction of serum bilirubin, the mean duration of adjunctive phototherapy and the level of rebound jaundice. There were no cases of kernicterus or reported adverse effects in either group 197.

7.3.6 Cholestyramine

Three articles were obtained but no RCT's were identified and one article was a duplicate publication. Two controlled clinical trials (CCT)[218;219] [EL2-], from Greece and Singapore, examining cholestyramine for the treatment of hyperbilirubinaemia were included. Babies were allocated to treatment groups on an alternate basis in both studies and neither study reported on allocation concealment. Babies in each study received 1.5gm/kg/day of cholestyramine powder mixed in milk.

In second study, for the pre-term sample (N = 20) the mean gestational age was 33.4 ± 0.3 weeks, mean birthweight was 2077 ± 88 grams, mean age at entry to study was 76 ± 2.9 hours and mean serum bilirubin was 198 ± 5 micromol/L. Nine participants (45.0%) were male. Among the term babies the mean gestational age ranged from 38.9 ± 0.2 to 39.1 ± 0.3 weeks, mean birthweight from 3154 ± 139 to 3286 ± 39 grams, mean age at entry to study from 84 ± 2.9 to 90 ± 1.5 hours and the mean serum bilirubin in both studies was 298 ± 5 micromol/L. Gender was reported in one study and 6 participants (30.0%) were male.

In the first study (conducted in babies with non-haemolytic hyperbilirubinaemia) control babies showed a significantly greater reduction in mean in serum bilirubin than those receiving cholestyramine (MD = 18.00 micromol/L (95% CI: 8.55, 27.45)).

In the second study (conducted in babies with both haemolytic and non-haemolytic jaundice), there was a significant reduction in the duration of phototherapy in babies treated with cholestyramine. For term babies the MD was -42.00 hours (95% CI: -50.98, -34.62) and for pre-term babies the MD was -26.30 (95% CI: -33.00, -19.60).

7.3.7 Agar

A total of 11 articles were obtained and 9 were excluded for the following reasons, studies examining prophylaxis (N = 4), correspondence or uncontrolled study (N = 4), incomplete data (N = 1). The remaining two studies[220;221], from Denmark and the USA, were non-randomised controlled trials [EL2-] which compared phototherapy alone with agar combined with phototherapy. Babies in both studies were allocated to treatment on according to their hospital numbers, and thus allocation concealment was not possible.

Agar was given in 250mg oral doses either every 8 hours during phototherapy or at each 3 hourly feed. The samples in both studies were comparable, with mean birthweight of 2767 ± 69 grams and 2729 ± 538 grams, mean age at entry to study of 80.6 ± 28.7 hours and 87 ± 26 hours, and mean serum bilirubin of 234 ± 46.8 micromol/L and 274 ± 51 micromol/L. One study reported the mean gestational age of 36.8 ± 2.5 weeks. Of the combined sample, 57 participants (56.4%) were male.

There was no significant difference between treatment and control groups in mean reduction in serum bilirubin (MD = -2.00 micromol/L (95% CI: -24.13, 20.13)). Also there there was no significant difference in terms mean duration of phototherapy (MD = -6.57 hours (95% CI: -16.06, 2.92)). Heterogeneity was not an issue at I^2 = 21%.

7.3.8 Barbiturates

18 articles were obtained, including one CCT from New Zealand [222;222] concerning phenobarbitone treatment of hyperbilirubinaemia. Seventeen papers were excluded for the following reasons; phototherapy not evaluated concurrently (N = 2), phenobarbitone evaluated for prophylaxis, not treatment, of jaundice (N = 12), maternal treatment with phenobarbitone evaluated (N = 2) and no jaundice-related outcomes included (N = 1).

In the included CCT [EL2-] the mean gestational age of the sample was 34.8 ± 2.7 weeks, mean birthweight was 2155 ± 632 grams, mean age at entry to study was 48.1 ± 14.7 hours and mean serum bilirubin was 174 ± 40 micromol/L 49 (49%) of the sample were male. Babies who met the criteria for phototherapy were allocated to routine care, routine care and phototherapy or routine care, phototherapy and phenobarbitone. Allocation to treatment was on a rotational basis and allocation concealment was not reported. Babies with birthweight > 3000 grams received 8mg of phenobarbitone three-times daily while those babies with birthweight <3000 grams received 2mg/kg of phenobarbitone three time daily.

No baby who received phototherapy alone required an exchange transfusion but one who received phenobarbitone combined with phototherapy had an exchange transfusion. This was attributed to extensive bruising aggravating hyperbilirubinaemia. Babies who received phenobarbitone received phototherapy for longer than control babies (72 ± 31 hours versus 67 ± 33 hours).

7.3.9 D-penicillamine

Three articles were obtained and all were excluded. Two were historical control studies and one was a CCT examining D-penicillamine as prophylaxis for hyperbilirubinaemia in pre-term babies.

7.3.10 Glycerin

Three articles were obtained and all were excluded as they examined glycerin suppositories or enemas as prophylaxis for non-haemolytic hyperbilirubinaemia.

