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

Neonatal jaundice

Clinical Guideline

May 2010

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Update information

October 2023: We updated recommendation 1.2.5 to highlight that skin pigmentation changes may be harder to see in darker skin, and recommendation 1.7.1 to advise that urine culture should only be considered if there is clinical suspicion of urinary tract infection. For more information, see the October 2023 surveillance report.

March 2023: We added a safety statement about using bilirubin thresholds to the threshold tables and to section 1.3 on how to manage hyperbilirubinaemia.

October 2016: Recommendation 1.4.9 was amended to clarify when intensified phototherapy should be used in relation to time since birth.

These changes can be seen in the short version of the guideline at:
http://www.nice.org.uk/guidance/CG98

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Royal College of Obstetricians and Gynaecologists

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This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

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1 Guidance summary

1.1 Key terms

Conventional phototherapy	Phototherapy given using a single light source (not fibreoptic) that is positioned above the baby
Direct Antiglobulin Test (DAT)	Also known as the direct Coombs' test; this test is used to detect antibodies or complement proteins that are bound to the surface of red blood cells
Fibreoptic phototherapy	Phototherapy given using a single light source that comprises a light generator, a fibre-optic cable through which the light is carried and a flexible light pad, on which the baby is placed or that is wrapped around the baby
Multiple phototherapy	Phototherapy that is given using more than one light source simultaneously; for example, two or more conventional units, or a combination of conventional and fibreoptic units
Near-term	35 to 36 weeks gestational age
Preterm	Less than 37 weeks gestational age
Prolonged jaundice	Jaundice lasting more than more than 14 days in term babies and more than 21 days in preterm babies
Significant hyperbilirubinaemia	An elevation of the serum bilirubin to a level requiring treatment
Term	37 weeks or more gestational age
Visible jaundice	Jaundice detected by a visual inspection

1.2 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. This information should be provided through verbal discussion backed up by written information. Care should be taken to avoid causing unnecessary anxiety to parents or carers. Information should include:

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

Care for all babies

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

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

In all babies:

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

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.

Additional care

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

Measuring bilirubin in all babies with jaundice

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

How to measure the bilirubin level

When measuring the bilirubin level:

- use a transcutaneous bilirubinometer in babies with a gestational age of 35 weeks or more and postnatal age of more than 24 hours
- 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 babies less than 35 weeks gestational age
- always use serum bilirubin measurement for babies at or above the relevant treatment threshold for their postnatal age, and for all subsequent measurements
- do not use an icterometer.

How to manage hyperbilirubinaemia

Use the bilirubin level to determine the management of hyperbilirubinaemia in all babies (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).

Care of babies with prolonged jaundice

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

1.3 Threshold table

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

Age (hours)	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 bilirubin measurement in 6–12 hours	**Consider phototherapy and repeat bilirubin measurement in 6 hours**	**Start phototherapy**	**Perform an exchange transfusion unless the bilirubin level falls below threshold while the treatment is being prepared**

1.4 Summary of all recommendations

ID	Recommendations	See Chapter/Section
	Information for parents and carers	
1	Offer parents or carers information about neonatal jaundice that is tailored to their needs and expressed concerns. This information should be provided through verbal discussion backed up by written information. Care should be taken to avoid causing unnecessary anxiety to parents or carers. Information should include: ● factors that influence the development of significant hyperbilirubinaemia ● how to check the baby for jaundice ● what to do if they suspect jaundice ● the importance of recognising jaundice in the first 24 hours and of seeking urgent medical advice ● the importance of checking the baby's nappies for dark urine or pale chalky stools ● the fact that neonatal jaundice is common, and reassurance that it is usually transient and harmless ● reassurance that breastfeeding can usually continue.	8
	Care for all babies	
2	Identify babies as being more likely to develop significant hyperbilirubinaemia if they have any of the following factors: ● gestational age under 38 weeks ● a previous sibling with neonatal jaundice requiring phototherapy ● mother's intention to breastfeed exclusively ● visible jaundice in the first 24 hours of life.	3.1
3	Ensure that adequate support is offered to all women who intend to breastfeed exclusively*	3.1
4	In all babies: ● check whether there are factors associated with an increased likelihood of developing significant hyperbilirubinaemia soon after birth ● examine the baby for jaundice at every opportunity especially in the first 72 hours.	5.1
5	Parents, carers and healthcare professionals should all look for jaundice (visual inspection).	5.1
6	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
7	Do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice.	5.1
8	Do not measure bilirubin levels routinely in babies who are not visibly jaundiced.	4.1

* Refer to 'Routine postnatal care of women and their babies' (NICE clinical guideline 37) for information on breastfeeding support.

ID	Recommendations	See Chapter/Section
9	Do not use any of the following to predict significant hyperbilirubinaemia ● umbilical cord blood bilirubin level ● end-tidal carbon monoxide (ETCOc) measurement ● umbilical cord blood direct antiglobulin test (DAT) (Coombs' test).	4.2
	Additional care	
10	Ensure babies with factors associated with an increased likelihood of developing significant hyperbilirubinaemia receive an additional visual inspection by a healthcare professional during the first 48 hours of life.	5.1
	Urgent additional care for babies with visible jaundice in the first 24 hours	
11	Measure and record the serum bilirubin level urgently (within 2 hours) in all babies with suspected or obvious jaundice in the first 24 hours of life.	4.1
12	Continue to measure the serum bilirubin level every 6 hours for all babies with suspected or obvious jaundice in the first 24 hours of life until the level is both: ● below the treatment threshold ● stable and/or falling.	4.1
13	Arrange a referral to ensure that an urgent medical review is conducted (as soon as possible and within 6 hours) for babies with suspected or obvious jaundice in the first 24 hours of life to exclude pathological causes of jaundice.	4.1
14	Interpret bilirubin levels according to the baby's postnatal age in hours and manage hyperbilirubinaemia according to the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6).	4.1
	Care for babies more than 24 hours old	
15	Measure and record the bilirubin level urgently (within 6 hours) in all babies more than 24 hours old with suspected or obvious jaundice.	5.1
	How to measure the bilirubin level	
16	When measuring the bilirubin level: ● use a transcutaneous bilirubinometer in babies with a gestational age of 35 weeks or more and postnatal age of more than 24 hours ● 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 babies less than 35 weeks gestational age ● always use serum bilirubin measurement for babies at or above the relevant treatment threshold for their postnatal age, and for all subsequent measurements ● do not use an icterometer.	5.2

ID	Recommendations	See Chapter/Section
	Information for parents or carers on treatment	
17	Offer parents or carers information about treatment for hyperbilirubinaemia, including: ● anticipated duration of treatment ● reassurance that breastfeeding, nappy-changing and cuddles 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
19	Provide lactation/feeding support to breastfeeding mothers whose baby is visibly jaundiced.	8
	How to manage hyperbilirubinaemia	
20	Use the bilirubin level to determine the management of hyperbilirubinaemia in all babies (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).	7.1.1
21	Do not use the albumin/bilirubin ratio when making decisions about the management of hyperbilirubinaemia.	6.1
22	Do not subtract conjugated bilirubin from total serum bilirubin when making decisions about the management of hyperbilirubinaemia (see management thresholds in the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).	6.1
	Measuring and monitoring bilirubin thresholds during phototherapy	
	Starting phototherapy	
23	Use serum bilirubin measurement and the treatment thresholds in the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6) when considering the use of phototherapy.	7.1.2
24	In babies with a gestational age of 38 weeks or more whose bilirubin is in the 'repeat bilirubin measurement' category in the threshold table (Section 1.3) repeat the bilirubin measurement in 6–12 hours.	7.1.2
25	In babies with a gestational age of 38 weeks or more whose bilirubin is in the 'consider phototherapy' category in the threshold table (Section 1.3) repeat the bilirubin measurement in 6 hours regardless of whether or not phototherapy has subsequently been started.	7.1.2
26	Do not use phototherapy in babies whose bilirubin does not exceed the phototherapy threshold levels in the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6).	7.1.2
	During phototherapy	
27	During phototherapy: ● repeat serum bilirubin measurement 4–6 hours after initiating phototherapy ● repeat serum bilirubin measurement every 6–12 hours when the serum bilirubin level is stable or falling.	7.1.2

ID	Recommendations	See Chapter/Section
	Stopping phototherapy	
28	Stop phototherapy once serum bilirubin has fallen to a level at least 50 micromol/litre below the phototherapy threshold (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).	7.1.2
29	Check for rebound of significant hyperbilirubinaemia with a repeat serum bilirubin measurement 12–18 hours after stopping phototherapy. Babies do not necessarily have to remain in hospital for this to be done.	7.1.2
	Type of phototherapy to use	
30	Do not use sunlight as treatment for hyperbilirubinaemia.	7.2.1
	Single phototherapy treatment for term babies	
31	Use conventional 'blue light' phototherapy as treatment for significant hyperbilirubinaemia in babies with a gestational age of 37 weeks or more unless: ● the serum bilirubin level is rising rapidly (more than 8.5 micromol/litre per hour) ● the serum bilirubin is at a level that is within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours (see the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).	7.2.1
32	Do not use fibreoptic phototherapy as first-line treatment for hyperbilirubinaemia for babies with a gestational age of 37 weeks or more.	7.2.1
	Single phototherapy treatment in preterm babies	
33	Use either fibreoptic phototherapy or conventional 'blue light' phototherapy as treatment for significant hyperbilirubinaemia in babies less than 37 weeks unless: ● the serum bilirubin level is rising rapidly (more than 8.5 micromol/litre per hour) ● the serum bilirubin is at a level that is within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours (see treatment threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).	7.2.1
	Continuous multiple phototherapy treatment for term and pre term babies	
34	Initiate continuous multiple phototherapy to treat all babies if any of the following apply: ● the serum bilirubin level is rising rapidly (more than 8.5 micromol/litre per hour) ● the serum bilirubin is at a level within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)). ● the bilirubin level fails to respond to single phototherapy (that is, the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting single phototherapy)	7.2.1
35	If the serum bilirubin level falls during continuous multiple phototherapy to a level 50 micromol/litre below the threshold for which exchange transfusion is indicated step down to single phototherapy.	7.1.1

ID	Recommendations	See Chapter/Section
	Information for parents or carers on phototherapy	
36	Offer parents or carers verbal and written information on phototherapy including all of the following: ● why phototherapy is being considered ● why phototherapy may be needed to treat significant hyperbilirubinaemia ● the possible adverse effects of phototherapy ● the need for eye protection and routine eye care ● reassurance that short breaks for feeding, nappy changing and cuddles will be encouraged ● what might happen if phototherapy fails ● rebound jaundice ● potential long-term adverse effects of phototherapy ● potential impact on breastfeeding and how to minimise this.	8
	General care of the baby during phototherapy	
37	During phototherapy: ● place the baby in a supine position unless other clinical conditions prevent this ● ensure treatment is applied to the maximum area of skin ● monitor the baby's temperature and ensure the baby is kept in an environment that will minimise energy expenditure (thermoneutral environment) ● monitor hydration by daily weighing of the baby and assessing wet nappies ● support parents and carers and encourage them to interact with the baby.	7.2.2, 7.2.3
38	Give the baby eye protection and routine eye care during phototherapy.	7.2.2
39	Use tinted headboxes as an alternative to eye protection in babies with a gestational age of 37 weeks or more undergoing conventional 'blue light' phototherapy.	7.2.2
	Monitoring the baby during phototherapy	
40	During conventional 'blue light' phototherapy: ● using clinical judgement, encourage short breaks (of up to 30 minutes) for breastfeeding, nappy changing and cuddles ● continue lactation/feeding support ● do not give additional fluids or feeds routinely. Maternal expressed milk is the additional feed of choice if available, and when additional feeds are indicated.	7.2.3
41	During multiple phototherapy: ● do not interrupt phototherapy for feeding but continue administering intravenous/enteral 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.	7.2.3

ID	Recommendations	See Chapter/Section
	Phototherapy equipment	
42	Ensure all phototherapy equipment is maintained and used according to the manufacturers' guidelines.	7.2.1
43	Use incubators or bassinets according to clinical need and availability.	7.2.4
44	Do not use white curtains routinely with phototherapy as they may impair observation of the baby.	7.2.4
	Factors that influence the risk of kernicterus	
45	Identify babies with hyperbilirubinaemia as being at increased risk of developing kernicterus if they have any of the following: ● a serum bilirubin level greater than 340 micromol/litre in babies with a gestational age of 37 weeks or more ● a rapidly rising bilirubin level of greater than 8.5 micromol/litre per hour ● clinical features of acute bilirubin encephalopathy.	3.2
	Formal assessment for underlying disease	
46	In addition to a full clinical examination by a suitably trained healthcare professional, carry out all of the following tests in babies with significant hyperbilirubinaemia as part of an assessment for underlying disease (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)): ● 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.	6.1
47	When assessing the baby for underlying disease consider whether the following tests are clinically indicated: ● full blood count and examination of blood film ● blood glucose-6-phosphate dehydrogenase levels, taking account of ethnic origin ● microbiological cultures of blood, urine and/or cerebrospinal fluid (if infection is suspected).	6.1
	Care of babies with prolonged jaundice	
48	In babies with a gestational age of 37 weeks or more with jaundice lasting more than 14 days, and in babies with a gestational age of less than 37 weeks with jaundice lasting more than 21 days: ● look for pale chalky stools and/or dark urine that stains the nappy ● measure the conjugated bilirubin ● carry out a full blood count ● carry out a blood group determination (mother and baby) and DAT (Coombs' test). Interpret the result taking account of the strength of reaction, and whether mother received prophylactic anti-D immunoglobulin during pregnancy. ● carry out a urine culture ● ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed.	6.2

ID	Recommendations	See Chapter/Section
49	Follow expert advice about care for babies with a conjugated bilirubin level greater than 25 micromol/litre because this may indicate serious liver disease.	6.2
	Intravenous immunoglobulin	
50	Use intravenous immunoglobulin (IVIG) (500 mg/kg over 4 hours) 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 per hour.	7.4
51	Offer parents or carers information on IVIG including: ● why IVIG is being considered ● why IVIG may be needed to treat significant hyperbilirubinaemia ● the possible adverse effects of IVIG ● when it will be possible for parents or carers to see and hold the baby.	8
52	**Exchange transfusion** Offer parents or carers information on exchange transfusion including: ● the fact that exchange transfusion requires that the baby be admitted to an intensive care bed ● why an exchange transfusion is being considered ● why an exchange transfusion may be needed to treat significant hyperbilirubinaemia ● the possible adverse effects of exchange transfusions ● when it will be possible for parents or carers to see and hold the baby after the exchange transfusion.	8
53	Use a double-volume exchange transfusion to treat babies: ● whose serum bilirubin level indicates its necessity (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)) **and/or** ● with clinical features and signs of acute bilirubin encephalopathy.	7.3
54	During exchange transfusion do not : ● stop continuous multiple phototherapy ● perform a single-volume exchange ● use albumin priming ● routinely administer intravenous calcium.	7.3
55	Following exchange transfusion: ● maintain continuous multiple phototherapy ● measure serum bilirubin level within 2 hours and manage according to threshold table (Section 1.3) and treatment threshold graphs (Section 1.6).	7.3

ID	Recommendations	See Chapter/Section
	Other therapies	
56	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.	7.4

1.5 Research recommendations

1.5.1 Key priorities for research

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 significant 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 develop significant hyperbilirubinaemia will be compared with infants with significant hyperbilirubinaemia. Outcome: Factors to be analysed include I) maternal factors, II) neonatal factors, III) blood analyses. Time stamp: Sept 2009

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 significant hyperbilirubinaemia is effective at preventing later significant hyperbilirubinaemia.Population: Babies in the first 28 days of life. Subgroups should include near-term babies 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) Significant hyperbilirubinaemiaii) Cost-effectiveness, III) Parental anxiety. Time stamp: Sept 2009

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

Why this is important

Evidence: The accuracy of transcutaneous bilirubinometers (Minolta JM-103 and BiliChek) has been adequately demonstrated in term babies below treatment levels (bilirubin < 250 micromol/litre). New research is needed to evaluate the accuracy of different transcutaneous bilirubinometers in comparison to serum bilirubin levels in all babies. Population: Babies in the first 28 days of life. Subgroups to include preterm babies, babies with dark skin tones, babies with high levels of bilirubin and babies after phototherapy. Exposure: Bilirubin levels taken from different transcutaneous bilirubinometers. 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 test and cost effectiveness. Time stamp: Sept 2009

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

Why this is important

Evidence: The effectiveness and tolerability of intermittent phototherapy has been adequately demonstrated in term babies at low treatment levels (bilirubin < 250 micromol/litre). New research is needed to evaluate the effectiveness and tolerability of different frequencies of interruptions of different durations. Population: Babies in the first 28 days of life in conventional phototherapy. Exposure: Interruptions of 45 or 60 minutes either on demand, every hour or every 2 hours. Comparison: Interruptions of up to 30 minutes every 3 hours. 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

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/litre which is the threshold for an exchange transfusion recommended by NICE. Exposure: All maternal, prenatal, 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

What is the clinical and cost-effectiveness of:

- **LED phototherapy compared to conventional phototherapy in term and preterm babies with significant 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 the need for additional fluids. New randomised controlled trials are needed to examine LED phototherapy. Population: Term and preterm babies with significant hyperbilirubinaemia 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 significant hyperbilirubinaemia?**

Why this is important

Existing research has demonstrated the effectiveness of fiberoptic phototherapy in preterm 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 randomised controlled trials are needed to examine fiberoptic phototherapy which uses larger pads. Population: Term babies with significant 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

What is the effectiveness, cost-effectiveness and safety of Clofibrate alongside phototherapy versus phototherapy alone for non-haemolytic significant 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 breastfeeding and mother-baby bonding. However no studies have been carried out in a UK population. New placebo-controlled double-blind randomised controlled trials in a UK population are needed. Population: Term and preterm babies with significant hyperbilirubinaemia in the first 28 days of life. Interventions: Clofibrate (a single 100mg/kg dose) combined with phototherapy versus phototherapy with a placebo. 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 when used to prevent exchange transfusion in newborns with haemolytic disease and rising bilirubin?

Why this is important

Existing research has demonstrated that IVIG is effective in preventing the need for an exchange transfusion in babies with Rhesus haemolysis. New placebo-controlled double-blind randomised controlled trials are needed to examine if IVIG is effective in sub-groups of babies with ABO haemolysis, ie preterm babies, babies with bilirubin rising greater than 10 micromol/litre per hour or babies with co-morbid illnesses such as infections. Population: Term and preterm babies with significant hyperbilirubinaemia in the first 28 days of life. Interventions: IVIG (500mg/kg over 4 hours) 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

1.6 Treatment threshold graphs

The graphs on pages 14–29 show the gestational age specific thresholds for inititiating and stopping treatment. An electronic interactive implementation tool for treatment thresholds is available at www.nice.org.uk/guidance/CG98.

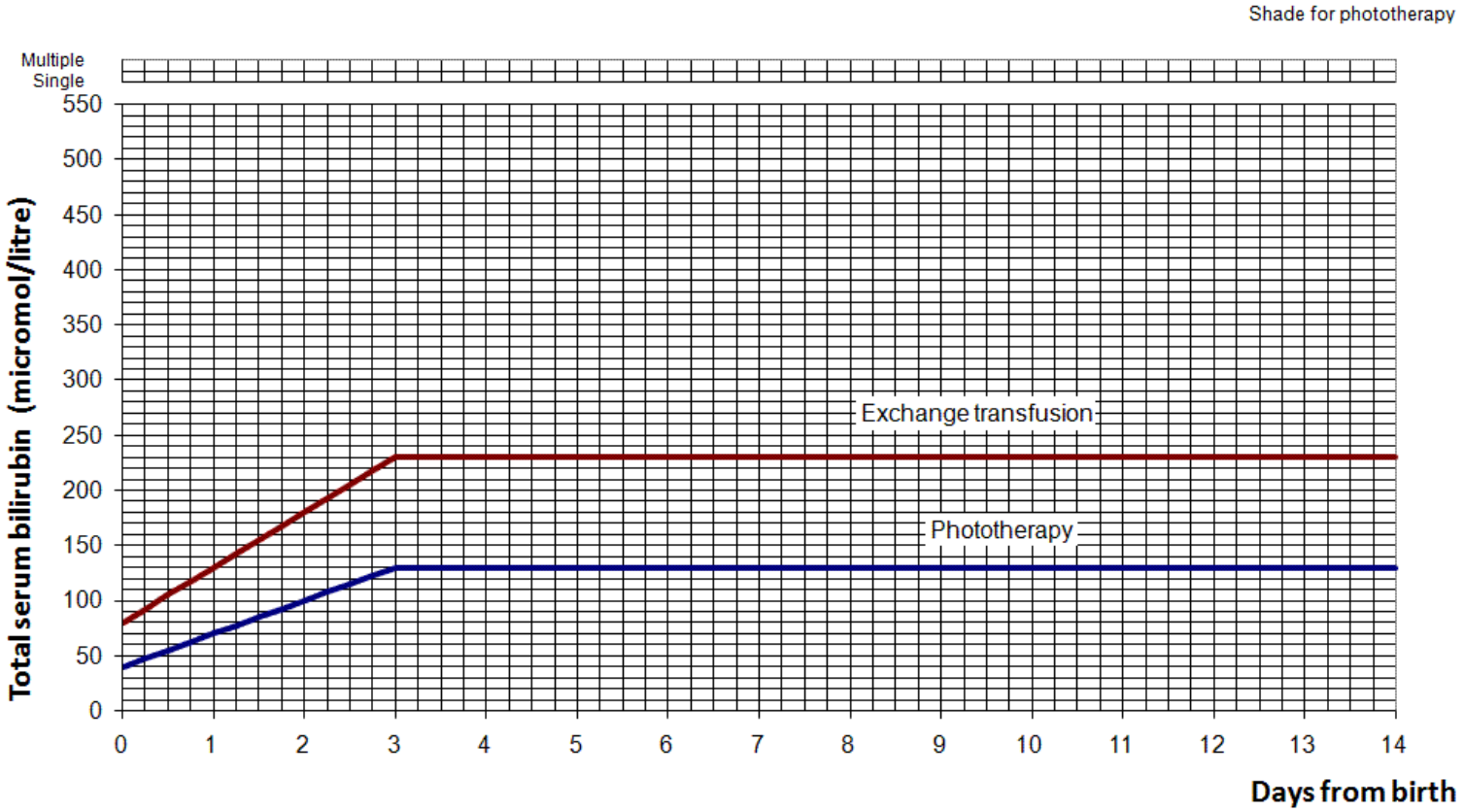
1.7 Investigation, phototherapy and exchange transfusion pathways

The pathways for investigation, phototherapy and exchange transfusion are on pages 30–32.