7.3.11 Charcoal

Two articles were obtained and were excluded: one was a non-randomised controlled study and the other a historical control study. The CCT was aborted when the charcoal preparation used was recalled by the Food and Drug Administration following two reports of raised serum nickel concentration in adults with rythropoietic rotoporphyria who were treated with this preparation.

7.3.12 Pojark Manna

One article was obtained and included. This RCT from Iran[223] compared Pojark Manna combined with phototherapy with phototherapy alone. Neither the method of randomisation nor the allocation concealment was reported. The study was double-blind. Pojark Manna ('Shirkhest') is derived from the Cotoneaster Tricolor plant. It has a high sugar content and is used as a laxative. Babies randomised to Pojark Manna received 6 grams of Shirkhest, and control babies received a starch solution caramel added so as to appear identical to the Shirkhest solution. The mean serum bilirubin in the study was 401 ± 53 micromol/L. No other demographic details were provided. Phototherapy was discontinued when serum bilirubin fell below 256.5 micromol/L. The mean duration of phototherapy was similar in treatment and control groups [EL1]

7.3.13 Traditional Chinese Medicine

Three articles were obtained; one was excluded as it was a prophylaxis study, and another as it was an uncontrolled comparative study. A third study, from Hong Kong[224] was an in-vitro study of the effects of Yin-chen "Artemisia scoparia" on bilirubin in pooled cord serum. Results indicated that Yin-chen is effective in displacing bilirubin from circulating albumin, leading to increased circulating unbound bilirubin.

7.3.14 Other interventions:

Only case reports were identified for homeopathy and acupuncture

Evidence summary

Most of the included RCT's were of varying quality. Important clinical outcomes such as the number of exchange transfusions or possible adverse effects of the interventions were often not reported.

Meta-analysis suggests that a single dose of clofibrate (100mg/kg) led to significant reductions in mean serum bilirubin levels and duration of phototherapy compared to phototherapy alone. However although all the studies were of good quality, they were all carried out in one country and may not be generalisable to the UK.

The use of IVIG in babies with haemolytic hyperbilirubinaemia is accompanied by significant reduction in the need for exchange transfusion. This effect is greater in rhesus haemolytic disease (NNT = 2) than in ABO incompatibility (NNT = 5).

Riboflavin at a dose of 10mg/kg showed promising results in babies awaiting exchange transfusion for haemolytic jaundice.

There was no evidence to support the use of metalloporphyrins, cholestyramine, albumin infusions, agar, barbiturates, d-penicillamine, glycerin, charcoal, Pojark manna, tradiational Chinese medicine, homeopathy or acupuncture.

GDG Translation

The evidence supports the current clinical practice of using IVIG alongside phototherapy in babies with rhesus and ABO haemolytic disease. This practice is also in line with recent guidance from the Department of health. In these babies, IVIG has been shown to reduce the need for exchange transfusion, a procedure which has associated morbidity and mortality. The GDG agreed that concern over donor over-exposure, potential adverse effects and costs dictate that this treatment should be reserved for cases with significant haemolysis evidenced by serum bilirubin rising by >8.5 micromol/L/hr despite multiple phototherapy. Whilst an economic analysis suggested that IVIG was cost-effective, some uncertainty remains especially for babies with ABO haemolytic disease because of the higher number needed to treat to avoid an exchange transfusion. Therefore, the GDG believe that further research could better inform cost-effective practice.

The evidence for effectiveness of clofibrate in neonatal jaundice is strong but is confined to pne population. The GDG notes that studies of clofibrate in adults reported significant adverse effects[225]. While these findings cannot be directly extrapolated to neonates, this concern together with the paucity of data led the GDG to conclude that clofibrate cannot currently be recommended for use in neonatal jaundice. However, the GDG considered that further investigations in UK populations was required and made a research recommendation on this topic.

No other interventions are recommended for the treatment of hyperbilirubinemia.

Recommendations

Intravenous immunoglobulin

Use intravenous immunoglobulin (IVIG) as an adjunct to continuous multiple 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/hour.

Offer parents or carers information on IVIG including:

- why IVIG is being considered
- why IVIG may be helpful in treating significant hyperbilirubinaemia
- the possible adverse effects of IVIG
- when it will be possible for parents or carers to see and hold the baby.

Other therapies

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.

Research recommendations

What is the effectiveness of Clofibrate in combination with phototherapy versus phototherapy alone for non-haemolytic hyperbilirubinaemia are needed to support the existing evidence base.

*Why this is important***.**
Existing research has demonstrated that Clofibrate in combination with phototherapy can shorten time spent undergoing phototherapy. This can help minimise the disruption to breast-feeding and mother-baby bonding. However no studies have been carried out in a UK population. New placebo-controlled double-blind randomized controlled trials in a UK population are needed. Population: Term and pre-term babies with hyperbilirubinaemia in the first 28 days of life. Interventions: Clofibrate (a single 100mg/kg dose) combined with phototherapy versus phototherapy with a placebo phototherapy. Outcome: Effectiveness in terms of mean decrease in bilirubin levels and mean duration of phototherapy. Extra outcomes should include adverse effects, parental bonding and parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

What is the clinical and cost-effectiveness of IVIG used to prevent exchange transfusion in newborns with haemolytic disease due to ABO incompatibility and rising bilirubin?