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **23** **weeks gestation**

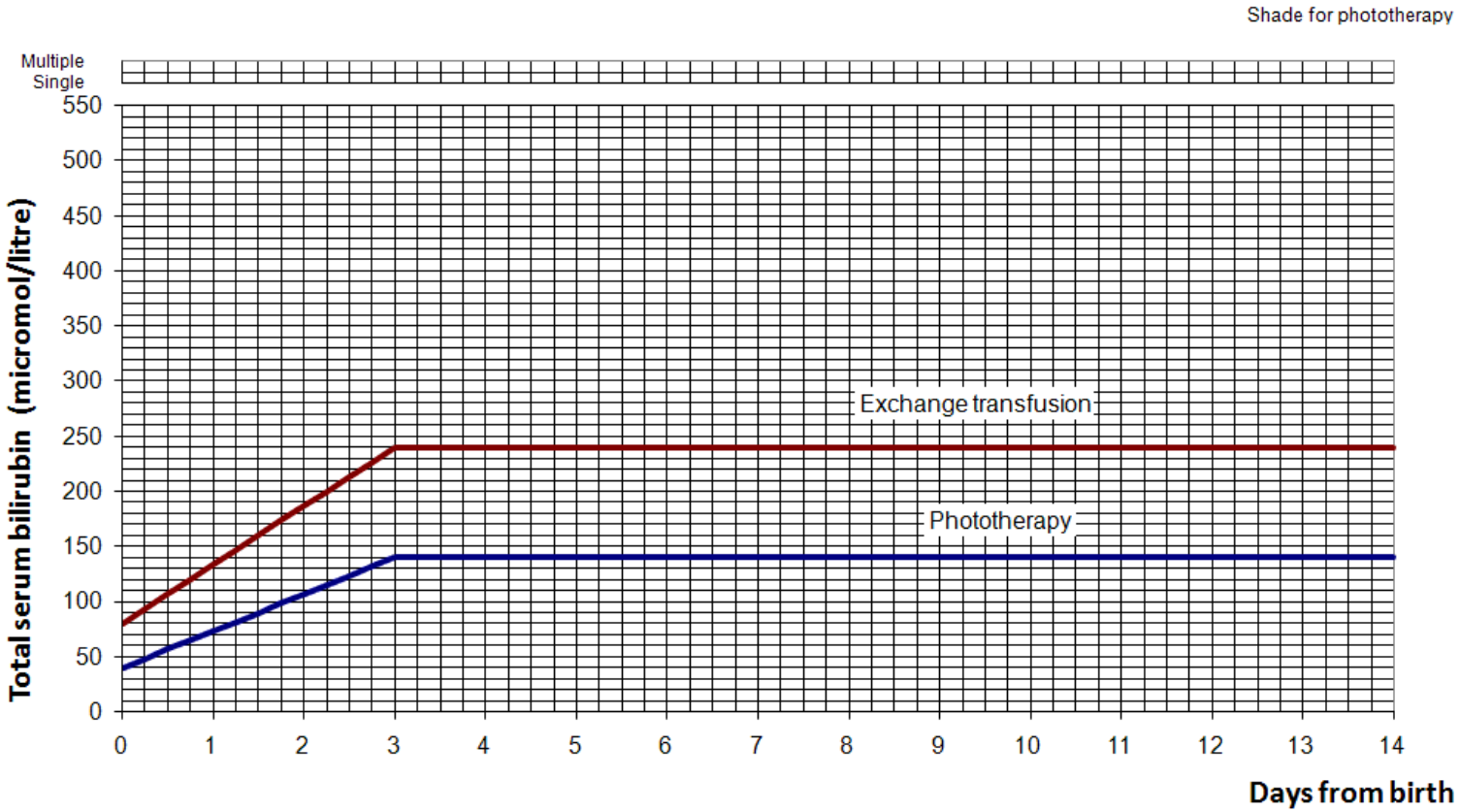


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **24** **weeks gestation**

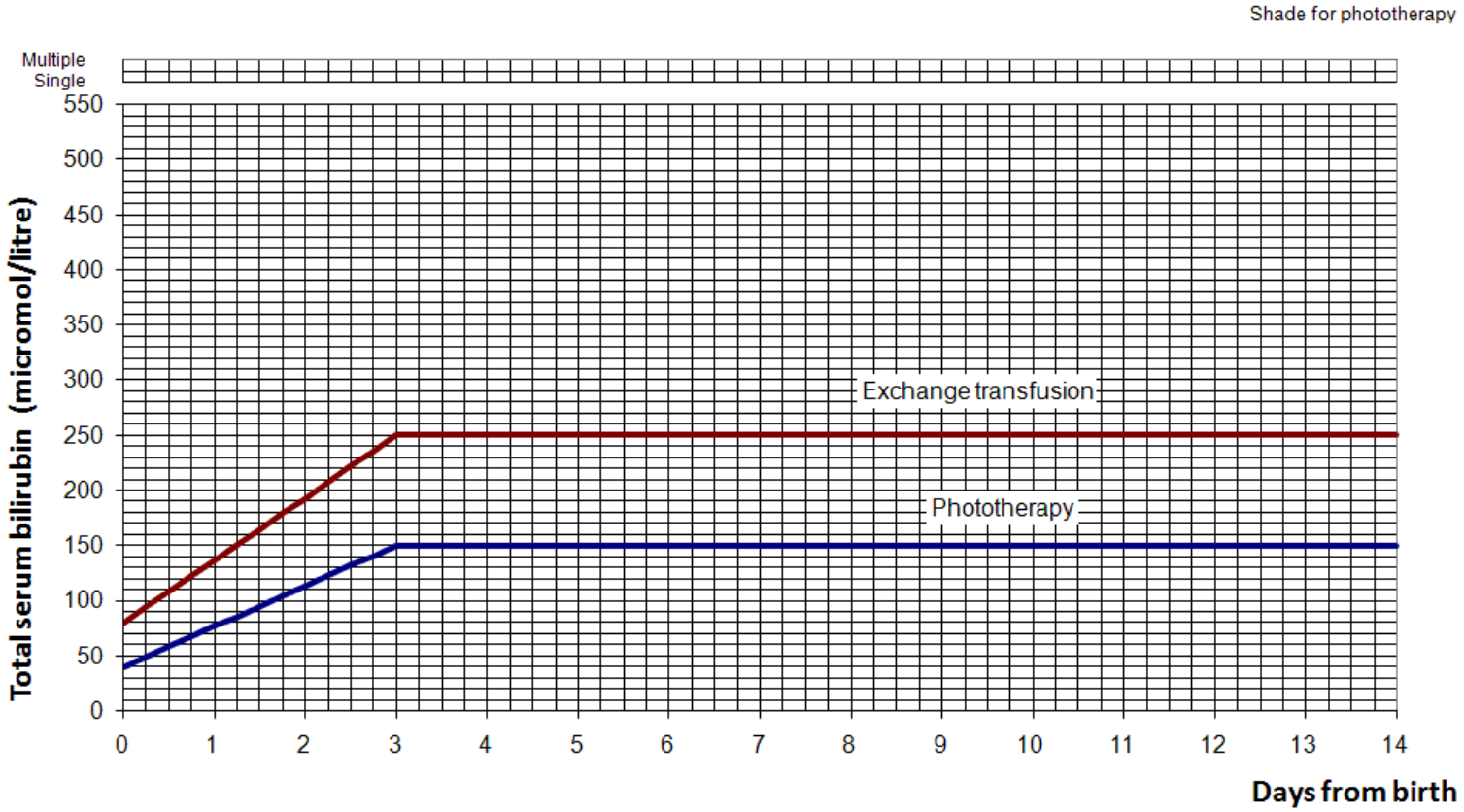


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **25** **weeks gestation**

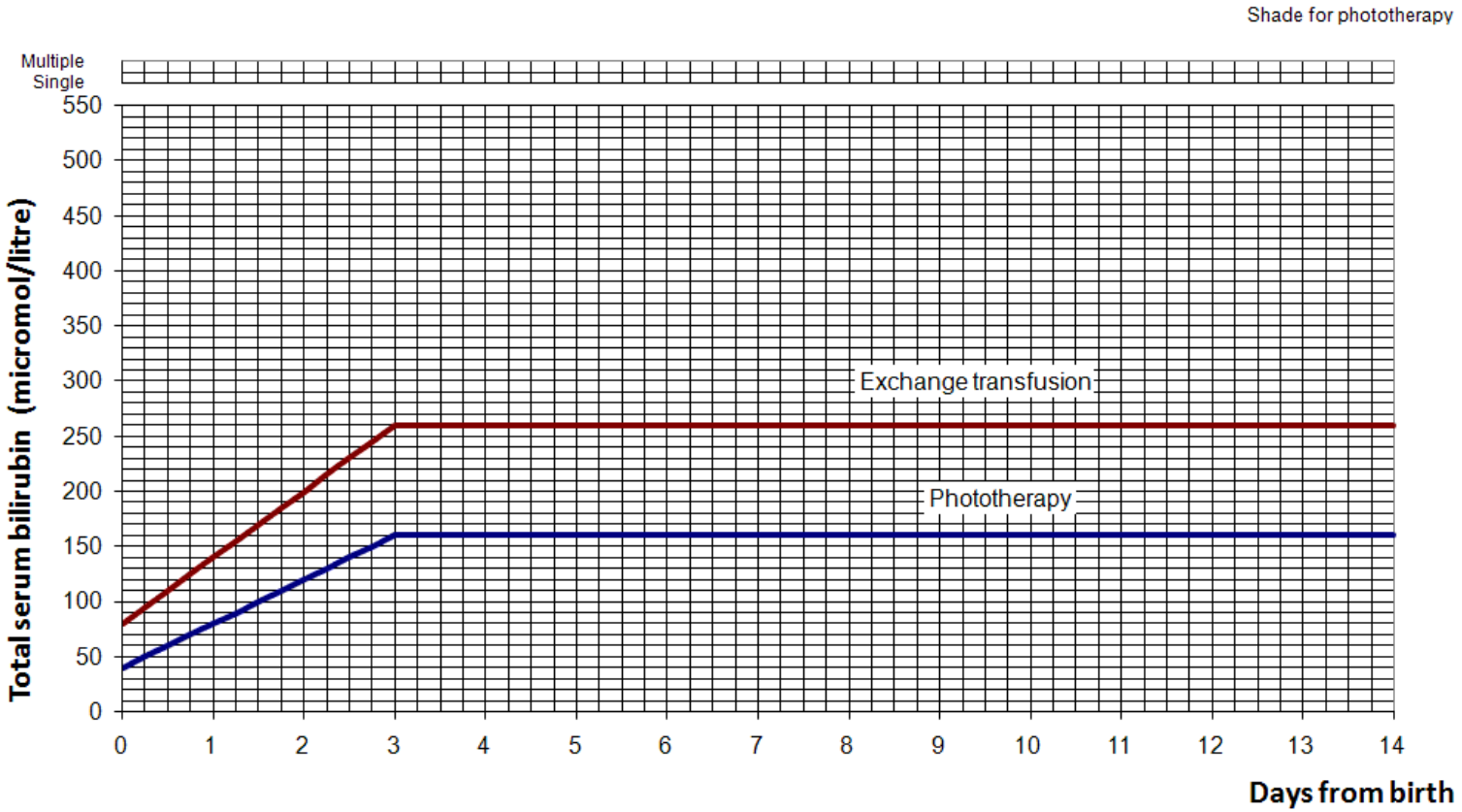


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **26** **weeks gestation**

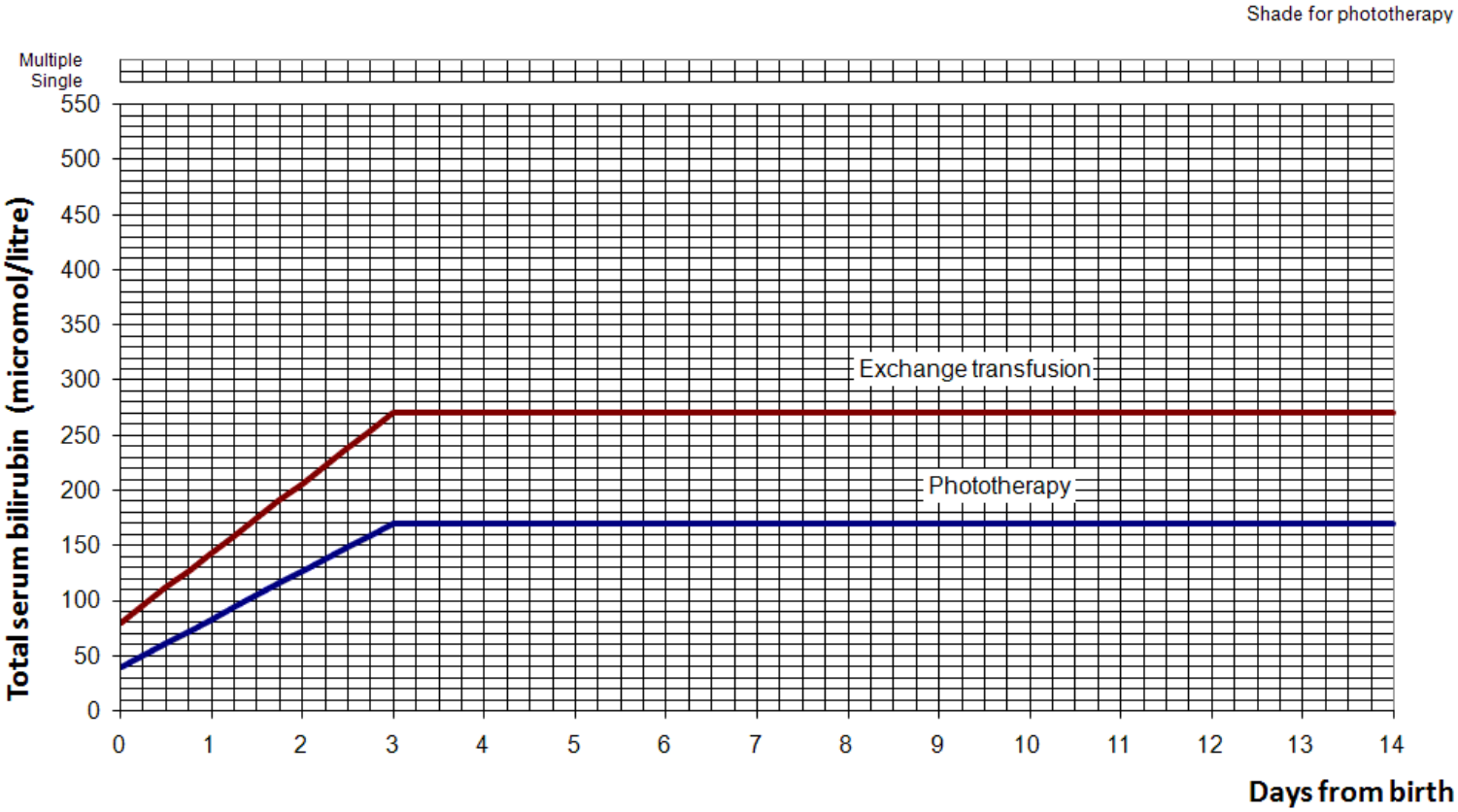


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **27** **weeks gestation**

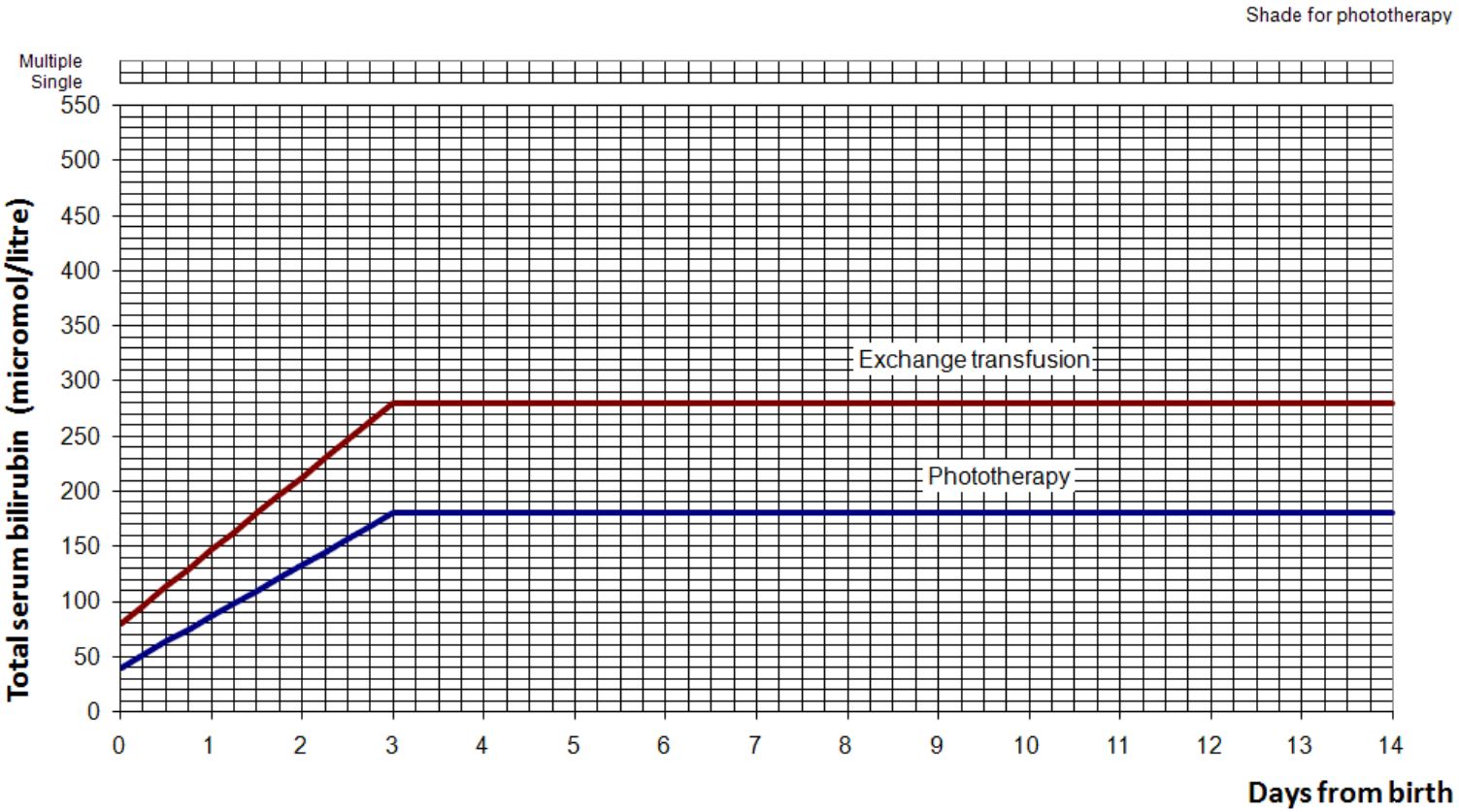


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **28** **weeks gestation**

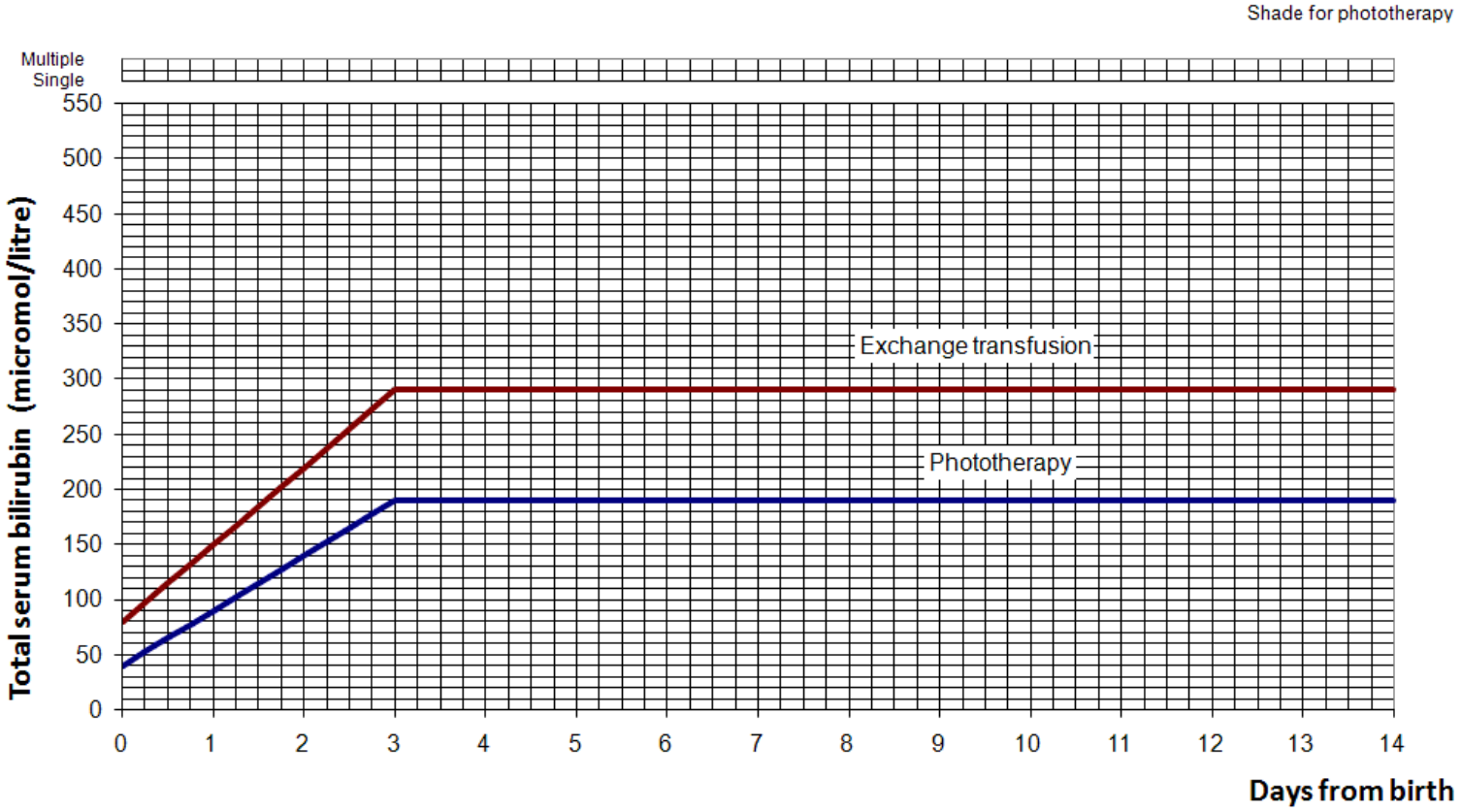


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **29** **weeks gestation**

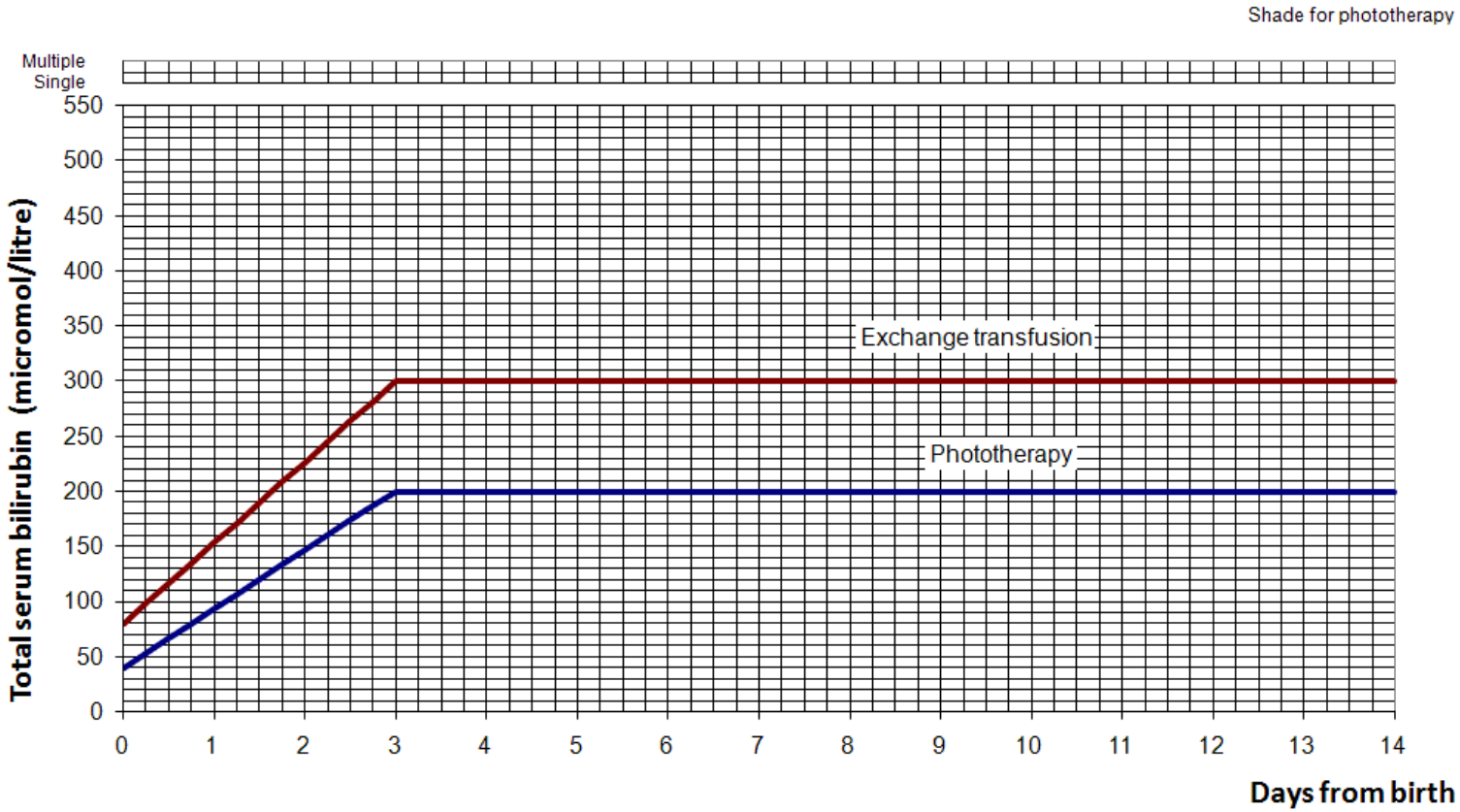


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **30** **weeks gestation**

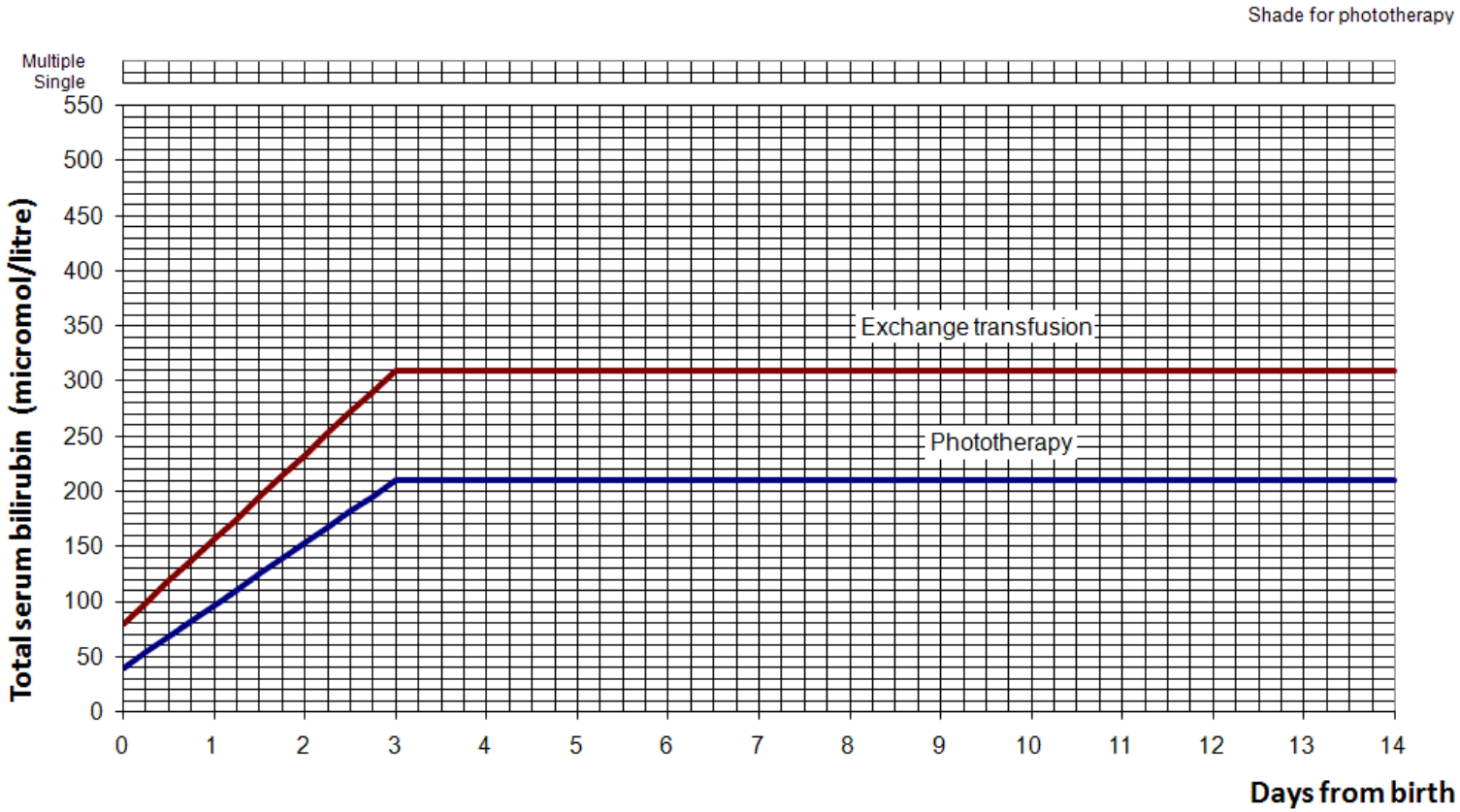


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **31** **weeks gestation**

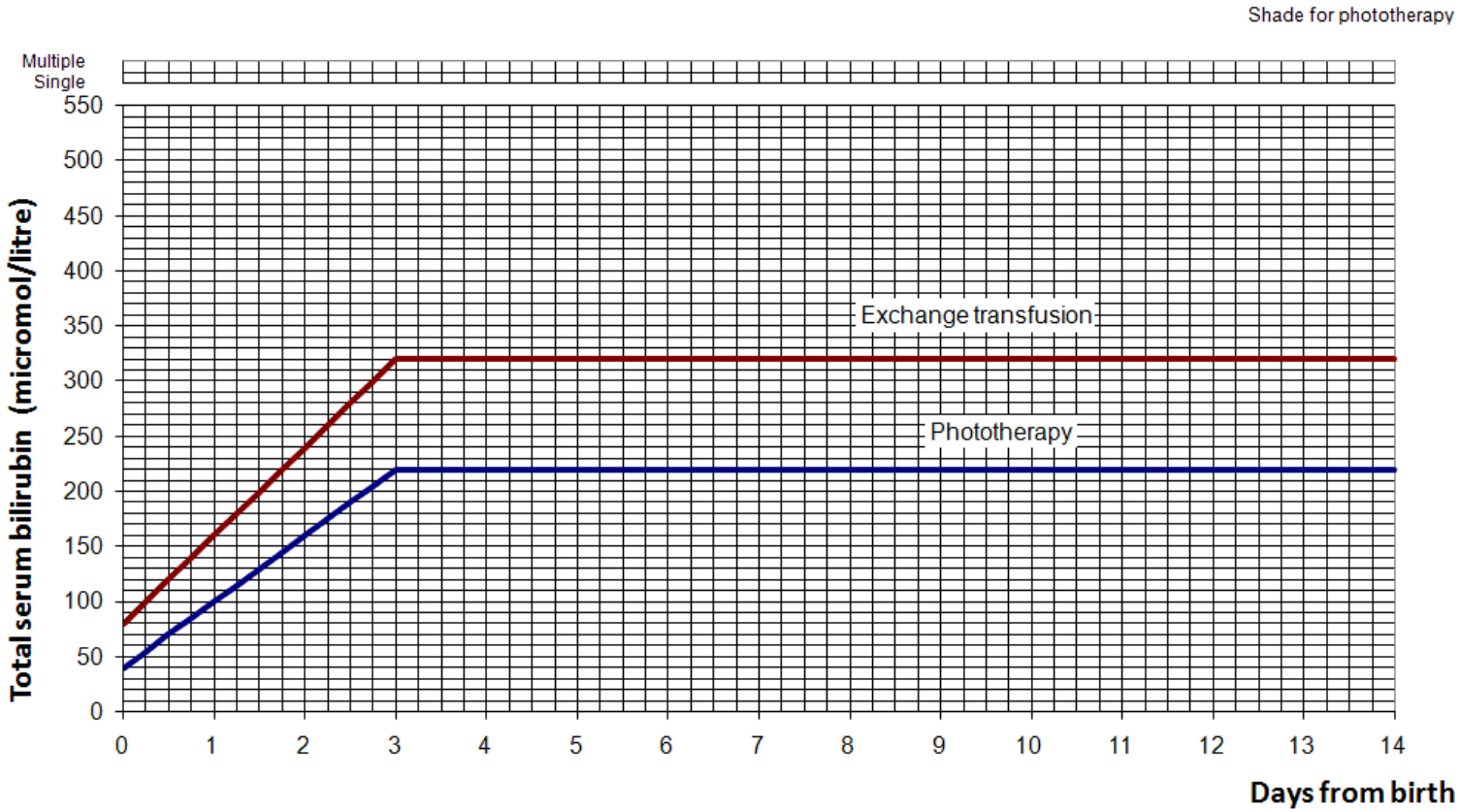


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **32** **weeks gestation**

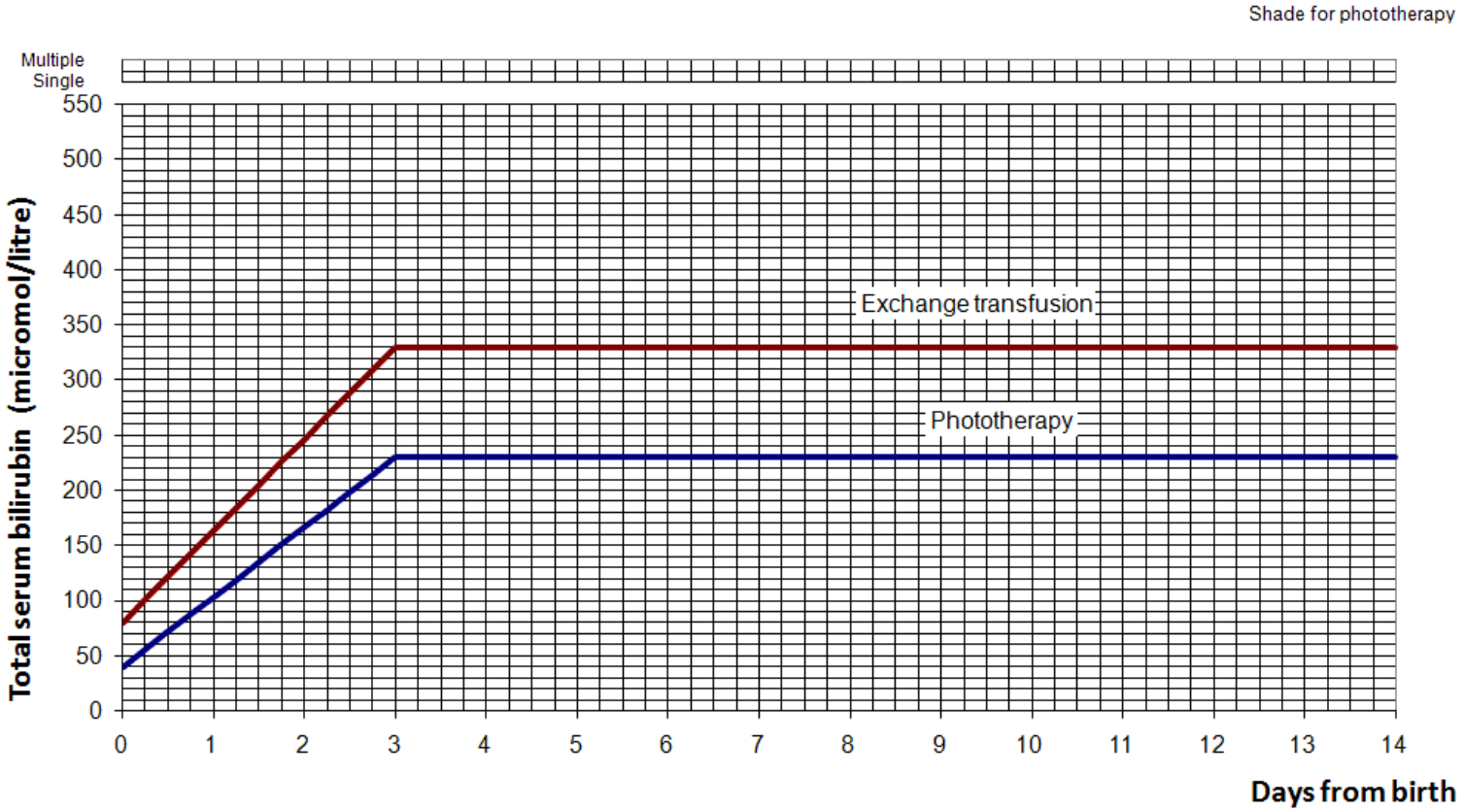


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **33** **weeks gestation**

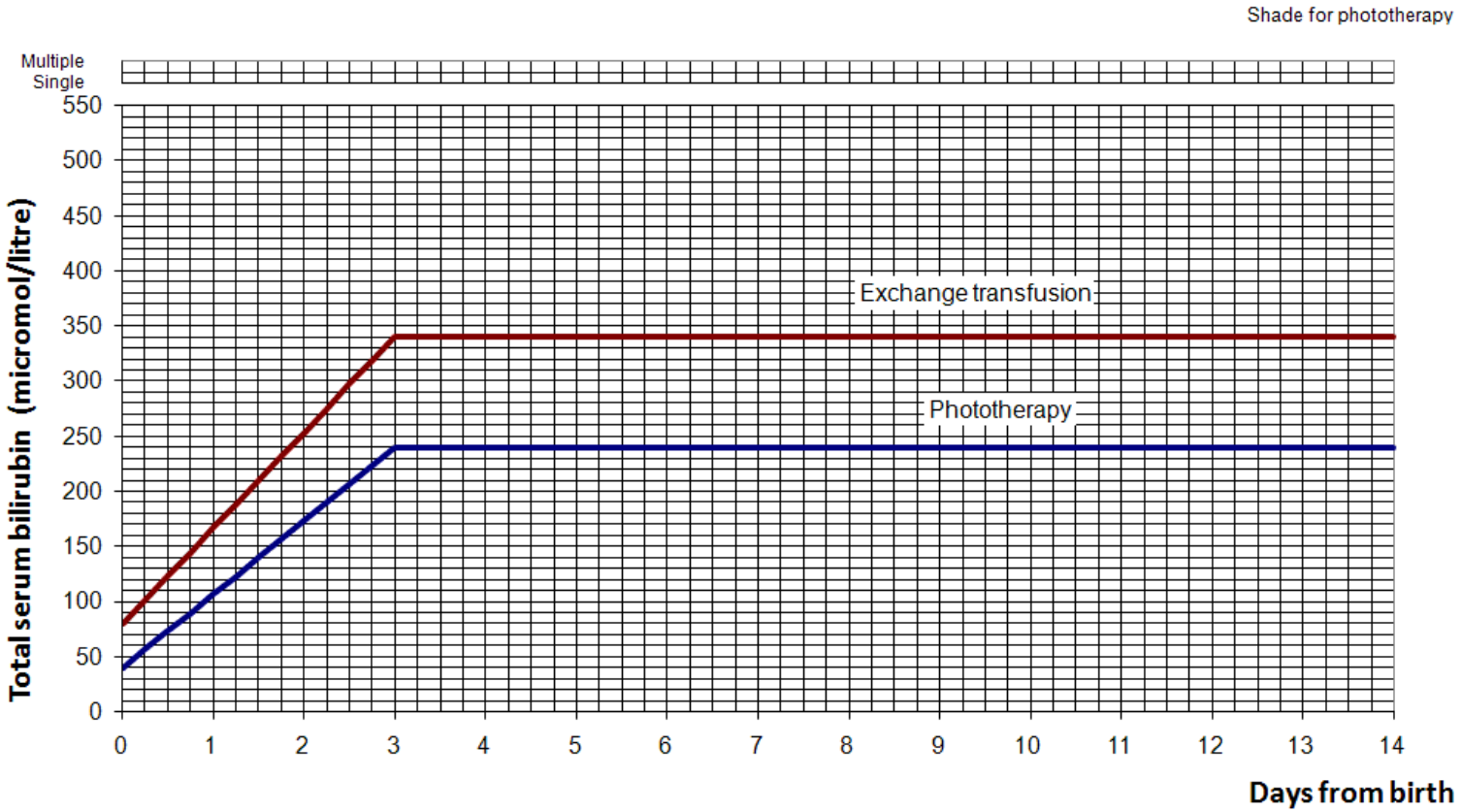


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **34** **weeks gestation**

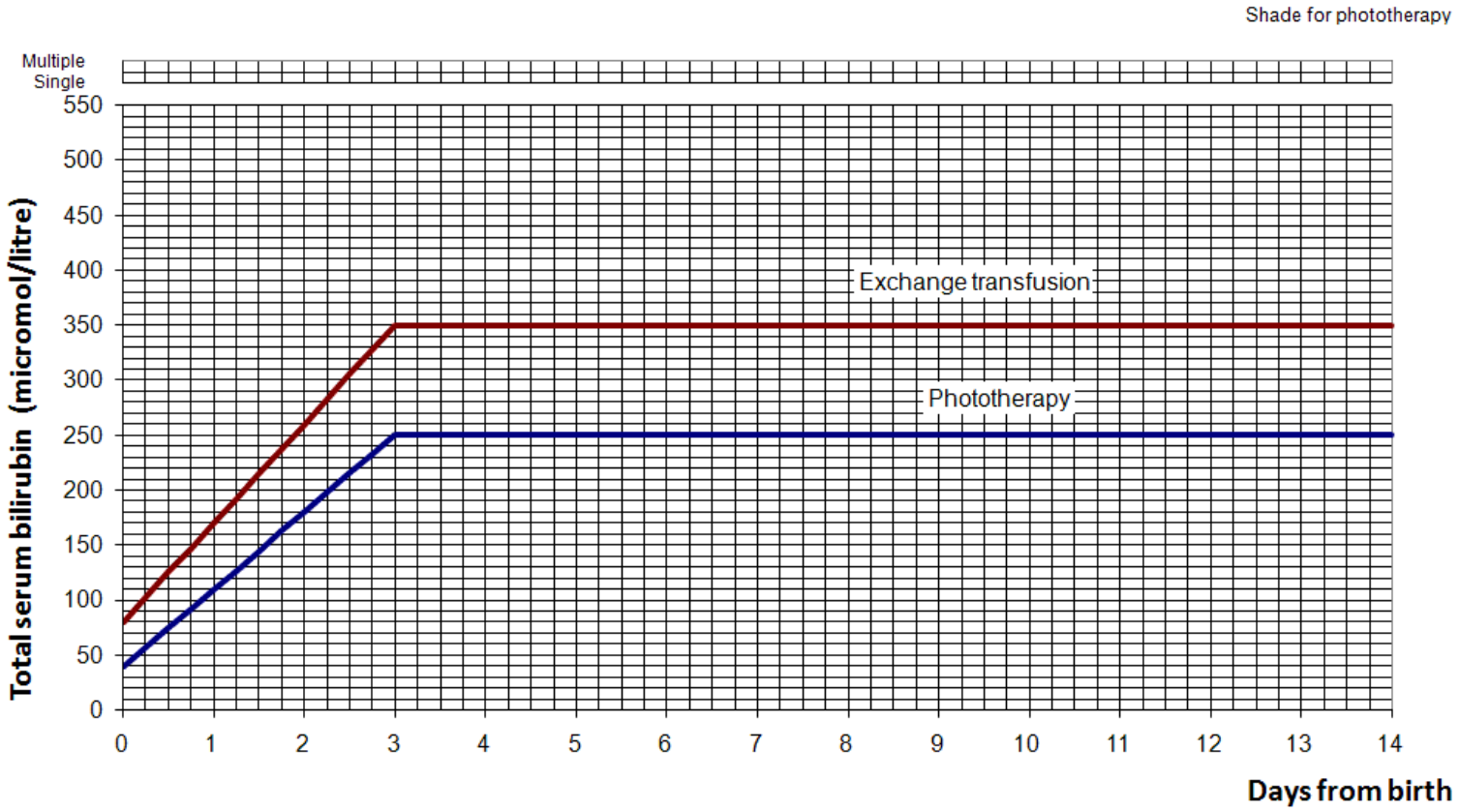


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **35** **weeks gestation**

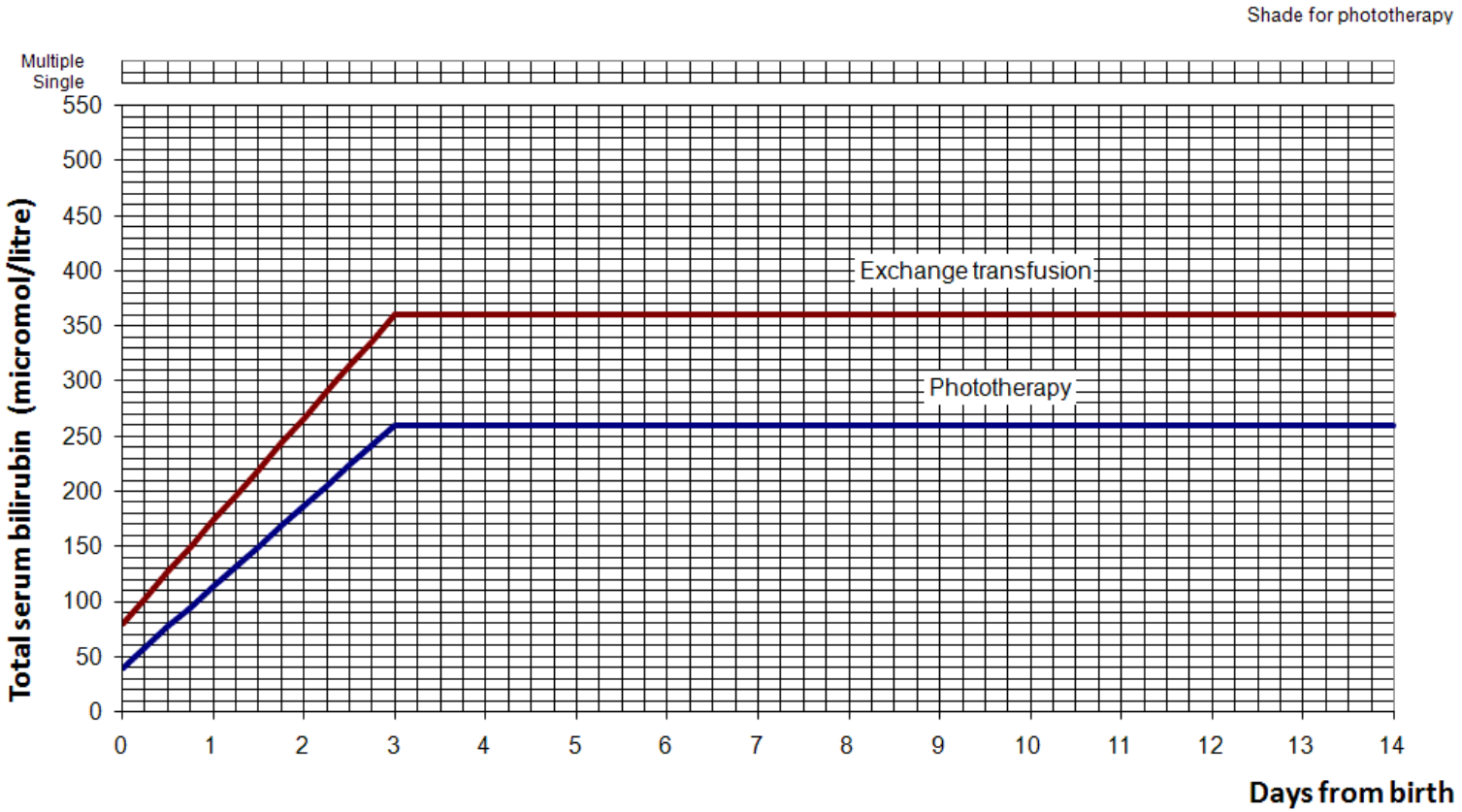


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **36** **weeks gestation**

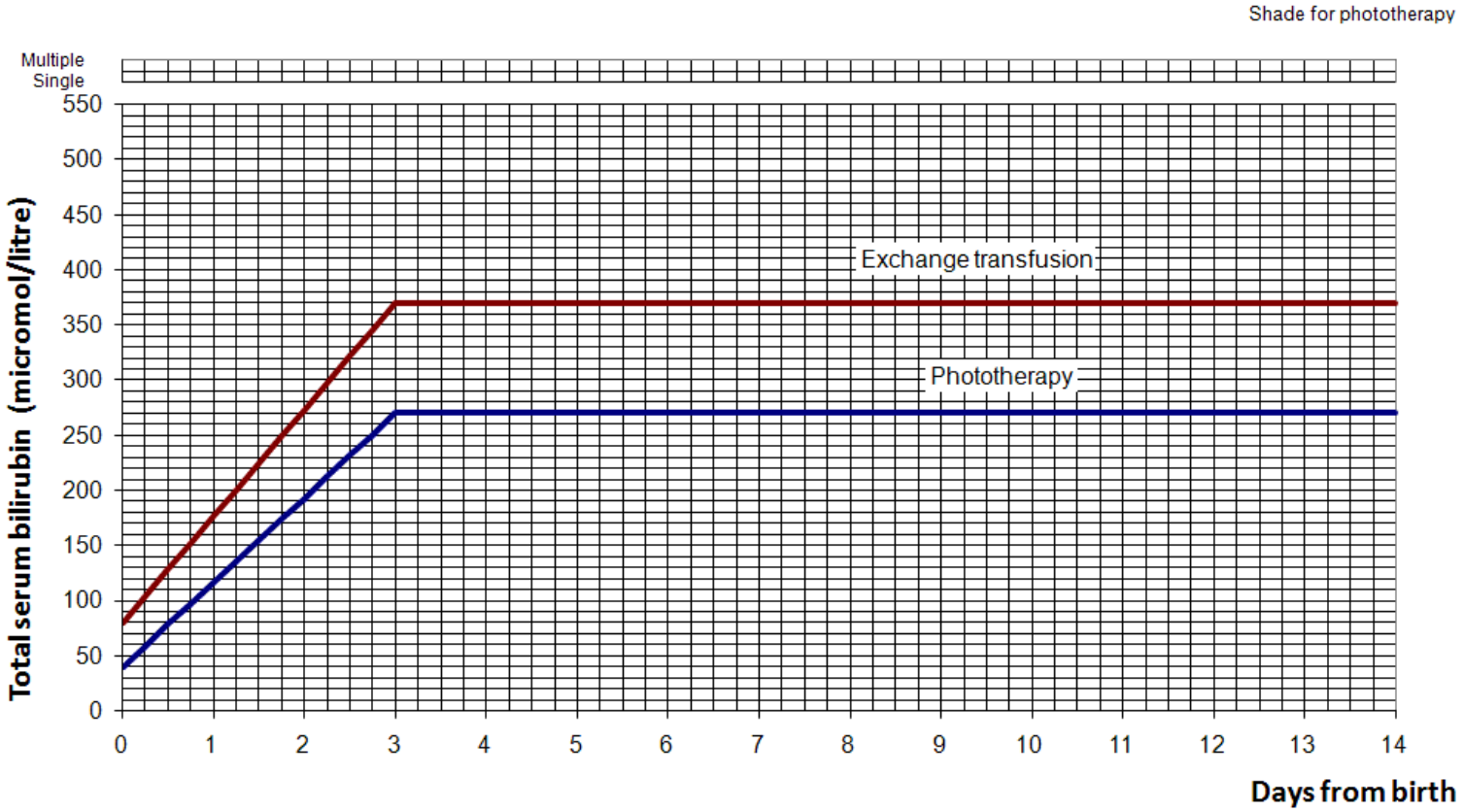


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **37** **weeks gestation**

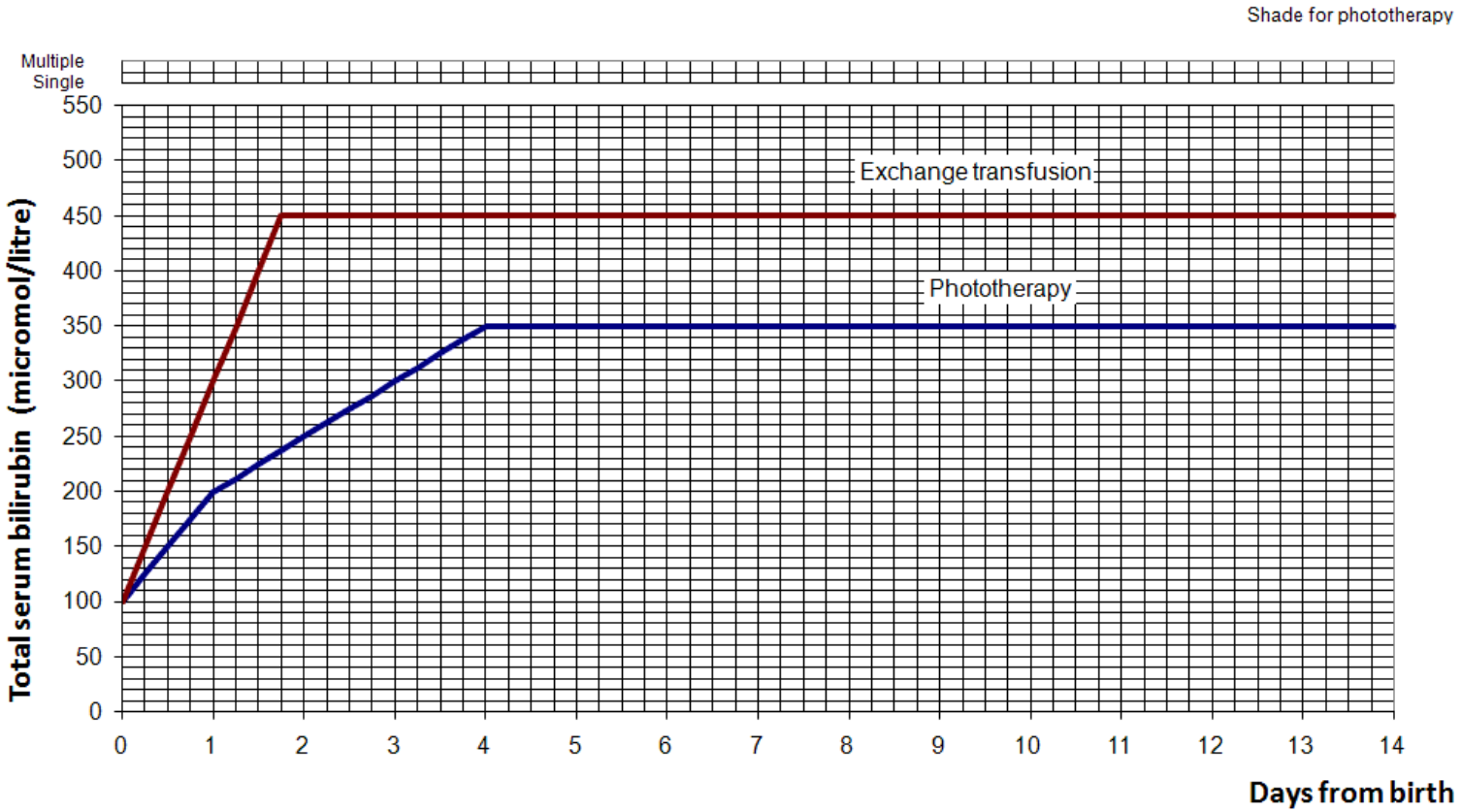


Baby's blood group _____ Mother's blood group _____

Treatment threshold graph for babies with neonatal jaundice

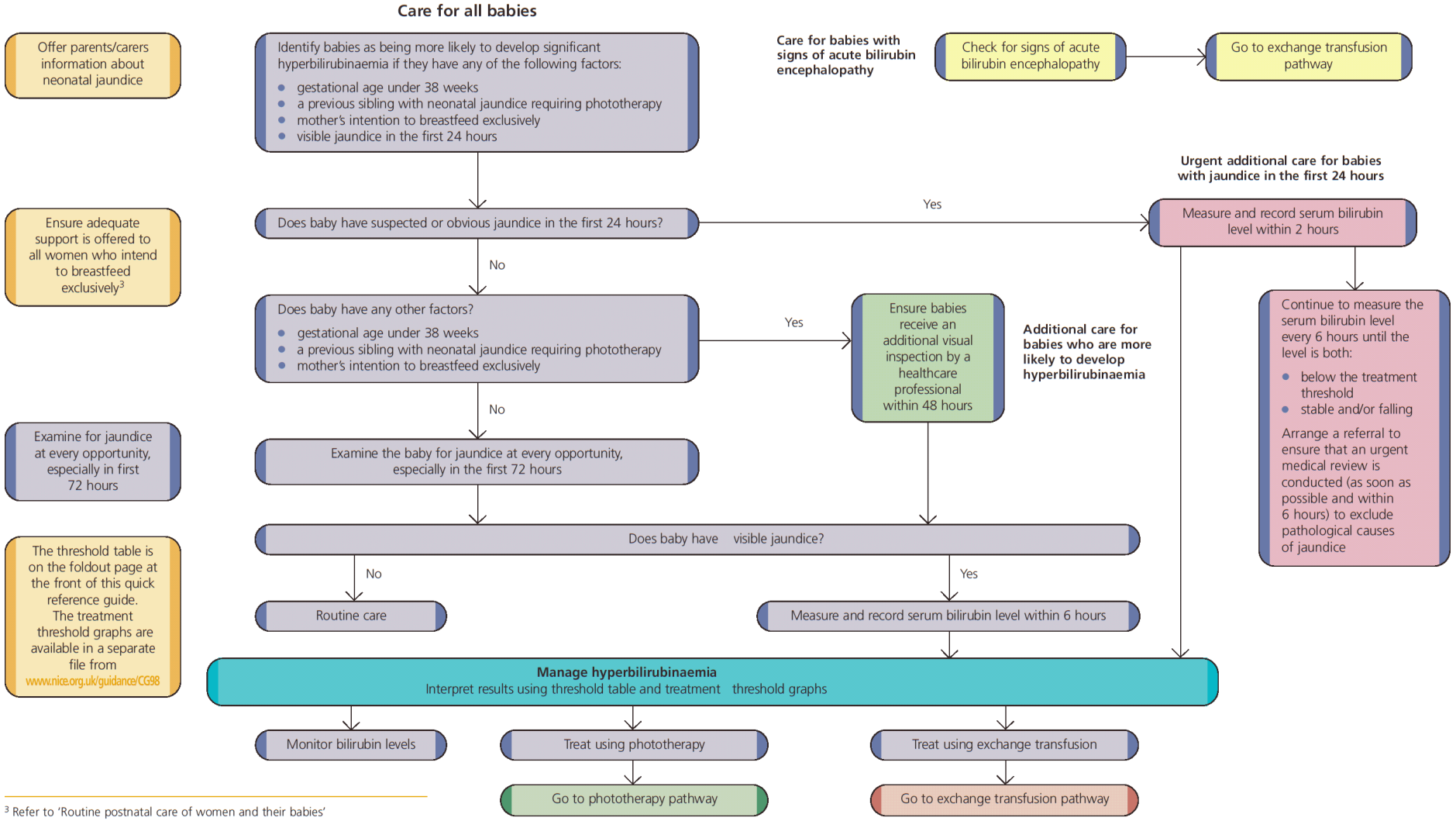
Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ **>=38 weeks gestation**



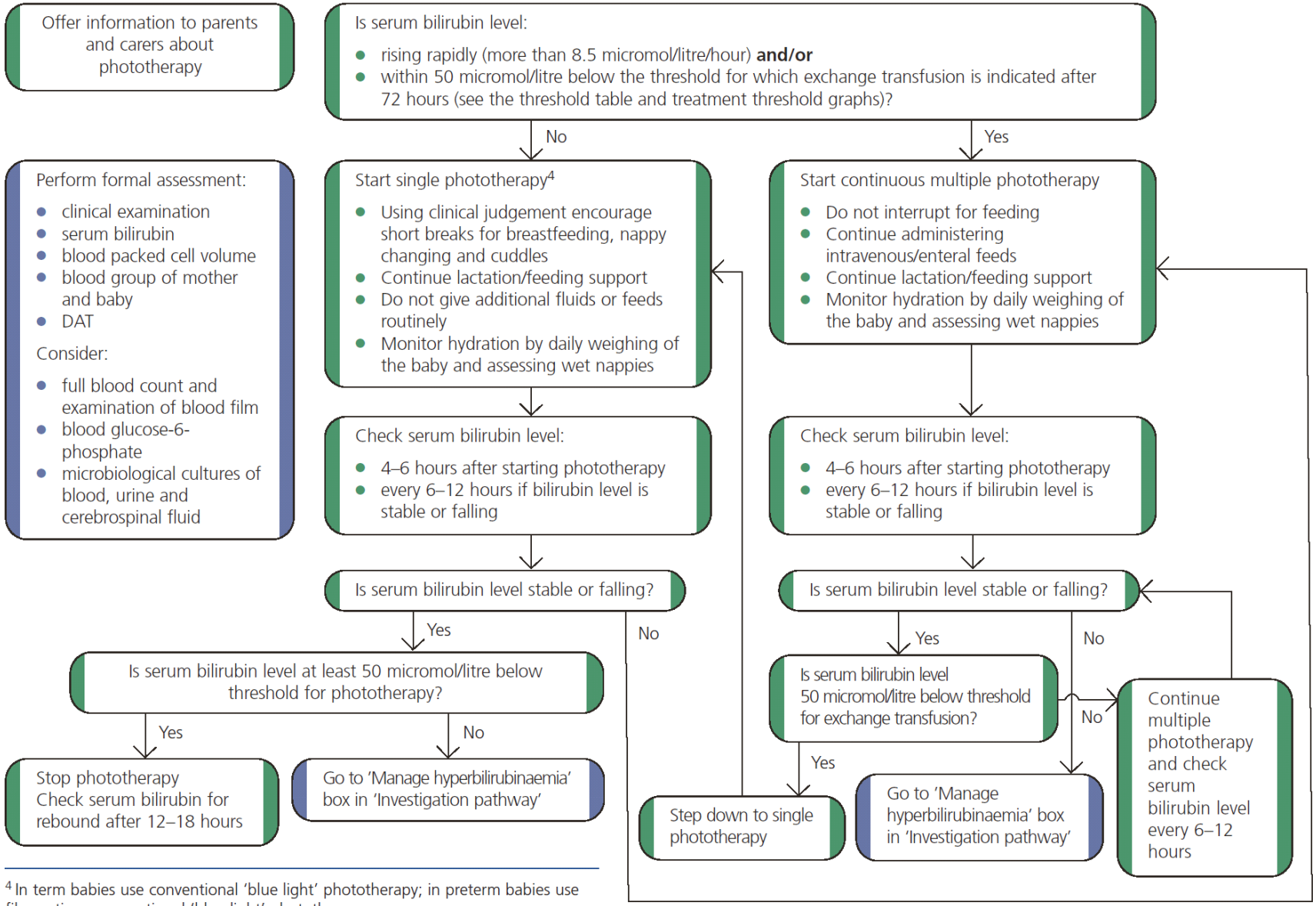
Baby's blood group _____ Mother's blood group _____

Investigation pathway



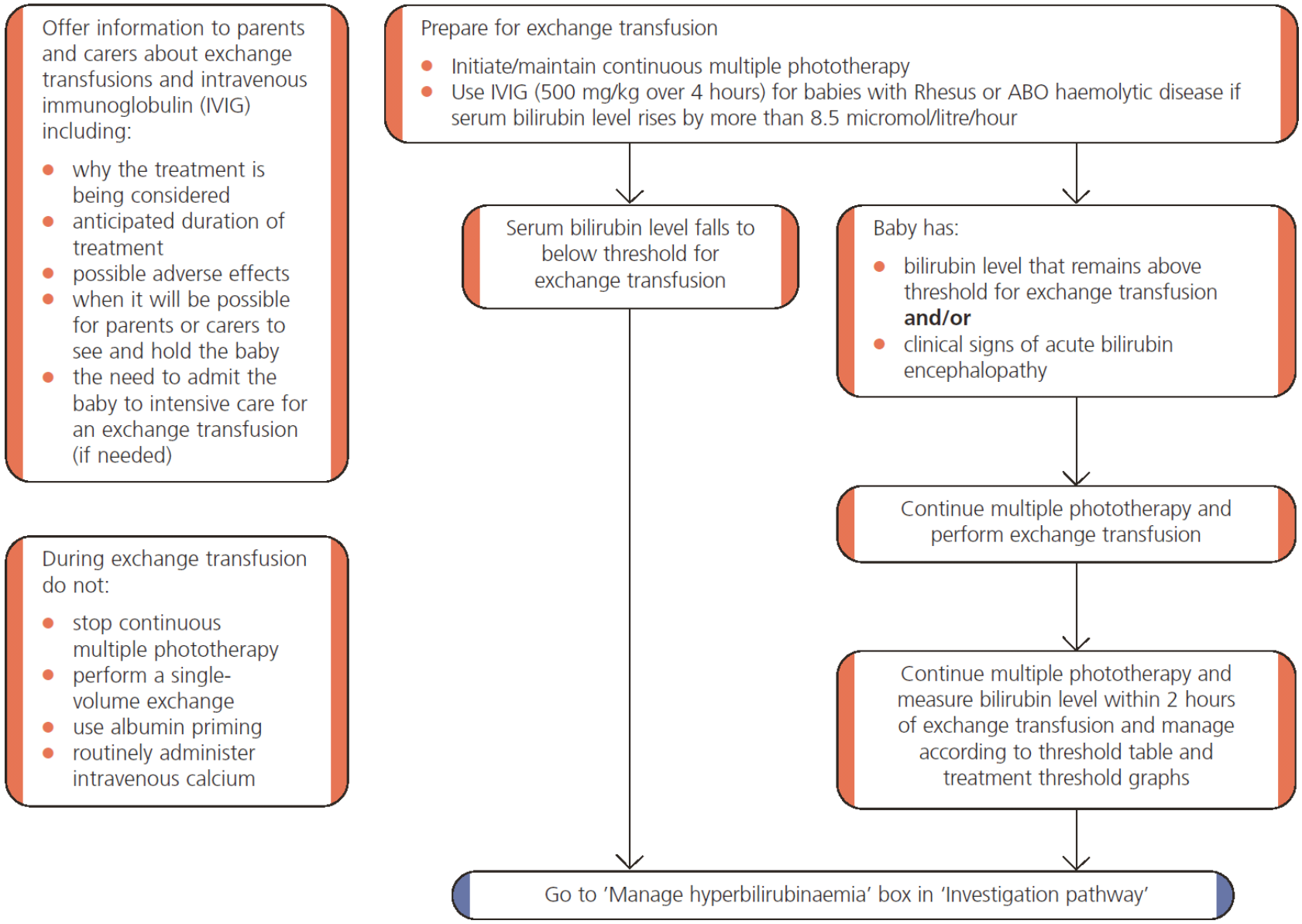
[3] Refer to 'Routine postnatal care of women and their babies' (NICE clinical guideline 37) for information on breastfeeding support.

Phototherapy pathway



[4] In term babies use conventional 'blue light' phototherapy; in preterm babies use fibreoptic or conventional 'blue light' phototherapy.

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 breastfed babies are still jaundiced at 1 month of age. In most babies with jaundice thevre 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 sclera (whites of the eyes) of newborn babies that results 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' red blood cells have a shorter lifespan than those of adults. The concentration of red blood cells in the circulation is also higher in newborns than it is in 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 harmless. It is difficult to tell which babies are at risk of developing high levels of bilirubin that 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

Breastfed 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 for which there is no underlying cause. 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 there 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, reduces the opportunity to assess whether 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 and have been referred to wherever appropriate.

Prolonged jaundice

Prolonged jaundice, that is jaundice persisting beyond the first 14 days, is also seen more commonly in term breastfed babies. The mechanism for this 'breast milk jaundice' 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 syndrome and Crigler–Najjar syndrome are rare causes of neonatal jaundice and are caused by liver enzyme problems. Deficiency of a particular enzyme, glucose-6-phosphate dehydrogenase (G6PD), can cause severe neonatal jaundice. G6PD 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 globus pallidus, 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, and 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 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 preterm birth, 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 G6PD 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/litre), but the incidence increases above this threshold level and the risk of kernicterus is greatly increased in term babies with bilirubin levels above 515 micromol/litre. Kernicterus is also known to occur at lower levels of bilirubin in preterm and 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, which is 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 when using charts, but there is already a degree of consistency in the NHS about treatment thresholds when healthcare professionals base their decisions on a formula that uses

gestational age.[1] 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'.[2] 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

This guideline does not address:

- 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 Who has developed the guideline

The guidance was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included:

- two neonatologists (one as Chair)
- two midwives
- one general practitioner
- one paediatrician
- one pathologist
- one specialist nurse
- one community nurse
- one health visitor
- two patient/carer members.

Staff from the NCC-WCH provided methodological support for the guidance development process, undertook systematic searches, retrieved and appraised the evidence, and wrote successive drafts of the guidance.

One external adviser was appointed by the GDG to advise on pharmacological interventions.

All GDG members' and external advisers' potential and actual conflicts of interest were recorded on declaration forms provided by NICE (summarised in Appendix B). None of the interests declared by GDG members constituted a material conflict of interest that would influence recommendations developed by the GDG.

2.5 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

2.6 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 (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		✓	
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 H.

Systematic searches to answer the clinical questions formulated and agreed by the Guideline Development Group (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 I.

Appraisal and synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[3-7;8] and classified using the established hierarchical system presented in Table 2.2 (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).[8]

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 H) 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 was 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 was carried out, the results from each included study are 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 reflect the evidence.

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

Specific considerations for this guideline

For this guideline, the effectiveness of interventions was 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 the SI unit micromol/litre 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 2.5 '2 x 2' table for calculation of number needed to treat (NNT)

	Outcome present	Outcome absent
Treated	A	C
Control	B	D

$$NNT = \frac{1}{A/(A+B) - C/(C+D)}$$

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 that may have implications for healthcare 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 healthcare system.

Therefore, the remaining areas where health economics was thought to be important in guiding recommendations was around testing for hyperbilirubinaemia and the use of intravenous immunoglobulin (IVIG). The results of the economic analyses are summarised briefly in the guideline text (Sections 5.2 and 7.4, respectively). A more detailed description of the health economic methods and results are presented in Appendices C and D, respectively.

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 ten 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 on 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 Factors that influence hyperbilirubinaemia and kernicterus

Introduction

Some disorders cause red cells to be more fragile than normal and to 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 that 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 that 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 of 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 many studies that 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: ten studies evaluating the risk factors for development of hyperbilirubinaemia and 3 studies each for the risk factors of kernicterus and adverse sequelae.

3.1 Factors that influence hyperbilirubinaemia

Description of included studies

Of the ten studies[9-18] included under this section, eight are from the USA[9-12;14;16-18] and two from Israel.[13;15] Except for one cross-sectional survey of EL III,[18] all studies are comparative observational studies, all of EL II. The results of all comparative studies on risk factors are presented in Table 3.1.

Review findings

A nested case–control study was carried out at 11 hospitals of a health maintenance organisation in the USA[9] to investigate predictors of hyperbilirubinaemia and evaluate the

predictive accuracy of a risk index model. The cohort consisted of 51 387 babies with birthweight ≥ 2000 g and gestational age ≥ 36 weeks born at these hospitals during a 2-year period. Babies with peak serum bilirubin levels ≥ 427 micromol/litre 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. The maternal factors considered included race, maternal age, history of jaundice in a previous sibling, and vacuum delivery. Neonatal factors considered included male sex, lower gestational age, early jaundice (defined either as bilirubin levels exceeding age-specific phototherapy thresholds, or phototherapy during birth hospitalisation, or jaundice noted in first 20 hours and bilirubin levels were not taken within 6 hours of that time), cephalohaematoma, bruising, and exclusively breastfed 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), gestational age (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 years (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[10] 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 4 years (compared to 2 years in the first study[9]) 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 (κ statistic for agreement = 0.75). Data on the use of phototherapy and development of hyperbilirubinaemia (maximum serum bilirubin levels ≥ 427 micromol/litre) 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 with newborns noted not to have jaundice in the first 24 hours (18.9% versus 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 above 427 micromol/litre (14.3% versus 5.9%; Mantel–Haenszel OR 2.9, 95% CI 1.6 to 5.2). [EL II]

Another nested case control study from the USA[11] estimated the effect of phototherapy and other factors on the risk of developing severe hyperbilirubinaemia (defined as serum bilirubin levels ≥ 427 micromol/litre) in babies who had serum bilirubin levels close to the American Academy of Pediatrics (AAP) phototherapy threshold levels.[19] The cohort included 285 295 babies with gestational age ≥ 34 weeks and birthweight ≥ 2000 g born between 1995 and 2004 in a health maintenance organisation. Babies with resolving jaundice, those whose serum bilirubin levels were not fully documented, and those with conjugated bilirubin level ≥ 34 micromol/litre were excluded. A subset of babies (n = 13 843) with a serum bilirubin level between 291 and 392 micromol/litre at ≥ 48 hours of age was identified. Babies with serum bilirubin concentration ≥ 427 micromol/litre 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 direct antiglobulin test (DAT) 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, birthweight or duration of hospitalisation. 