*Why this is important***.**
Existing research has demonstrated that IVIG is effective in reducing the need for an exchange transfusion in one in two hyperbilirubinaemic babies with rhesus haemolysis. The evidence is less convincing in hyperbilirubinaemic babies with ABO haemolysis. New placebo-controlled double-blind randomized controlled trials are needed to examine if IVIG is effective in sub-groups of babies with ABO haemolysis, ie pre-term babies, babies with bilirubin rising greater than 10 mincromol/L/hr or babies with co-morbid illness such as infections.. Population: Term and pre-term babies with hyperbilirubinaemia in the first 28 days of life. Interventions: IVIG (500mg/kg) alongside phototherapy versus phototherapy alone. Outcome: Number of exchange transfusions needed. Extra outcomes should include adverse effects, mean duration of phototherapy, parental anxiety, staff and parental satisfaction with treatment and cost effectiveness. Time stamp: Sept 2009

8 Information

Clinical question
What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia?
a) At the time of birth
b) At the time of recognition of jaundice (FOR ALL BABIES)
c) At the time of formal assessment/diagnosis
d) During monitoring
e) During treatment with phototherapy and other interventions
f) At discharge and follow-up

A total of 227 records were identified from the electronic searches, and 21 papers were selected for retrieval. Eighteen were excluded as they dealt with physician education or information (N = 9), were overviews of appropriate information for parents (N = 4), examined maternal knowledge of jaundice (N = 3), dealt with training mothers to recognise jaundice (N = 1) and dealt with postpartum counselling (N = 1). Of the included studies one examined barriers to follow-up in the first week of life and the final study (reported in two publications) investigated maternal concerns about jaundice

Review findings

A qualitative study in the USA[226] examined barriers to first week follow-up for jaundice. Four focus groups, one each for physicians and nurses and two for parents, comprising 7 to 9 participants each, were held. Sessions lasted from 90 to 120 minutes and were led by an experienced facilitator supported by a second observer/facilitator. Participants were asked about their experiences, and for possible suggestions for improving this experience. In total 9 physicians, 8 nurses and 14 parents attended the focus groups. Tapes of each session were transcribed and summarized. Responses were grouped into categories based on themes including communication and information, systems and processes of care and knowledge/education. The experiences and solutions relating to information are listed in the table below:

Heading to be added

Experiences	Reported by	Solutions	Reported by
Communication gaps during hand-over	MD, RN	Email community-based provider	MD, RN
Missing key information, ie birth details, lab tests	MD, RN	Provide easy access to lab,	MD, RN
		Provide parents with contact numbers	P
Early discharge limits time for parental education	RN	Parental education throughout continuum of care	MD, RN, P
Reluctance to educate parents prenatally	MD, RN	Increase physician awareness of risk to near-terms	MD, RN
Poor understanding of risks to near-terms	MD		

An ethnographic study from the USA[227;228] examined maternal concerns about neonatal jaundice. In all, 45 mothers of healthy breastfeeding babies with jaundice were interviewed. The mean maternal age was 27 years. Over 50.5% of multiparous mothers had a previous baby with jaundice and 75% had breastfed a previous baby. Hyperbilirubinaemia was defined

as serum bilirubin > 170 micromol/L. The interviews were held between 2.5 and 14.5 weeks postpartum. Regarding causes of jaundice, 26 mothers (55.3%) believed that the quality and quantity of breastfeeding was pertinent to this. The next most commonly raised theme was uncertainty, with most mothers saying they had not been given an explanation of jaundice. These mothers were exclusively Spanish-speaking, young, non-high-school graduates whose babies had undergone blood testing because of jaundice.

Guilt was a theme in 18 (38.3%) of the interviews, with quotes such as 'got it from me', 'not a good mother' and 'doing something wrong' recorded. Some mothers believed that babies were born with jaundice or that it was a normal part of giving birth, attributing it to labour or bruising during delivery, or adjustment to a new environment. The mothers indicated that blood sampling was distressing both for them and their babies.

In all, 27 mothers (57.4%) perceived neonatal jaundice to be a serious condition and outlined the following important issues as causing them concern; lack of preparedness for seeing their baby become yellow, lack of knowledge about, and understanding of, jaundice, severity of the clinical course, concerns about possible effects of jaundice on their baby, and prolonged jaundice. Of the 20 mothers who were not concerned, 10 reported that their baby appeared healthy and was feeding well despite being jaundiced. These mothers expressed confusion about the need to seek medical advice for jaundice if the baby appeared healthy. Of these 20 mothers, 5 of their babies had breastmilk jaundice and 5 had had blood tests but did not require treatment. The remaining 10 women had no concerns because they had received prompt information and reassurance about jaundice. Again their babies had needed only minimal intervention.

Maternal anxiety increased in proportion to the severity of hyperbilirubinaemia. Many mothers had been told that high bilirubin levels can cause brain damage, but only some had been given the specific advice about such levels, so others were uncertain, and worried about the risks facing their own babies. For the 23 babies who underwent phototherapy, mothers recalled hearing and seeing their babies crying, and their own distress at being unable to comfort them at the time.