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/litre occurring during birth hospitalisation, serum bilirubin increase of ≥ 102 micromol/litre per day, and exclusive breastfeeding (after qualifying serum bilirubin levels) were statistically significantly associated with an increased risk of hyperbilirubinaemia ($P < 0.04$), while inpatient phototherapy was found to significantly reduce 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 38–39 weeks and adjusted OR 3.7, 95% CI 0.6 to 22.7 for 34–37 weeks compared with 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/litre per day (adjusted OR 2.5, 95% CI 1.2 to 5.5) and exclusive breastfeeding 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 qualifying 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 with pre-discharge serum bilirubin measurements plotted on the bilirubin nomogram. The study population included babies with birthweight ≥ 2000 g (if gestational age ≥ 36 weeks) and birthweight ≥ 2500 g (if gestational age ≥ 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 gestational age < 38 weeks and ≥ 40 weeks, large for gestational age, high pre-discharge serum bilirubin and higher birthweight; the maternal factors included maternal diabetes, breastfeeding 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, parity and caesarean section. All these factors were then analysed for the final risk factor model using step-wise logistic regression, except for pre-discharge serum bilirubin level/risk zone, which was analysed separately. Results from the regression analysis showed the following factors to be statistically significantly associated with hyperbilirubinaemia: gestational age < 38 weeks (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 birthweight (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 1177 babies (≥ 37 weeks of 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 1177) of babies developed hyperbilirubinaemia (defined as serum bilirubin level > 171 micromol/litre at day 2, > 239 micromol/litre at day 3, and > 291 micromol/litre at day 4–5. Using multiple logistic regression analysis, serum bilirubin level > 85 micromol/litre on day 1 had a statistically

significant association with hyperbilirubinaemia (adjusted OR 36.5, 95% CI 15.9 to 83.6) There was also a statistically significant association when analysed by 17 micromol/litre increments on day 1 (adjusted OR 3.1, 95% CI 2.4 to 4.1 per 17 micromol/litre). Change in bilirubin levels between day 1 and day 2 was also found to have a statistically significant association with hyperbilirubinaemia (adjusted OR 2.4, 95% CI 1.9 to 3.0 per 17 micromol/litre). 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 gestational age ≥ 36 weeks and birthweight ≥ 2000 g, or gestational age ≥ 35 weeks and birthweight ≥ 2500 g. About 7% of 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/litre of the hour-specific phototherapy treatment thresholds recommended by the AAP). Using univariate analysis, the factors that 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, gestational age < 38 weeks, mother's intention to breastfeed, either exclusively or combined with bottle-feeds, grade 4 or higher jaundice observed clinically as per the 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: gestational age < 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 1154 term babies (11.4%) who developed serum bilirubin levels ≥ 221 micromol/litre constituted the test group, while, from the remainder, every tenth admission with serum bilirubin levels < 221 micromol/litre was randomly selected to form the comparison group ($n = 1154$). Univariate analysis was done to compare the two groups and it showed high serum bilirubin levels to be statistically significantly associated with a number of maternal, baby and delivery variables. These variables were then included in a step-wise 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 > 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 3301 offspring of 1669 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/litre) was present in 4.5% of the babies (147 of 3301). Newborns who had one or more prior siblings with

hyperbilirubinaemia showed a three-fold higher risk of developing hyperbilirubinaemia compared with those who had prior sibling without hyperbilirubinaemia (10.3% versus 3.6%; OR 3.1, 95% CI 1.4 to 6.8). In the next stage of analysis, potential confounding factors (race, sex, gestational age, 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/litre), moderate (205–256 micromol/litre) and severe hyperbilirubinaemia (≥ 256 micromol/litre). 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 sibling with mild jaundice (25.3% versus 11.1%; OR 2.7, 95% CI 1.8 to 4.1), and the risk was four times greater for the moderate jaundice group (8.8% versus 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 with those who had no sibling with severe hyperbilirubinaemia (10.5% versus 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 readmitted for hyperbilirubinaemia (total serum bilirubin > 291 micromol/litre). 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 step-wise logistic regression analysis to determine the smallest subset of predictors of the difference between the groups. Three factors were identified: early gestation (for 35 to 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 1.91 to 115.38), exclusive breastfeeding (adjusted OR 10.75, 95% CI 2.37 to 48.82 and finally transcutaneous bilirubin levels 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 gestational age ≥ 35 weeks discharged from a well-baby nursery of a health maintenance organisation in the USA[18] was conducted to evaluate how closely mother's race documented in medical records correlated with self-reported race, and to analyse 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 organisation's database and maternal race was placed in one of seven 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 up to five responses for ancestry of each) was elicited through a computerised telephone survey. Of the 3021 mothers available for potential inclusion, only 41% could be contacted and, of them, 69% (866 of 1248) completed the survey. Of these, 145 mothers were documented as white in the medical records, but only 64% of them 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 as being of multiracial (two or more 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 being of two or more races, the primary race matched that of the parents in 41% of cases only. In 23% of babies, the primary race was assigned to the mother's race and in 25% to the 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]

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 clinically apparent jaundice and intention to breastfeed exclusively. Five studies evaluated family history of jaundice as a risk factor and four found it to be statistically significantly associated with hyperbilirubinaemia. Bruising was reported as a statistically significant risk factor in only two studies. Results from most studies show no statistically significant association between cephalohaematoma, vacuum delivery, male sex or race and hyperbilirubinaemia.

GDG translation from evidence

Factors significantly associated with hyperbilirubinaemia are gestational age < 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/CG37).

The GDG has used the term 'intention to breastfeed exclusively' in a practical sense because most babies are discharged home before breastfeeding has been fully established. At this time the only risk factor that can be identified is the intention to breastfeed exclusively as opposed to 'breastfeeding exclusively'. 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 while 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 is being treated for jaundice. The GDG has recommended that adequate lactation/feeding support be provided, including support for expressing breast milk if the baby requires treatment. The GDG feels that this support would be augmented if more were known about factors underlying the association between breastfeeding and jaundice, and to this end has made a research recommendation on this topic.

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

Recommendations – 3.1 Factors that influence hyperbilirubinaemia

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

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

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.

Research recommendations

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 significant 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 develop significant hyperbilirubinaemia will be compared with infants with significant hyperbilirubinaemia. Outcome: Factors to be analysed include I) maternal factors, II) neonatal factors, III) blood analyses. Time stamp: Sept 2009

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 significant hyperbilirubinaemia is effective at preventing later significant hyperbilirubinaemia.Population: Babies in the first 28 days of life. Subgroups should include near-term babies 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) Significant hyperbilirubinaemia, 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[20-22] were identified that examined the association between risk factors and the development of kernicterus: two comparative studies[21;22] [EL II] and one descriptive study.[20] [EL III]

For adverse sequelae, two studies[23;24] [EL II] looked at the association between hyperbilirubinaemia and neurodevelopmental outcomes (one in term babies[23] and the other in extremely low birthweight babies[24]) and one study[25] [EL II] evaluated risk factors for hearing loss.

Review findings

A prospective study conducted over a 1 year period in a tertiary referral neonatal unit in India[22] 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/litre, 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/litre. There were 64 babies eligible for the study, of whom 14 (21.9%) had kernicterus. In all cases, stage II encephalopathy was reported: all the babies with kernicterus had stage II bilirubin encephalopathy characterised by presence of opisthotonos, rigidity and paralysis of upward gaze. There was no statistically significant difference between affected and unaffected babies in gender, mean gestational age, mean birthweight, proportion exclusively breastfed and postnatal weight. Mean peak serum bilirubin levels, free bilirubin levels, bilirubin/albumin ratio and free fatty acid levels were statistically 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 statistically 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, birthweight, 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 gestational age of 31 weeks for both the groups, while birthweight ranged between 750 and 5000 g (mean 1800 g). 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 that was statistically significant. [EL II]

A retrospective study from the USA[20] compared clinical and demographic histories of late preterm babies who suffered kernicterus with 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 birthweight of the study population was 3281 g and the mean gestational age was 38 weeks. Mortality among cases was 4.8%. The total serum bilirubin levels, age at re-hospitalisation, and birthweight 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% versus 25%; $P < 0.05$). Similarly, severe post-icteric sequelae occurred in 83% of the late preterm babies compared with 71% in the term babies. The percentage of large for gestational age babies among the late preterm group who developed kernicterus was statistically significantly higher compared with that in the term group (34.9% versus 24.7%; $P < 0.01$). [EL III]

A multicentre 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 birthweight $\geq$ 2500 g 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 $\geq$ 342 micromol/litre 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 ($\geq$ 342 micromol/litre) compared with those with lower serum bilirubin levels, but the difference was statistically not significant (4.5% versus 3.8%; RR 1.2, 95% CI 0.7 to 2.1). However, it was observed that there was a statistically 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 statistically significant when serum bilirubin levels were analysed 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[25] evaluated the risk factors associated with hearing loss in term babies with serum bilirubin levels $>$ 339 micromol/litre. 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/litre); hearing loss was detected in 22% of the babies. Although there was a higher percentage of babies with hearing loss among those with hyperbilirubinaemia compared with babies with serum bilirubin levels below 40 micromol/litre, the difference was not statistically significant (33% versus 16%; $P = 0.11$). After controlling for various confounding factors in a logistic regression analysis, variables statistically significantly associated with hearing loss were jaundice that required exchange transfusion and an earlier onset of hyperbilirubinaemia. [EL II]

Another retrospective multicentre study from the USA[24] assessed the association between peak serum bilirubin levels and neurodevelopmental outcomes in extremely low birthweight babies (birthweight range 401–1000 g) 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 18–22 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, hearing impairment (needing hearing aids), and a composite category designated as neurodevelopmental impairment (NDI). Of 3167 babies eligible for the study, 2575 (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, statistically 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 statistically significant association between peak serum bilirubin levels and cerebral palsy, MDI < 70 or NDI in extremely low birthweight 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 statistically significant risk factors for kernicterus in term babies. A poor-quality retrospective study found no statistically 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 with term babies, but the difference was not statistically significant.

Three studies evaluated the association of high serum bilirubin levels (> 340 micromol/litre) with adverse sequelae: two studies were in term babies and one in babies with birthweight less than 1000 g. One study in term babies found no statistically 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 statistically 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 1000 g.

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 (criterion was bilirubin > 340 micromol/litre) and early onset of jaundice (within 24 hours) are statistically significant risk factors for hearing loss. Deafness is a clinical manifestation of kernicterus. Haemolytic disorders such as G6PD 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 on formal assessment). A study of low-

birthweight babies found a weak association between high serum bilirubin levels (> 340 micromol/litre) 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 recommendation for surveys of severe hyperbilirubinaemia and kernicterus which would lead to better understanding of the risk factors for kernicterus.

Recommendation – 3.2 Risk factors for kernicterus/or adverse sequelae

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

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

Research recommendation

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/litre which is the threshold for an exchange transfusion recommended by NICE. Exposure: All maternal, prenatal, 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 Comparative studies evaluating risk factors for hyperbilirubinaemia

Study details	Study population	Risk factor									
		Family history of jaundice	GA < 38 weeks or early gestation	Sex	Race	Exclusive breastfeeding	Early clinical jaundice	Severity of jaundice	Bruising or cephalo-haematoma	Delivery characteristics	Maternal characteristics
Newman *et al.* (2000)[9] [EL II]	BW ≥ 2000 g 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 (2.8–19.0)		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)[10] [EL II]	BW ≥ 2000 g and GA ≥ 36 weeks						RR 2.9 (1.6–5.2)				
Kuzniewicz *et al.* (2008)[11] [EL II]	GA ≥ 34 weeks and BW ≥ 2000 g with serum bilirubin levels of 291–392 micromol/litre at ≥ 48 hours of age	OR 3.8 (0.9–15.7) NS	For 34–37 weeks: OR 3.7 (0.6–22.7) For 38–39 weeks: OR 3.1 (1.2–8.0) 40 weeks 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 micr omol/litre per 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 g if GA ≥ 36 weeks, and BW ≥ 2500 g if GA ≥ 35 weeks		GA < 38 weeks: OR 2.6 (1.5–4.5)	Male sex: NS	Asian, Hispanic, black: NS	OR 2.6 (1.5–4.5	Analysed separately as pre-discharge risk zones	Analysed 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, hypertension, diabetes: NS
Seidman *et al.* (1999)[13] [EL II]	Healthy term babies (GA ≥ 37 weeks)	Jaundice in sibling: NS		Male sex: NS	Jewish ethnicities: NS	Full breastfeeding: NS	Day 1 serum bilirubin level > 85 micromo l/litre: OR 36.5 (15.9–83.6)	Change in serum bilirubin from day 1 to day 2 per 17 micromol /litre: 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 weeks and BW ≥ 2000 g, or GA ≥ 35 weeks and BW ≥ 2500 g		GA < 38 weeks: 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 breastfeeding: OR 3.7 (1.1–13)	Analysed 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

Study details	Study population	Risk factor									
		Family history of jaundice	GA < 38 weeks or early gestation	Sex	Race	Exclusive breastfeeding	Early clinical jaundice	Severity of jaundice	Bruising or cephalo-haematoma	Delivery characteristics	Maternal characteristics
Gale *et al.* (1990)[15] [EL II]	Term singleton babies (GA ≥ 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)
Khoury *et al.* (1988)[16] [EL II]	Both term and preterm babies	Risk of recurrence in siblings depending on degree of jaundice (in micromol/litre): 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] [EL II]	Both term and preterm babies		For 35 to 36 6/7 weeks: OR 20.79 (2.34–184.74) For 37 to 37 6/7 weeks: OR 14.86 (1.91–115.38) 40 to 40 6/7 weeks as reference			OR 10.75 (2.37–48.82)					

BW = birthweight; CI = confidence interval; EL = evidence level; GA = gestational age; NS = not statistically significant; OR = odds ratio; RR = risk ratio.
Results from multivariate analysis are reported as an OR with a 95% CI.

4 Early prediction of serious hyperbilirubinaemia

Introduction

This chapter builds on the work that has been done in recognition and risk factor assessment for neonatal hyperbilirubinaemia. A tool or test that 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 that 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 questions

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

i) umbilical cord blood bilirubin levels
ii) timed serum bilirubin levels
iii) transcutaneous bilirubin levels
iv) end-tidal CO levels nomograms
v) risk assessment
vi) Coombs' test

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

Since the tests routinely used for recognising/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:

1. the diagnostic accuracy of tests in recognising jaundice
2. the prediction of hyperbilirubinaemia at a later age.

Primary screening of 2840 titles and abstracts from the database led to the retrieval of 148 papers.

Altogether, 22 studies[9;12-14;26;26-42] were selected for inclusion in this prediction chapter. Four studies each were included for evaluating the predictive accuracy of umbilical cord blood bilirubin levels[26;29-31] and serum bilirubin levels measured within the first 24 hours of age,[13;26-28] respectively. End-tidal carbon monoxide (CO) levels were assessed in two studies[32;33] with different population characteristics and threshold values. Eight studies were 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 five studies.[38-42] Furthermore, two or more strategies were compared in three of these studies.

Regarding the effectiveness of these tests, nine studies[43-51] have been included: four evaluated transcutaneous bilirubin measurement,[43-46] two[47;48] evaluated pre-discharge bilirubin estimation and three[49-51] evaluated DAT. No studies were identified that evaluated the effectiveness of clinical assessment, risk index scoring, umbilical cord blood bilirubin or corrected end-tidal carbon monoxide (ETCOc) measurement.

4.1 Tests that predict hyperbilirubinaemia

Serum bilirubin levels in the first 24 hours of life (serum bilirubin–day 1)

Description of included studies

One EL Ib study[27] and three EL II studies[13;26;28] have been included. They were conducted in Spain,[26] India,[27] Turkey[28] and Israel.[13] The study population in three studies[13;26;28] included healthy term babies (≥ 37 weeks) and serum bilirubin was measured within 24 hours of birth. The Indian study[27] included healthy babies with gestational age > 35 weeks and serum bilirubin was measured at 24 ± 6 hours of age. In three studies,[26-28] the ability of serum bilirubin–day 1 (threshold value ≥ 102 micromol/litre) to predict hyperbilirubinaemia (defined as serum bilirubin ≥ 290 micromol/litre on day 3–5) was calculated, and results from these studies were pooled to obtain the summary results. Since the Spanish study[26] was conducted in two phases, data have been given separately for both phases. The fourth study,[13] 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[26-28] used in the meta-analysis, hyperbilirubinaemia was defined as serum bilirubin levels ≥ 290 micromol/litre 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 (Figure 4.1). 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% (Figure 4.2).

The study[13] from Israel showed serum bilirubin value > 85 micromol/litre 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/litre on day 1 to the model with all other variables increased the sensitivity to 82% but the specificity decreased to 80%.

Evidence summary

Evidence from one EL 1b[27] and two EL II studies[26;28] indicates that serum bilirubin ≥ 102 micromol/litre on day 1 is a sensitive predictor of later hyperbilirubinaemia. In another study,[13] combining serum bilirubin > 85 micromol/litre 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/litre in the first 24 hours of life is predictive of serum bilirubin > 290 micromol/litre between days 3 and 5. This supports the evidence reviewed in Chapter 3 on risk factors, that visible jaundice in the first 24 hours is a risk factor for later significant hyperbilirubinaemia and underlies the recommendation in Table 7.1. In babies with light skin tones, jaundice is usually visible at levels of bilirubin > 90 micromol/litre.[52] 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 or suspected jaundice in the first 24 hours requires urgent medical review (within 2 hours), which must include serum bilirubin measurement and an investigation of the underlying causes (see Chapter 6 on formal assessment).

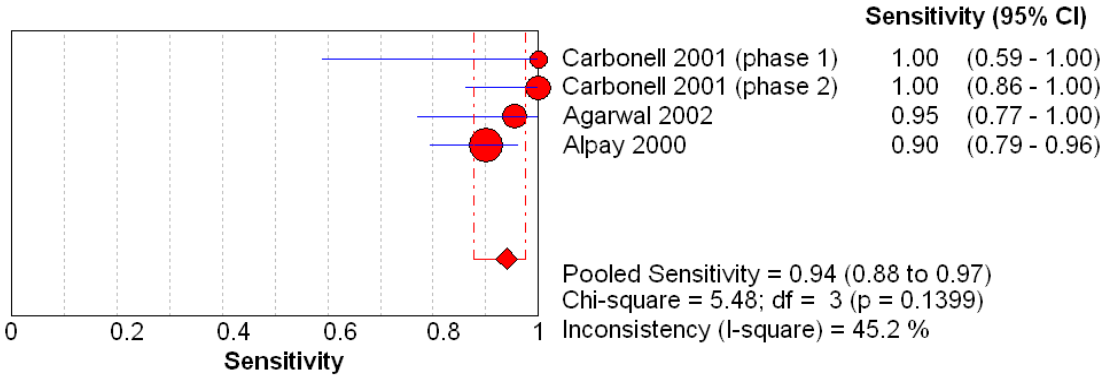


Figure 4.1 Pooled sensitivity of serum bilirubin levels in the first 24 hours of life in predicting later hyperbilirubinaemia

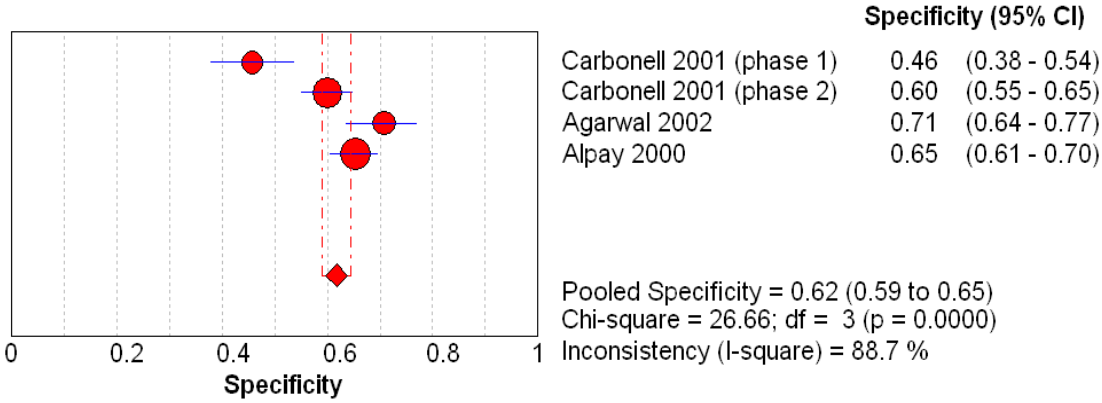


Figure 4.2 Pooled specificity of serum bilirubin levels in the first 24 hours of life in predicting later hyperbilirubinaemia

Serum bilirubin levels should be measured every 6 hours in babies with visible or suspected jaundice whether in treatment or not (see also GDG translation for Section 7.1.1). These measurements should continue until the serum bilirubin level is stable and/or falling and is also below the treatment thresholds in table 1 and treatment threshold graphs (1.5)

Recommendations

See the end of Section 4.1.

Effectiveness of transcutaneous bilirubin measurement

Description of included studies

Four studies[43-46] have been included in this section. One retrospective study[43] 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[44-46] evaluated the impact of transcutaneous bilirubin measurement on the need for blood sampling. These three studies are described in detail in Chapter 5 on recognition of jaundice.

Review findings

A retrospective cohort study from the USA[43] 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, 6603 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 exchange transfusion. The two groups were similar with regard to gender and ethnicity. There was no statistically significant difference in terms of total monthly births or the number of readmissions for hyperbilirubinaemia within 7 days of discharge. No statistically significant change was observed in the proportion of newborns tested by serum bilirubin (31.8% versus 36.7%; $P = 0.21$) or in the mean number of laboratory measurements per baby (1.51 versus 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 statistically significant increase in the total number of bilirubin measurements (transcutaneous bilirubin and serum bilirubin) per baby (mean before transcutaneous bilirubin 0.37, mean after transcutaneous bilirubin 0.61; $P = 0.007$). The mean number of readmissions for hyperbilirubinaemia decreased statistically 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 a 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,[45] the BiliChek was evaluated both in sick babies in the neonatal intensive care unit (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 retrospective 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,[44] a reduction of 55% in blood sampling was reported if serum bilirubin testing was limited to babies with transcutaneous bilirubin levels > 195 micromol/litre only. The third study evaluated the Minolta JM-102 in 285 healthy babies > 34 weeks of gestation in a UK setting.[46] In this study a reading of > 18 reflectance units was taken as an indicator for serum bilirubin, resulting in a reduction of 34% in the number of blood samples taken.

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, although 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.

Recommendations

See the end of Section 4.1.

Pre-discharge risk assessment

Description of included studies

Seven studies have been included in this section, six from the USA[9;12;14;34-36] and one from Italy.[37] Four cohort studies[14;34;36;37] were conducted prospectively and two retrospectively,[12;35] while one study was a nested case–control study.[9] Apart from one study[36] 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. Two studies[34;37] evaluated the predictive accuracy of pre-discharge serum bilirubin plotted on an hour-specific nomogram, while one study[36] assessed pre-discharge transcutaneous bilirubin measurements using BiliChek. Clinical risk factors were evaluated in four studies,[9;12;14;35] either alone or in combination with pre-discharge bilirubin measurement. In one nested case–control study,[9] a risk index model was assessed; in two retrospective cohort studies[12;35] 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 was assessed.