Most women expressed a preference for being informed about jaundice prenatally, while others wanted information at discharge or only in the event of their baby becoming jaundiced. Preferred formats for communicating information included individual verbal communication, small group discussions, written pamphlets and videos. Mothers requested more detailed information regarding causes of jaundice, information that addressed maternal responsibilities, management procedures, potential effects of jaundice and its treatment, anticipated duration of jaundice, and measures that they could take themselves to prevent jaundice and to care for jaundiced babies.

Support from mothers who had previously experienced neonatal jaundice was especially welcome; their shared experiences reassured mothers and improved their understanding of jaundice. [EL3]

Evidence Summary

The focus group studies from the USA, both EL3, illustrate the need for provision of more information to parents of newborn babies about jaundice. Mothers expressed a preference for prenatal information and for further information and support to be given at diagnosis and during treatment. Maternal anxiety increased in proportion to the severity of jaundice, but prompt information and reassurance can help to allay this.

GDG translation

There is little published evidence concerning the effectiveness of, and satisfaction, with provision of parental information in the management of jaundice. Qualitative research highlights areas of both good and bad practice. In one small study mothers who received timely information reported less concern than mothers who were not kept informed of their baby's progress. The same study found that most women expressed a preference for being informed about jaundice prenatally. More detailed information regarding causes of jaundice, information that addressed maternal responsibilities, management, potential effects of

jaundice and its treatment, anticipated duration of jaundice, and what mothers can do for their babies, both pre-emptively and after jaundice has appeared.

The GDG suggests that increasing awareness of jaundice in pre-natal classes and on postnatal wards will empower and support mothers of newborn babies. Timely information and support throughout the monitoring and treatment process will help to allay parental anxiety.

Recommendation

Offer parents or carers information about neonatal jaundice that is tailored to their needs and expressed concerns. They should receive information on:

- factors that influence the development of 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 (see recommendation X) and of seeking urgent medical advice (recommendation X)
- 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.

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.

Offer parents or carers information about treatment, including:

- anticipated duration of treatment
- reassurance that breastfeeding and physical contact with the baby can usually continue.

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

Provide lactation/feeding support to breastfeeding mothers whose baby is visibly jaundiced.

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

- why phototherapy is being considered
- why phototherapy may be helpful in treating 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 supported as long as the bilirubin levels are not significantly elevated
- what might happen if phototherapy fails
- rebound jaundice
- potential long-term adverse effects of phototherapy
- the potential impact on breastfeeding and how to minimise this.

References, abbreviations and glossary

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Abbreviations

ABR	Auditory brainstem response
AROC	Area under the ROC curve
BW	Birthweight
CB	Cord bilirubin
CMA	A form of cost-effectiveness analysis where the treatment alternatives are considered to be equally effective. Where treatments are equally effective the least costly is the most cost-effective
DAT	Direct Antiglobulin test also known as 'Coombs' test'
DVET	Double volume exchange transfusion
ETCOc	End-tidal carbon monoxide concentration (the concentration at the end of an expired breath)
GA	Gestational age
GDG	Guideline Development Group
G-6-PD	Glucose-6-phosphate dehydrogenase. Lack of this enzyme (G6PD deficiency or G6PDD) is associated with a tendency to haemolytic disease. This can present in the newborn period, and can thus be associated with neonatal jaundice.
HMO	Health maintenance organisation
IVIG	Intravenous immunoglobulin
LED	Light-emitting diode
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
RMSSD	Root mean square of successive differences
ROC	Receiver operating characteristic
RR	Risk ratio
TCB	Transcutaneous bilirubin
SD	Standard deviation
SD1	Width of Poincare plot images
SD2	Length of Poincare plot images
SVET	Single volume exchange transfusion
TSB	Total serum bilirubin

Glossary

ABO incompatibility	ABO incompatibility describes an antibody reaction that occurs when mother and baby have different blood groups, typically maternal blood group O and baby blood group A or B. Foetal red cells "leak" into the maternal circulation, and the immune system recognises them as foreign and makes antibodies against them, which can then pass back into the foetus and bind to foetal red cells.
Acidosis	A blood pH below 7.25.
Acute bilirubin encephalopathy	Acute bilirubin encephalopathy is the clinical manifestation of bilirubin toxicity. The clinical course is hypotonia followed by hypertonia, retrocollis (backward arching of the neck), or opisthotonos (backward arching of the back) or both.
Albumin	Albumin is one of the proteins found in blood
Aminoglycosides	Aminoglycosides are a group of antibiotics that are used to treat certain bacterial infections
Apnoea	Term used when a baby stops breathing for more than 20 seconds
Basal ganglia	The part of the brain affected by bilirubin neurotoxicity
Best available evidence	The strongest research evidence available to support a particular guideline recommendation.
Bias	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see Selection bias, Performance bias, Information bias, Confounding, Publication bias.
Biliary atresia	The biliary tract has not formed properly and is not patent so that although the liver conjugates bilirubin it cannot be excreted and so backflows into the bloodstream giving rise to conjugated hyperbilirubinaemia. A serious congenital problem which require urgent surgery
Bilirubin	Bilirubin is a product that results from the breakdown of haemoglobin
Bilirubinometer, transcutaneous	A device that used light reflectance to measure the yellow colour (bilirubin level) in the skin
Bilirubinaemia	Term used for the presence of bilirubin in the blood
Blinding or masking	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias. See also Double blind study, Single blind study, Triple blind study.
Bradycardia	Term used for a slower than normal heart rate
Case-control study	A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to

	things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called retrospective as they look back in time from the outcome to the possible causes.
Case report (or case study)	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Cephalo-Caudal progression	This refers to the phenomenon of jaundice progressing from the head (cephalo) down the trunk as bilirubin level rises, eventually reaching the legs. Caudal refers to tail so it literally means spread from head to tail.
Cephalohaematoma	Collection of blood that develops beneath the outer layer of periosteum of a neonate's skull. Clinically, it appears as a firm, tense mass at birth and resolves in a few weeks to months.
Cerebral palsy	A permanent neurological disorders which affects movement
Chalky pale stools	This is a descriptive term for the pale stools that accompany obstructive jaundice, such as occurs in biliary atresia. Since bile is not excreted from the liver/bile duct into the intestine, the stools are paler than normal and appear chalky
Checklist	See Study checklist.
Cholestasis	Term used for a condition where bile cannot flow from the liver to the duodenum
Chronic bilirubin encephalopathy	Persistent brain dysfunction arising from hyperbilirubinaemia
Chronic sequelae	Persistent morbidity arising from acute events
Clinical effectiveness	The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as efficacy.
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment, or treatment outcomes, of the target population.
Clinical importance	The importance of a particular guideline recommendation to the clinical management of the target population.
Clinical question	This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a focused question.
Clinical trial	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials.
Clinician	A health care professional providing patient care, e.g. doctor, nurse, physiotherapist.
Clofibrate	A lipid lowering agent used for controlling high cholesterol and triacylglyceride level in the blood.
Cochrane Collaboration	An international organisation in which people find, appraise and review specific types of studies called randomised controlled trials.

	The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the Cochrane Library.
Cochrane Library	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). The Cochrane Library is available on CD-ROM and the Internet.
Cohort	A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.
Cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.
Combined modality	Use of different treatments in combination (for example surgery, chemotherapy and radiotherapy used together for cancer patients).
Co-morbidity	Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Confidence interval	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Confounder or confounding factor	Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.
Conjugated bilirubin	A term used to describe the form of bilirubin which has been processed by the liver. This is otherwise described as direct bilirubin. Conjugated bilirubin is released into the bile by the liver

	and stored in the gallbladder, or transferred directly to the small intestines. Bilirubin is further broken down by bacteria in the intestines, and those breakdown products contribute to the colour of the faeces.
Conjugated hyperbilirubinaemia	A term used when large amounts of conjugated bilirubin appear in the bloodstream.
Consensus statement	A statement of the advised course of action in relation to a particular clinical topic, based on the collective views of a body of experts.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Conventional phototherapy	For this guideline a single phototherapy unit, comprising of a number of fluorescent, halogen or LED tubes which is placed above the baby. See also multiple phototherapy
Coombs' test	Also known as DAT, the direct Coombs' test is used to detect antibodies or complement proteins that are bound to the surface of red blood cells; a blood sample is taken and the RBCs are washed (removing the patient's own plasma) and then incubated with antihuman globulin (also known as "Coombs' reagent"). If this produces agglutination of RBCs, the direct Coombs test is positive, a visual indication that antibodies (and/or complement proteins) are bound to the surface of red blood cells.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of health care treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-minimisation analysis	A form of cost-effectiveness analysis where the treatment alternatives are considered to be equally effective. Where treatments are equally effective the least costly is the most cost-effective
Cost effectiveness	Value for money. A specific health care treatment is said to be 'cost-effective' if it gives a greater health gain than could be achieved by using the resources in other ways.
Cost effectiveness analysis	A type of economic evaluation comparing the costs and the effects on health of different treatments. Health effects are measured in 'health-related units', for example, the cost of preventing one additional heart attack.
Cross-sectional study	The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a longitudinal study which follows a set of people over a period of time.)
Data set	A list of required information relating to a specific disease.