Review findings

The first study, conducted in the USA,[34] 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 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 those 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 2840 eligible babies (recorded in epochs of 4 hours for the first 48 hours of age, 12 hours for 48–96 hours of age, and 24 hours 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 the 75th and 95th centile), low intermediate risk (between the 75th and 40th centile) and low risk (below the 40th centile). The nomogram was used as the reference standard to determine the ability of pre-discharge serum bilirubin (measured between 18 and 72 hours of age) to predict subsequent severe hyperbilirubinaemia, which was defined as serum bilirubin level in the high-risk zone (≥ 95th centile). For 8.1% (230 of 2840 babies), serum bilirubin fell within this zone at some time. In 58 babies (2.0%), this occurred after discharge. Among 172 of 2840 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% of 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 appropriate for gestational age babies without 'asphyxia' and without Rhesus or ABO incompatibility were included. Serum bilirubin curves for babies with levels > 12 mg/dl (205 micromol/litre) and those with serum bilirubin > 15 mg/dl (255 micromol/litre) 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 was '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, $n = 1244$; Hospital B, $n = 498$). The study population included term babies who had serum bilirubin measured between 30 and 72 hours because of clinical jaundice. Most of the babies had a single serum bilirubin measurement, but 514 of 1244 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,[36] compared transcutaneous bilirubin measurement with serum bilirubin for prediction of hyperbilirubinaemia in a multiracial population. The study population comprised 490 healthy babies with gestational age ≥ 36 weeks and birthweight ≥ 2000 g, or gestational age ≥ 35 weeks and birthweight ≥ 2500 g, 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 high-performance liquid chromatography (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.*[34] Hyperbilirubinaemia was defined as serum bilirubin levels ≥ 95th centile on the nomogram (i.e. in the high-risk zone). Altogether, 30 of 490 (6.1%) babies had HPLC serum bilirubin values > 95th centile and only 1.1% had serum bilirubin levels > 255 micromol/litre. The correlation between transcutaneous bilirubin and serum bilirubin values was linear and statistically significant ($r = 0.91$; $P < 0.001$), and the values for correlation coefficient were similar when the data were categorised by race. The mean difference between paired serum bilirubin and transcutaneous bilirubin values was 8 micromol/litre (95% CI −38.9 to 54.9 micromol/litre). For predicting hyperbilirubinaemia, pre-discharge transcutaneous bilirubin > 75th centile showed a sensitivity of 100%, a 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 organisation in the USA[9] to investigate predictors of hyperbilirubinaemia and evaluate the predictive accuracy of a risk index model. This study has been described in Chapter 3 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 gestational age, early jaundice, cephalohaematoma, bruising, breastfeeding 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), gestational age per week (OR 0.6, 95% CI 0.4–0.7), breastfeeding 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 years (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 statistically 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) that were found to be statistically 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/litre 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,[35] 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 hours for predicting subsequent hyperbilirubinaemia. To validate the risk index score in predicting serum bilirubin ≥ 427 micromol/litre, 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 study.[9] 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/litre) 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 5706 babies born in the same setting over a period of 4 years and who had serum bilirubin measured at < 48 hours of age were reviewed retrospectively. A partial clinical risk index was derived by deleting family history of jaundice, breastfeeding and bruising, and by substituting scalp injury with cephalohaematoma. The serum bilirubin levels measured at < 48 hours 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/litre. 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 versus 0.69). Within each percentile category there was a five- to fifteen-fold increase in the risk of hyperbilirubinaemia for those with a risk index score > 10 compared with 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;14] 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 in Chapter 3 on risk factors. The population was the same as that used in a previous study[36] 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 birthweight, gestational age < 38 weeks, 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 Chapter 3 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/litre, 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 five other factors: gestational age, 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% of babies developed hyperbilirubinaemia, (bilirubin levels on day 3–5 exceeding or within 17 micromol/litre 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 versus 0.91). After combining clinical risk factors with pre-discharge bilirubin risk zone assignment, the only factors that remained statistically significant were gestational age and percentage weight loss per day. This combination model showed improved predictive accuracy (*c*-statistic 0.96) when compared with 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 pre-discharge 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.*, but the universal application of hour-specific bilirubin estimation could not be relied on as data were

lacking for babies in the 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 on 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 Section 5.1) and deciding on management options (see Section 7.1.1).

Recommendations

See the end of Section 4.1.

Effectiveness of a pre-discharge bilirubin screening programme

Description of included studies

Two studies[47;48] from the USA have been included in this section. The first study[47] 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 programme. The second study[48] was a retrospective cohort study that assessed the effectiveness of a universal pre-discharge bilirubin screening programme on the number of readmissions and incidence of hyperbilirubinaemia.

Review findings

An observational study was conducted in a large urban hospital in the USA[47] 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 1 January 1990 to 31 December 2000 who were discharged from the well-baby nursery of the hospital. Low-birthweight 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 birthweight 3318 ± 457 g and mean gestational age 38.7 ± 1.3 weeks. The approaches implemented in chronological order were:

1. selective pre-discharge serum bilirubin measurements (1990–92)
2. 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)
3. universal serum bilirubin screening along with post-discharge follow-up based on the serum bilirubin position on the hour-specific nomogram[34] (1996–98)
4. comprehensive, systems-based management of newborn jaundice (1999–2000).

The impact of the complete approach 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% of 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.[19] 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 in 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 2001–2003. During 1990–2000, the incidence of exchange transfusion following the failure of intensive

phototherapy was 1 in 1827, and it declined to 1 in 11 995 during 2001–2003. A similar reduction in readmission rates for intensive phototherapy was reported: from 14 per 1000 babies discharged in 1994 to 5.5 per 1000 in 2001–2003. No babies developed serum bilirubin levels ≥ 513 micromol/litre during the study period, while the frequency of reported serum bilirubin levels ≥ 427 micromol/litre was 1 in 15 000 compared with the reported incidence of 1 in 625 in previous studies.[9] [EL III]

Another historical cohort study from the USA[48] evaluated the effectiveness of a bilirubin screening programme in a private healthcare organisation involving 18 hospitals. The programme, 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 healthcare provider and the baby managed according to his/her discretion. All babies born at gestational age ≥ 35 weeks were enrolled in the study. Those born after the initiation of the programme (1 January 2003 to 31 December 2004) formed the cohort group (n = 52 483), while those born before the programme started (1 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 programme 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 programme. The proportion of babies with serum bilirubin levels ≥ 342 micromol/litre declined from 1 in 77 to 1 in 142 ($P < 0.0001$), while the proportion with serum bilirubin levels ≥ 427 micromol/litre) declined from 1 in 1522 to 1 in 4037 ($P < 0.005$). The incidence of hospital readmission for hyperbilirubinaemia also fell significantly, from 5.5 per 1000 before the programme to 4.3 per 1000 babies after its introduction ($P < 0.005$). The authors concluded that a universal screening programme 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 EL III and EL II 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/litre.

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 readmission, exchange transfusions and bilirubin encephalopathy means that it is not possible to make a recommendation on the role of universal pre-discharge bilirubin testing in the UK but a research recommendation has been made on this topic.

Recommendations – 4.1 Tests that should be used to predict significant hyperbilirubinaemia

Measure and record the serum bilirubin level urgently (within 2 hours) in all babies with suspected or obvious jaundice in the first 24 hours of life.

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

- below the treatment threshold
- stable and/or falling.

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

Interpret bilirubin levels according to the baby's postnatal age in hours and manage hyperbilirubinaemia according to threshold table (Section 1.3) and treatment threshold graphs (Section 1.6).

Do not measure bilirubin levels routinely in babies who are not visibly jaundiced.

Research recommendation

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

Why this is important

Evidence: The accuracy of transcutaneous bilirubinometers (Minolta JM-103 and BiliChek) has been adequately demonstrated in term babies below treatment levels (bilirubin < 250 micromol/litre). New research is needed to evaluate the accuracy of different transcutaneous bilirubinometers in comparison to serum bilirubin levels in all babies. Population: Babies in the first 28 days of life. Subgroups to include preterm babies, babies with dark skin tones, babies with high levels of bilirubin and babies after phototherapy. Exposure: Bilirubin levels taken from different transcutaneous bilirubinometers. 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 test and cost effectiveness. Time stamp: Sept 2009

4.2 Tests that do not predict hyperbilirubinaemia

Umbilical cord blood bilirubin

Description of included studies

Four studies of EL II conducted in various countries (Germany,[30] India,[31] Denmark[29] and Spain[26]) have been included. The study population was made up of healthy term babies in three studies,[26;29;31] while in the German study[30] the population included healthy term babies who were appropriate for gestational age, healthy term babies who were small for gestational age and healthy preterm babies (gestational age > 34 weeks). Data from this study[30] were extracted and analysed separated for both appropriate for gestational age and small for gestational age. In three studies cord blood bilirubin 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 three studies[26;30;31] that had defined hyperbilirubinaemia as serum bilirubin levels ≥ 290 micromol/litre. The threshold values of cord blood bilirubin in these studies were ≥ 30, > 34 and ≥ 37 micromol/litre, respectively. In the Danish study,[29] the ability of cord blood bilirubin at levels ≥ 35 micromol/litre (best cut-off value derived from the ROC curve) to

predict serum bilirubin levels ≥ 200 micromol/litre was calculated. Blinding of the outcome assessors was not specified in three studies.

Review findings

The prevalence of hyperbilirubinaemia (serum bilirubin ≥ 290 micromol/litre) 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/litre. The sensitivity of cord blood bilirubin to predict serum bilirubin levels ≥ 290–300 micromol/litre 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 with I^2 at 99.3% and 90.5%, respectively(Figures 4.3 and 4.4). The Danish study[29] showed that cord blood bilirubin levels with threshold value ≥ 35 micromol/litre had a sensitivity of 71% and specificity of 68% in predicting serum bilirubin ≥ 200 micromol/litre. [EL II]

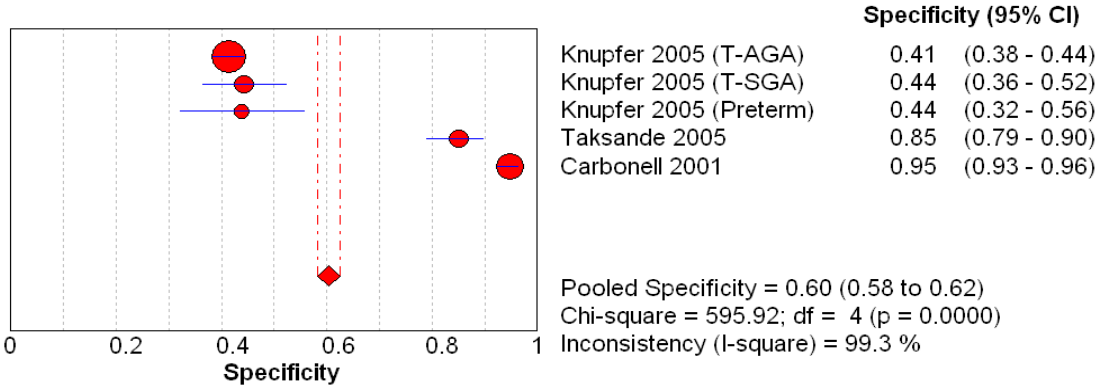


Figure 4.3 Pooled specificity of umbilical cord blood bilirubin in predicting later hyperbilirubinaemia

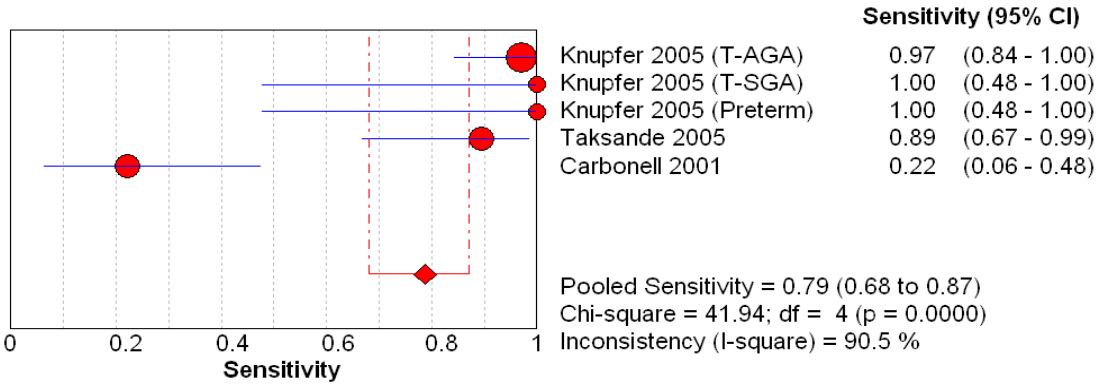


Figure 4.4 Pooled sensitivity of umbilical cord blood bilirubin in predicting later hyperbilirubinaemia

Evidence summary

Results from three EL II studies indicate great variation in the ability of cord blood bilirubin 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. The remaining study had a sensitivity of 71% and specificity of 68% in predicting serum bilirubin ≥ 200 micromol/litre.

GDG translation from evidence

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

Recommendations

See the end of Section 4.2.

End-tidal carbon monoxide measurement (ETCOc)

Description of included studies

Two studies[32;33] with EL II have been included in this section. The first study[32] had a large sample size of both term and near-term babies while the second, smaller, study[33] 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[32] carried out at nine sites (four in the USA, two in China, two in Israel and one in Japan). All newborn babies with gestational age ≥ 35 weeks were enrolled in the first 36 hours of life. Of the 1895 babies enrolled, 1370 (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 analyser 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 *et al.*[34] and adopted by the AAP.[19] 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 1370) of babies had serum bilirubin levels ≥ 95th centile at 30 ± 6 hours or at 96 ± 12 hours. The mean ETCOc levels in this group were statistically 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,[33] 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. An ROC curve was developed to evaluate the accuracy of ETCOc at different ages in predicting hyperbilirubinaemia, which was defined as serum bilirubin ≥ 257 micromol/litre. Hyperbilirubinaemia occurred in seven babies, while 44 babies had serum bilirubin levels < 257 micromol/litre. There were no statistically significant differences between the hyperbilirubinaemic and non-hyperbilirubinaemic babies in terms of sex, gestational age, mode of delivery, Apgar score at 1 minute, age at peak transcutaneous bilirubin, or 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 various times and their accuracy evaluated with various 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 from evidence

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

Recommendations

See the end of Section 4.2.

Umbilical cord direct antiglobulin (Coombs') test (DAT)

Description of included studies

One study[41] with EL II and four EL III studies[38-40;42] from the USA[41;42], Norway,[38] Taiwan[40] and Turkey[39] examining the predictive ability of the DAT have been included but no meta-analysis was possible as the studies used different criteria for defining hyperbilirubinaemia.

Review findings

In the first study, from the USA,[41] universal DAT was evaluated with reference to ETCOc, and its accuracy in predicting hyperbilirubinaemia was then assessed. The study population included 660 babies (mean gestational age 38.9 ± 1.4 weeks, mean birthweight 3267 ± 480 g) 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 hours and again at 24 ± 6 hours. 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 microlitre/litre) 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/litre). The accuracy of DAT in predicting hyperbilirubinaemia was evaluated and compared with that of high ETCOc levels. A positive DAT 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 compared with ETCOc was 98.2% and 97.9%, respectively. [EL II]

The second study, from the USA,[42] evaluated selective DAT and cord blood bilirubin measurement in predicting hyperbilirubinaemia. The study population included 91 ABO incompatible babies in a state-sponsored neonatal programme; Rhesus incompatible babies were excluded. Demographic information on gestational age, birthweight, gender and 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 cord blood bilirubin threshold for a positive test was a measurement > 68 micromol/litre. Babies with serum bilirubin levels > 273 micromol/litre between 12 and 36 hours were classed as severely hyperbilirubinaemic. Blinding of outcome assessors was not specified. DAT was

positive in 34.1% of babies (31 of 91). A positive DAT and the cord blood bilirubin threshold ≥ 68 micromol/litre both showed a sensitivity of 92.3% in predicting subsequent severe hyperbilirubinaemia. Specificities for both positive DAT and cord blood bilirubin tests were 75.6% and 100%, respectively. [EL III]

A Norwegian study[38] examined the ability of universal DAT testing to predict the need for phototherapy, using the Hillingdon Hospital bilirubin chart[53] to inform treatment. The study population included 2463 babies born in a general hospital. Exclusion criteria included high-risk deliveries and severe neonatal illness but no more details were given. Information on gestational age, birthweight, gender and ethnicity was not provided. Phototherapy was started in term babies at serum bilirubin > 350 micromol/litre at > 72 hours and > 250 micromol/litre at > 120 hours. Blinding of outcome assessors was not specified. DAT was positive in 4.1% of babies (100 of 2463). 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[40] evaluated selective DAT testing and cord blood bilirubin as predictors of hyperbilirubinaemia. The study population included 88 babies with birthweight > 2500 g born to group O, Rhesus-positive mothers; 53 babies were ABO incompatible. Information on ethnicity, gestational age and gender was not provided. Serum bilirubin levels were measured daily for 1 week. Hyperbilirubinaemia was defined as serum bilirubin > 255 micromol/litre within 96 hours of birth and/or early jaundice with serum bilirubin > 171 micromol/litre within 24 hours of birth. Blinding of outcome assessors was not specified. DAT was positive in 26% (14 of 53). The DAT test and the cord blood bilirubin threshold level > 68 micromol/litre showed sensitivity of 45% and 41% in predicting subsequent hyperbilirubinaemia. The specificity for the DAT and cord blood bilirubin tests was 96% and 100%, respectively. [EL III]

A Turkish study[39] examined selective DAT to predict serum bilirubin levels at 6, 30, 54, 78 and 102 hours. All babies > 38 weeks of gestation with blood groups A or B born to mothers with blood group O, without a simultaneous Rhesus blood factor incompatibility, were included ($n = 150$). The mean birthweight was 3212 ± 415 g 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/litre with an increase of 8.5 micromol/litre per hour in the first 24 hours, levels > 205 micromol/litre on day 2, > 255 micromol/litre on day 3, or > 289 micromol/litre 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 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 EL II study the DAT test showed a sensitivity of 8.5% and specificity of 97.6% in detecting haemolysis. Similar levels of sensitivity and specificity in predicting subsequent hyperbilirubinaemia were found in three of the other four EL III studies. Sensitivity ranged from 14.4% to 44.8% and specificity from 95.8% to 100%. The fourth EL III study showed a sensitivity of 92.3% and specificity of 75.6%.

GDG translation from evidence

Routine DAT (Coombs') testing on umbilical cord blood 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.[54] However, a strongly positive DAT, particularly in a baby 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 on formal assessment).

Recommendations

See the end of Section 4.2.

Effectiveness of DAT

Description of included studies

For the effectiveness analysis, two studies[50;51] comparing selective versus universal DAT and a third study[49] comparing readmission rates and phototherapy rates for tested and untested babies were included.

Review findings

A retrospective observational study from the USA[49] studied the effectiveness of DAT testing in a sample of births within a 1 year period (January to December 2000). Mean gestational age, mean birthweight and gender were not specified; 46% of babies studied were Asian and 36.8% were white. Cord blood DAT was performed on 2443 babies of mothers with blood group O or Rhesus negative while 2097 babies of mothers with groups A, B, AB or Rhesus 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 the 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 were 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 statistically significant (OR 1.17, 95% CI 0.65 to 2.13). [EL III]

A cohort study from a tertiary centre in the USA[51] compared universal with selective newborn cord blood testing. 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 Rhesus-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, 2253 of 4003 eligible babies (56.3%) were tested. Of the prospective cohort, 1048 of 4498 babies (23.3%) were tested selectively. Cord blood collection difficulties and specimen handling problems were given as reasons for the 1750 missing test results in the retrospective sample. Fifteen babies were readmitted 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[50] 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, Rhesus-positive mothers. Altogether, 301 babies with a mean gestational age of 39.4 weeks and mean birthweight of 3343.6 g were included; 50.5% were male, 44.5% were white and 16.3% were black. Of 113 babies tested, 29 (26%) were ABO incompatible and 14 (12%) were DAT positive. A total of 188 babies were not tested routinely. Of these, 34 (18%) 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% (27 of 301 babies). Phototherapy was used in four of 113 universally tested babies (3.5%) and eight 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% (two of 113) among universally tested babies and 0.5% (one of 188). Again, this difference was not statistically significant (OR 1.12, 95% CI 0.56 to 2.30). [EL III]

Evidence summary

Three EL III 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 statistically significant difference was found in the readmission rates or phototherapy rates between those undergoing universal testing and those

tested selectively. In the third 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. EL III 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.