Decision analysis	Decision analysis is the study of how people make decisions or how they should make decisions. There are several methods that decision analysts use to help people to make better decisions, including decision trees.
Decision tree	A decision tree is a method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or overall cost-effectiveness of different actions can then be compared.
Declaration of interest	A process by which members of a working group or committee 'declare' any personal or professional involvement with a company (or related to a technology) that might affect their objectivity e.g. if their position or department is funded by a pharmaceutical company.
Diagnostic study	A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.
Direct Antibody Test	See Coombs' test
Direct bilirubin	See Conjugated bilirubin
Double blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Economic evaluation	A comparison of alternative courses of action in terms of both their costs and consequences. In health economic evaluations the consequences should include health outcomes.
Effectiveness	See Clinical effectiveness.
Efficacy	The extent to which a specific treatment or intervention, under ideally controlled conditions (e.g. in a laboratory), has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care.
Empirical	Based directly on experience (observation or experiment) rather than on reasoning alone.
End-tidal carbon monoxide concentration	The concentration of carbon monoxide at the end of an expired breath.
Enteral	Enteral refers to any form of administered treatment or food that involves the gastrointestinal tract: • by mouth (orally), many drugs as tablets, capsules, or drops • by gastric feeding tube, duodenal feeding tube, or gastrostomy
Entero-hepatic circulation of bilirubin	The uptake of bilirubin into the blood from bowel contents
Epidemiology	Study of diseases within a population, covering the causes and means of prevention.
Evidence based	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Evidence based clinical practice	Evidence based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research

Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exchange transfusion	This procedure involves slowly removing the baby's blood and replacing it with fresh donor blood
Exclusion criteria	See Selection criteria.
Experimental study	A research study designed to test if a treatment or intervention has an effect on the course or outcome of a condition or disease - where the conditions of testing are to some extent under the control of the investigator. Controlled clinical trial and randomised controlled trial are examples of experimental studies.
Experimental treatment	A treatment or intervention (e.g. a new drug) being studied to see if it has an effect on the course or outcome of a condition or disease.
Fibreoptic phototherapy	Given using a light generator, termed the light box, a fibre-optic cable through which the light is carried and a light pad, on which the baby is placed or that is wrapped around the baby.
Forest plot	A graphical display of results from individual studies on a common scale, allowing visual comparison of results and examination of the degree of heterogeneity between studies.
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also External validity.
Gilbert Syndrome	A genetic liver disorder in which the liver shows impaired processing of bilirubin
Glucose-6-phosphate dehydrogenase	Lack of this enzyme (G-6-PD deficiency) is associated with a tendency to haemolytic disease. This can present in the newborn period, and can thus be associated with neonatal jaundice.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in bibliographic retrieval systems.
Guideline	A systematically developed tool which describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available, rather than opinion. It is used to assist clinician and patient decision-making about appropriate health care for specific clinical conditions.
Guideline recommendation	Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.
Haemoglobin	The coloured pigment inside red blood cells that carries oxygen round the body.
Haemolysis	The breakdown of red blood cells.
Haemolytic disease of the newborn	Abnormal breakup of red blood cells in the fetus or newborn. This is usually due to antibodies made by the mother directed against the baby's red cells (also known as Isoimmune haemolytic disease)
Health economics	A branch of economics which studies decisions about the use and distribution of health care resources.
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (e.g. the role of diet versus medicines in disease management) and other therapeutic interventions.

Health Technology Appraisal (HTA)	A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost effectiveness of a health technology. NICE health technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well conducted study. Well-conducted randomised controlled trials (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than say one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
Homogeneity	This means that the results of studies included in a systematic review or meta analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also Consistency.
Hyperbilirubinaemia	Raised levels of bilirubin in the blood.
Hyperbilirubinaemia, significant	Hyperbilirubinaemia at levels where an exchange transfusion is indicated
Hyperglycaemia	Raised level of glucose in the bloodstream.
Hyperkalaemia	A high serum potassium concentration
Hypernatraemia	An electrolyte disturbance in which the sodium concentration in the plasma is too high
Hyper-reflexia	Overactive or over-responsive reflexes.
Hypertonicity (hypertonia)	High muscle tension, when used to describe clinical examination findings.
Hypoglycaemia	Lowered levels of glucose in the bloodstream.
Hyponatraemia	Lowered levels of is sodium concentration in the bloodstream
Icterometer	A tool for estimating the level of jaundice. It consists of strips of perspex with varying degrees of yellow colour shown in bands. These are placed against the baby's skin and the colour closest to the baby's skin colour is used to indicates the severity of the jaundice.
Indirect bilirubin	See Unconjugated bilirubin
In depth interview	A qualitative research technique. It is a face to face conversation between a researcher and a respondent with the purpose of exploring issues or topics in detail. Does not use pre-set questions, but is shaped by a defined set of topics or issues.
Information bias	Pertinent to all types of study and can be caused by inadequate questionnaires (e.g. difficult or biased questions), observer or interviewer errors (e.g. lack of blinding), response errors (e.g. lack of blinding if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).

Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.
Interventional procedure	A procedure used for diagnosis or treatment that involves making a cut or hole in the patient's body, entry into a body cavity or using electromagnetic radiation (including X-rays or lasers). The National Institute for Clinical Excellence (NICE) has the task of producing guidance about whether specific interventional procedures are safe enough and work well enough for routine use.
Intravenous	The giving of liquid substances intermittently or continuously, directly into a vein.
Isoimmunisation	The situation which occurs when fetal erythrocytes of a different blood group to the mother leak into her circulation during pregnancy, and are recognised as foreign by the maternal immune system. Isoimmunisation is the most common cause of severe early onset jaundice. See ABO incompatability, rhesus.
Jaundice	The yellow colouration of the sclera caused by the accumulation of bilirubin in the skin and mucous membranes
Kernicterus	A term from pathology which means 'yellow staining of the basal nuclei of the brain'. This term is often used to refer to the acute and chronic brain effects of severe hyperbilirubinaemia. There are other causes of yellow staining of the brain other than jaundice. However, the term is often to the clinical syndrome and sequelae of bilirubin encephalopathy
LED (light emitting diode) phototherapy	A phototherapy unit consists of light-emitting diodes rather than fluorescent or halogen tubes.
Level of evidence	A code (e.g. 1++, 1+) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles.
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a cross sectional study which observes a defined set of people at a single point in time.)
Masking	See Blinding.
Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also Systematic review & Heterogeneity.
Methodology	The overall approach of a research project, e.g. the study will be a randomised controlled trial, of 200 people, over one year.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Multicentre study	A study where subjects were selected from different locations or populations, e.g. a co-operative study between different hospitals; an international collaboration involving patients from more than one country.
Multiple phototherapy	The use of more than one phototherapy units at the same time. It can be a combinational of conventional phototherapy and fibreoptic phototherapy or atwo sets of overhead lights.
Near-term	Generally refers to a gestation of 35 to 36 weeks gestation

Necrotising enterocolitis	A gastrointestinal condition that mostly affects premature babies. It involves infection and inflammation which causes destruction of all or part of the bowel (intestine)
Neonatal	Related to the first 28 days of life
Neurotoxicity	Neurotoxicity occurs when the exposure to natural or artificial toxic substances, called neurotoxins, damages nerve tissue and alters its normal activity
Nominal group technique	A decision making method for use among groups of many sizes, who want to make their decision quickly, as by a vote, but want everyone's opinions taken into account
Number Needed to Treat (NNT)	This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event which would otherwise occur. E.g. if the NNT=4, then 4 patients would have to be treated to prevent one bad outcome. The closer the NNT is to 1, the better the treatment is. Analogous to the NNT is the Number Needed to Harm (NNH), which is the number of patients that would need to receive a treatment to cause one additional adverse event e.g. if the NNH=4, then 4 patients would have to be treated for one bad outcome to occur.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and study participants.
Observation	A research technique used to help understand complex situations. It involves watching, listening to and recording behaviours, actions, activities and interactions. The settings are usually natural, but they can be laboratory settings, as in psychological research.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also Relative risk, Risk ratio.
Outcome	The end result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.
Parenteral	Refers to a route of treatment administration that involves giving drugs into body cavities, usually the blood (by intravenous infusions).
Patent ductus arteriosus	A condition in which the connection (the ductus) between pulmonary artery and aorta, which is open normally before birth, fails to close after birth

Peer review	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional and/ or patient/ carer representatives.
Phototherapy	This is treatment which consists of exposure to specific wavelengths of light using light-emitting diodes, fluorescent lamps, dichroic lamps or very bright, full-spectrum light,
Physiological jaundice	Term used to describe comon, generally harmelss, jaundice seen I babies if the first 2 weeks of life
Pilot study	A small scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full scale study begins.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Power	See Statistical power.
Preterm	Refers to less tha37 weeks of gestation
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other health care professionals, dentists, pharmacists and opticians.
Primary Care Trust	A Primary Care Trust is an NHS organisation responsible for improving the health of local people, developing services provided by local GPs and their teams (called Primary Care) and making sure that other appropriate health services are in place to meet local people's needs.
Prognostic factor	Patient or disease characteristics, e.g. age or co-morbidity, which influence the course of the disease under study. In a randomised trial to compare two treatments, chance imbalances in variables (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis these prognostic factors become confounding factors. See also Prognostic marker.
Prognostic marker	A prognostic factor used to assign patients to categories for a specified purpose – e.g. for treatment, or as part of a clinical trial, according to the likely progression of the disease. For example, the purpose of randomisation in a clinical trial is to produce similar treatment groups with respect to important prognostic factors. This can often be achieved more efficiently if randomisation takes place within subgroups defined by the most important prognostic factors. Thus if age was very much related to patient outcome then separate randomisation schemes would be used for different age groups. This process is known as stratified random allocation.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.

Protocol	A plan or set of steps which defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.
Psychomotor	Refers to neurological and motor develoment
Publication bias	Studies with statistically significant results are more likely to get published than those with non-significant results. Meta-analyses that are exclusively based on published literature may therefore produce biased results. This type of bias can be assessed by a funnel plot.
P value	If a study is done to compare two treatments then the P value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the P-value was P=0.03. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of P is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of P is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way does the P value relate to how big the effect might be, for this we need the confidence interval.
Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. a patient's description of their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
Quality adjusted life years (QALYs)	A measure of health outcome which looks at both length of life and quality of life. QALYS are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a zero to one scale). One QALY is equal to one year of life in perfect health, or two years at 50% health, and so on.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Quasi experimental study	A study designed to test if a treatment or intervention has an effect on the course or outcome of disease. It differs from a controlled clinical trial and a randomised controlled trial in that: a) the assignment of patients to treatment and comparison groups is not done randomly, or patients are not given equal probabilities of selection, or b) the investigator does not have full control over the allocation and/or timing of the intervention, but nonetheless

	conducts the study as if it were an experiment, allocating subjects to treatment and comparison groups.
Random allocation/Randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Receiver operating characteristic curve	A curve can be used to evaluate the goodness of fit for a binary classifier. It is a plot of the true positive rate (rate of events that are correctly predicted as events) against the false positive rate (rate of nonevents predicted to be events) for the different possible cutpoints
Retrospective study	A retrospective study deals with the present/past and does not involve studying future events. This contrasts with studies that are prospective.
Review	Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.
Rhesus	A blood group system which comprises the rhesus antigens
Riboflavin	Vitamin B2
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term relative risk is sometimes used as a synonym of risk ratio.
Royal Colleges	In the UK medical/nursing world the term royal colleges, as for example in 'The Royal College of….', refers to organisations which usually combine an educational standards and examination role with the promotion of professional standards.
Safety netting	The provision of support for patients in whom the clinician has some uncertainty as to whether the patient has a self-limiting illness and is concerned that their condition may deteriorate. Safety netting may take a number of forms, such as dialogue with the patient or carer about symptoms and signs to watch for, advice about when to seek further medical attention, review after a set period, and liaising with other healthcare services
Sclerae	The whites of the eyes (singular sclera)
Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Sampling	Refers to the way participants are selected for inclusion in a study.

Sampling frame	A list or register of names which is used to recruit participants to a study.
Secondary care	Care provided in hospitals.
Selection bias	Selection bias has occurred if, the characteristics of the sample differ from those of the wider population from which the sample has been drawn or there are systematic differences between comparison groups of patients in a study in terms of prognosis or responsiveness to treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Semi-structured interview	Structured interviews involve asking people pre-set questions. A semi-structured interview allows more flexibility than a structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.
Sensitivity	In diagnostic testing, it refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To fully judge the accuracy of a test, its Specificity must also be considered.
Sensorineural deafness	A type of hearing loss in which the root cause lies in the vestibulocochlear nerve (Cranial nerve VIII), the inner ear, or central processing centers of the brain.
Serum	A fluid component of clotted blood that lacks clotting factors and other elements which plasma includes. It retains antibodies, electrolytes and soluble proteins. In this guideline, when referring to bilirubin measurements on blood made on spun-down blood samples, sderum is also used to refer to plasma.
Single blind study	A study in which either the subject (patient/participant) or the observer (clinician/investigator) is not aware of which treatment or intervention the subject is receiving.
Specificity	In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its Sensitivity must also be considered.
Split bilirubin	Laboratory test measuring conjugated and unconjugated bilirubin
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a P value of less than 5% in a

	statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also P value.
Sternum	The breastbone. For the purposes of the guideline we are specifically referring to the section of the skin and chest wall overlying the breastbone.
Stools	Term used for faeces or poo.
Structured interview	A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.
Study checklist	A list of questions addressing the key aspects of the research methodology that must be in place if a study is to be accepted as valid. A different checklist is required for each study type. These checklists are used to ensure a degree of consistency in the way that studies are evaluated.
Study population	People who have been identified as the subjects of a study.
Study quality	See Methodological quality.
Study type	The kind of design used for a study. Randomised controlled trial, case-control study, cohort study are all examples of study types.
Subject	A person who takes part in an experiment or research study.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Systematic	Methodical, according to plan; not random.
Systematic error	Refers to the various errors or biases inherent in a study. See also Bias.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.
Systemic	Involving the whole body.
Tachycardia	Rapid heart-rate.
Tachypnoea	Rapid breathing.
Target population	The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study – e.g. in terms of age, disease state, social background.
Term	37 weeks or more of pregnancy. For the purposes of this guideline babies of 27 weeks are considered differently to those of 38 weeks.
Tertiary centre	A major medical centre providing complex treatments which receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre. See also Primary care and Secondary care.
Thermo-neutral environment	Surroundings of an ambient temperature which minimizes the baby's energy expenditure on keeping warm or cool
Transcutaneous	Passing, entering, or made by penetration through the skin
Transepidermal	Passes across the epidermal layer (skin) to the surrounding atmosphere via diffusion and evaporation processes.

Triple blind study	A study in which the statistical analysis is carried out without knowing which treatment patients received, in addition to the patients and investigators/clinicians being unaware which treatment patients were getting.
Unconjugated bilirubin	This is the term used to describe bilirubin which has not been processed by the liver. Normally unconjugated bilirubin is taken up by the liver where an enzyme produces conjugated bilirubin. It is then transported by the biliary system to the intestine and excreted. Unconjugated hyperbilirubinaemia arises if the liver cannot handle the amount of unconjugated bilirubin presented to it. This can occur as a result of excessive red blood cell breakdown – (haemolysis) and/or because of immaturity of the liver enzymes involved in conjugation.
Univariate analysis	Analysis of data on a single variable at a time
Urinary tract infection	A bacterial infection that affects any part of the urinary tract.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure. See also External validity, Internal validity.
Variable	A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature which can be assessed or measured.
Vasodilator effects	Refers to widening of blood vessels