Recommendation – 4.2 Tests that do not predict significant hyperbilirubinaemia

Do not use any of the following to predict significant hyperbilirubinaemia

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

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 have a serious, potentially lethal disease. In babies with liver disease, the degree of jaundice does not correlate with 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'[52] attempt to quantify this progression. This review of the evidence is a crucial part of the guideline, because if babies are not recognised to be jaundiced in the first place they cannot 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 predefined 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.

As in Chapter 4, the primary screening of 2840 titles and abstracts from the database led to the retrieval of 148 papers.

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/litre (1 mg/dl = 17.1 micromol/litre) 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 the Minolta JM-102 and JM-103 using the statistical programme Meta-DiSc (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 the area under the ROC curve (AROC) was calculated. In order to obtain 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

5.1.1 Examining the baby

Description of included studies

Seven studies[55-61] have been included in this section. Three studies[57;59;60] were carried out in the USA and two each in Israel[58;61] and Switzerland.[55;56] All the studies evaluated the correlation of clinical assessment of jaundice by experienced healthcare professionals, while one study[57] also evaluated parental assessment. Six studies[55-58;60;61] were conducted in a hospital setting and one[59] in a community setting. One study[61] was of EL I and the remaining six[55-60] were of EL II.

Review findings

In the first study, from Israel,[61] 1129 term and late preterm babies of Jewish (73%) and Arab (26%) ethnicity were clinically assessed for jaundice by experienced clinicians (five 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 that 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 al.*,[34] and the ability of BiliEye to detect significant hyperbilirubinaemia (defined as zones C and D on the nomogram) was analysed 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 and D on the nomogram) were clinically misclassified as being in the lower risk zones. Moreover, 8.1% (230 of 2857) 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 an 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 and D was 0.82. After adjusting for postpartum age and gestational age, 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 weeks gestational age (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 gestational age (AROC = 0.61). [EL I]

The second study was conducted in an urban public hospital in the USA.[60] The sample population comprised 122 healthy full0term babies with jaundice, with a Rhesus-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. Although there was good agreement between pairs of observers regarding the baby's skin tone ($\kappa = 0.56$), agreement for jaundice at each site was generally poor (only marginally better than chance), with the best agreement seen at the 'nipple line to umbilicus' site ($\kappa = 0.23$, 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 two groups of

observers; $P < 0.01$). The presence of visible jaundice between the 'nipple line and the umbilicus' (i.e. the lower chest) had the best diagnostic accuracy (among all the sites) for detecting serum bilirubin levels > 205 micromol/litre with a sensitivity of 97% but a specificity of 19% only. If visible jaundice was absent in the lower chest, it had an NPV of 94% in ruling out serum bilirubin levels above 205 micromol/litre. [EL II]

The third study was conducted in a community setting in the USA[59] 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 considered 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 three babies had serum bilirubin > 291 micromol/litre and nurses were able to predict the levels in two of them correctly. For detecting serum bilirubin > 205 micromol/litre, 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,[58] 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 (they were asked which newborns were clinically jaundiced and to decide on whether to draw blood) and their estimated serum bilirubin levels. Laboratory serum bilirubin levels were measured within 30 minutes. The physicians were unaware of the babies' 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,[57] 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/litre. There was poor agreement between physicians, nurses and parents about whether a baby was jaundiced ($\kappa = 0.48$ for all the three 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, respectively). 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[55;56] 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 and 37 weeks, of whom 87% were white. In both studies, babies with birthweight of at least 2000 g 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 the 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 analysing the linear correlation between the three tests and serum bilirubin levels, their diagnostic accuracy was evaluated by measuring the area under the ROC curve for serum bilirubin > 250 micromol/litre in term babies and serum bilirubin > 190 micromol/litre in preterm babies.

In term babies, transcutaneous bilirubin recordings using the Minolta JM-102 showed the best results in terms of linear correlation and diagnostic accuracy ($R^2 = 0.82$; $P < 0.01$ and AROC = 0.98). Clinical assessment showed variable results for the correlation coefficient among the white and non-white babies ($R^2 = 0.74$ by nurse and 0.70 by investigator for white babies, $R^2 = 0.71$ by nurse and 0.65 by investigator for non-white babies). The AROC 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/litre. The second study done on healthy preterm babies showed similar results: Minolta JM-102 showed the best performance with a AROC of 0.96 and squared correlation coefficient $R^2 = 0.76$ ($P < 0.001$). The BiliChek performed worse than the 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, respectively).

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 with babies with light skin tones and term babies. 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/litre, while the other study reported 76% sensitivity with 60% specificity. Results from the EL 1 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 (Table 5.1).

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, healthcare 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 assessment of all infants including examination of sclerae, 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.

Table 5.1 Negative predictive value (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 *et al.* (2008)[61]	Healthy full-term and late preterm babies with GA ≥ 35 weeks before discharge (*n* = 1129)	Mean: 62 ± 24 hours (median 55 hours; range 9–252 hours)	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 *et al.* (2000)[60]	Full-term healthy babies with BW > 2000 g and GA > 36 weeks (*n* = 122)	Mean age 2 days (range 8 hours to 7 days)	Presence of icterus in lower chest (nipple line to umbilicus)	Serum bilirubin levels > 205 micromol/litre	NPV: 94.3% (33/35) Negative LR: 0.15
Szabo *et al.* (2004)[56]	Healthy full-term babies with BW > 2000 g and no older than 6 days (*n* = 140) Excluded: jaundice within 36 hours	Data not given	Kramer zone 2 assessed by nurses (data not given for zone 0 or 1)	Serum bilirubin levels > 250 micromol/litre	NPV: 100%

BW = birthweight; GA = gestational age; LR = likelihood ratio; NPV = negative predictive value

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

Whenever parents or healthcare 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

See the end of Section 5.1.

5.1.2 Examining urine/stool

Description of included studies

One study[62] of EL III from the UK was identified.

Review findings

A single non-diagnostic study (project report) from the UK[62] 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 baby's stools during the first 28 days of age. The first phase recruited 109 parent–baby pairs and 5053 stool observations were 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 3629 mothers at the time of the 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 (fewer than three 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 although prolonged jaundice is common in breastfed 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. [EL III]

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 of EL III reported that although prolonged jaundice is common in breastfed 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 breastfed babies with prolonged jaundice pass stools and urine of normal colour. (See Section 6.2 for prolonged jaundice.)

Recommendations – 5.1 Visual/clinical examination

In all babies:

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

Parents, carers and healthcare professionals should all look for jaundice (visual inspection).

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.

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

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

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

5.2 Devices for measuring bilirubin

5.2.1 Icterometers

Description of included studies

Five studies[57;63-66] have been included – four in term babies[57;63;64;66] including two in dark-skinned babies,[63;64] and one in preterm babies.[65] The studies were carried out between 1974 and 1998 in the USA (two studies[57;65]), Rhodesia,[63] Tanzania[64] and Turkey.[66] The Ingram[63;66] and the Gosset[64;65] icterometers were used in two studies each while the fifth study[57] did not report the type of icterometer evaluated.

Review findings

The first study, conducted in a community setting in the USA,[57] has already been described in detail in Section 5.1.1 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/litre with a threshold reading ≥ 2.5. [EL II]

Another study, from Turkey,[66] 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 3380 ± 419 g. Within 30 minutes of blood sampling for serum bilirubin levels, and without 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. The 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/litre. 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. [EL II]

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 1676 g and the mean gestational age was 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[63;64] with EL III measured the correlation of icterometer readings with serum bilirubin values in black newborn babies. In the first study from Tanzania,[64] icterometer gradings were recorded in 70 babies (gestational age 30–42 weeks) with jaundice who were admitted to the neonatal unit. No exclusion criteria were 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,[63] investigated the usefulness of the icterometer as a screening test in 55 babies with jaundice. The birthweight of the study sample ranged from 1050 to 3925 g, 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 icterometers in term babies from two studies with EL II were variable. While one study reported a correlation of 0.48 with 75% sensitivity and 72% specificity in detecting serum bilirubin levels > 205 micromol/litre, the other study showed correlation of 0.78 and 100% sensitivity with 48% specificity in detecting high serum bilirubin levels (> 220 micromol/litre). 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 EL III 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.

Recommendations

See the end of Section 5.2.

5.2.2 Transcutaneous bilirubinometers

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.

Description of included studies – Minolta JM-102

Seven studies[26;46;66-70] are included in this section – one each from Denmark,[70] Turkey,[66] the UK,[46] Spain,[26] Saudi Arabia,[69] the USA[68] and Taiwan.[67] The sample populations comprised term babies in six studies,[26;66-70] while in the seventh study[46] both term and near-term babies > 34 weeks of gestational age were included. Five of the studies[26;46;66;68;69] are of EL II quality with blinding not reported in most while two[67;70] are EL III. Exclusion criteria were not defined in three studies.[26;68;70] 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 four studies gave sufficient data to be used for meta-analysis.

Review findings – Minolta JM-102

The sample size in the studies ranged from 76 to 2004. 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[26;46] for which detailed data were not available for meta-analysis, sensitivity and specificity were reported separately. One study[46] showed transcutaneous bilirubin (Minolta 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/litre, while the other study[26] reported 98% sensitivity and 72% specificity for detecting serum bilirubin levels > 222 micromol/litre.

Data from the other four studies[66-69] were pooled to examine the diagnostic accuracy of transcutaneous bilirubin readings (with various thresholds) with the Minolta JM-102 in detecting serum bilirubin levels > 220 micromol/litre 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 (I^2 = 78.5% and 92.8% for sensitivity and specificity, respectively) (Figures 5.1 and 5.2). In the summary ROC curve, AROC was 0.93 but a threshold effect could not be seen, indicating further evidence of heterogeneity among the included studies (Figure 5.3).

Evidence summary – Minolta JM-102

Results from EL II studies show great variation in the accuracy of transcutaneous bilirubin measurement using the Minolta JM-102 at the forehead. The correlation coefficient ranged from 0.76 to 0.93 in the included studies. Meta-analysis showed transcutaneous bilirubin readings at the forehead to have an AROC of 0.93 for the detection of serum bilirubin levels > 220 micromol/litre 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.

Study	Sen	[95% Conf. Interval]	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 χ^2 = 13.98 (d.f. = 3) P = 0.003
Inconsistency (I^2) = 78.5 %
No. studies = 4.

Figure 5.1 Summary sensitivity of JM-102 in predicting later hyperbilirubinaemia

Study	Spe	[95% Conf. Interval]	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 χ^2 = 41.74 (d.f. = 3) P = 0.000
Inconsistency (I^2) = 92.8 %
No. studies = 4.

Figure 5.2 Summary Specificity of JM-102 in predicting later hyperbilirubinaemia

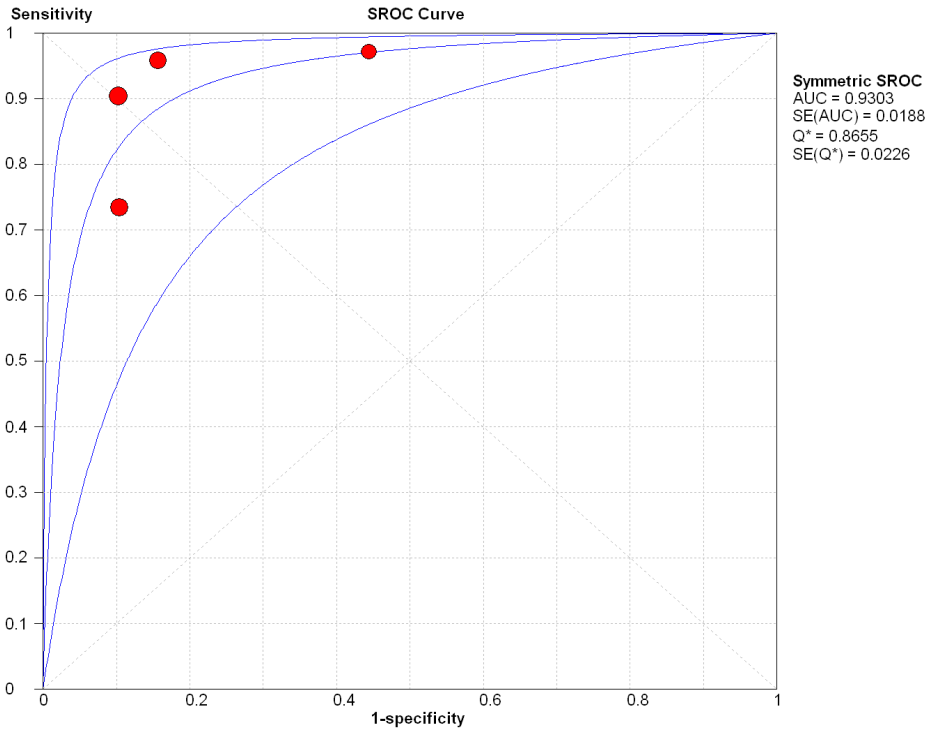


Figure 5.3 Summary ROC curve for JM-102 in predicting later hyperbilirubinaemia

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 and in those with yellow skin tones.

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

Recommendations

See the end of Section 5.2.

Description of included studies – Minolta JM-103

Of the six included studies in this section, three were conducted in the USA,[71-73] two in Thailand[74;75] and one in Taiwan.[76] The study population in one study from Thailand[75] and one[73] from the USA comprised healthy preterm babies with gestational age < 36 weeks, while all the other studies[71;72;74;76] 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,[71] while in two[72;73] it was predominantly Hispanic. No exclusion criteria were specified in two studies.[72;76]

Transcutaneous bilirubin was measured at the forehead in three studies[72;74;76] in term babies and in one study in preterm babies[75], while the sternum was used as the only site in two studies.[71;73] Detailed data for meta-analysis were available from three studies,[72;74;76] but they all reported different thresholds and thus a summary ROC was developed. All the studies are of EL II.

Review findings – Minolta JM-103

The sample size in the studies in term babies ranged from 90 to 849 babies, while there were 196 babies with mean birthweight of 1887 ± 344 g in one study[75] on preterm babies and in the other study[73] of preterm babies the birthweight ranged from 370 g to 2989 g. 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[71] from USAreported variable coefficients for different ethnicities: 0.95 for white babies, 0.82 for black babies and 0.92 for all other babies. This study[71] 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/litre in 17.4% of the black babies compared with 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,[74] 17[76] and 27[72] micromol/litre. This discrepancy did not increase with a rise in the serum bilirubin levels in two of the studies.[72;76] One study[75] 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[73] reported $r = 0.92$ for gestational age between 24 and 28 weeks, $r = 0.91$ for gestational age between 29 and 31 weeks and $r = 0.82$ between gestational age 32 and 34 weeks. This study[73] also noted that the JM-103 underestimated the serum bilirubin by 19 ± 32 micromol/litre in babies with gestational age between 24 and 28 weeks, by 14 ± 22 micromol/litre in babies with gestational age between 28 and 31 weeks and by 17 ± 27 micromol/litre in babies with gestational age between 32 and 34 weeks. Data from three studies[72;74;76] in term babies were pooled to calculate the predictive accuracy of the device in detecting serum bilirubin levels > 255 micromol/litre when transcutaneous bilirubin was measured from the forehead with threshold level > 200–204 micromol/litre. The pooled sensitivity and specificity were 85% (95% CI 78% to 91%) and 80% (95% CI 77% to 82%), respectively (Figures 5.4 and 5.5). There was strong evidence of statistical heterogeneity for both results ($I^2 = 55\%$ 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 (Figure 5.6).

Study	Sen	[95% Conf. Interval]	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 χ^2 = 4.44 (d.f. = 2) P = 0.109
Inconsistency (I^2) = 54.9 %
No. studies = 3.

Figure 5.4 Summary sensitivity of JM-103 in predicting later hyperbilirubinaemia

Study	Spe	[95% Conf. Interval]	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 χ^2 = 27.17 (d.f. = 2) P = 0.000
Inconsistency (I^2) = 92.6 %
No. studies = 3.

Figure 5.5 Summary specificity of JM-103 in predicting later hyperbilirubinaemia

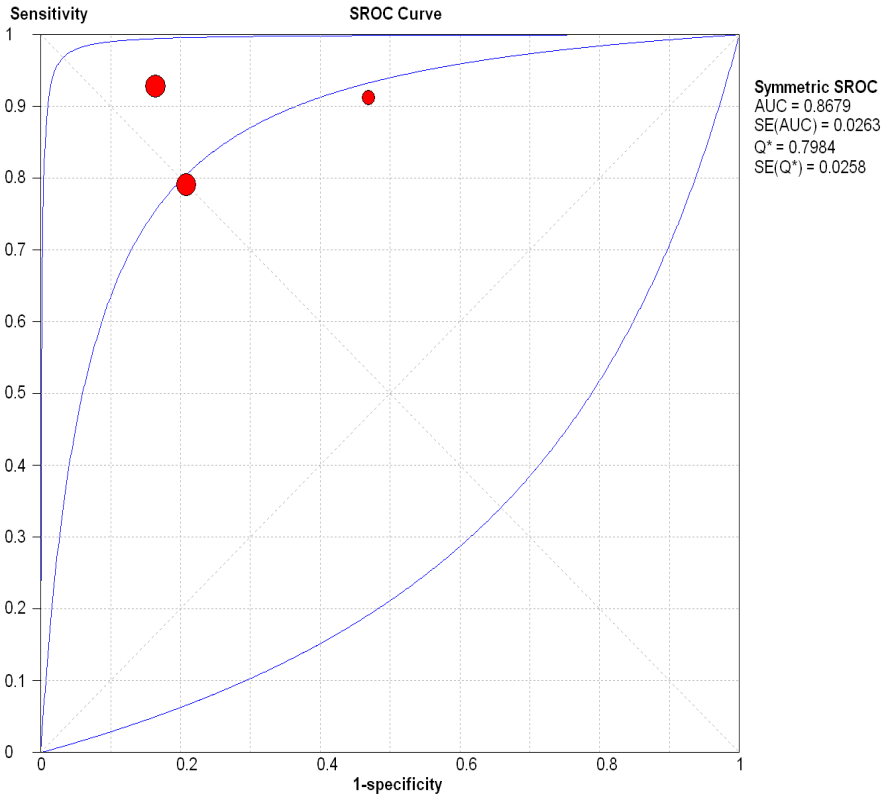


Figure 5.6 Summary ROC curve of JM-103 in predicting later hyperbilirubinaemia

Evidence summary – Minolta JM-103

The EL II evidence on diagnostic accuracy of the 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 that was much higher in babies with dark skin tones compared with 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%, respectively, 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/litre.

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/litre.

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 with those with light skin tones.

Recommendations

See the end of Section 5.2.

Description of included studies – BiliChek

Seven studies[44;45;77-81] have been included in this section – three[77-79] with EL Ib, two[44;80] with EL II and two[45;81] with EL III. The study population comprised term babies in one study,[78] term and preterm babies in five studies,[44;45;77;80;81] and preterm babies only in one study.[79] One study[80] 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 – BiliChek

The first study is a multicentre European study[77] conducted in six hospitals across five countries – the UK, France, Germany, Italy and Switzerland. A total of 210 term and preterm 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 sternum 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 statistically significant ($r = 0.93$; $P < 0.001$).

The difference between the mean serum bilirubin values and the mean transcutaneous bilirubin measurements was not statistically significant at either the forehead (MD = 2.4 micromol/litre, 95% CI −2.4 to 7.1 micromol/litre) or the sternum (MD = −14.8 micromol/litre, 95% CI −19.9 to 9.5 micromol/litre). An 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/litre, transcutaneous bilirubin had a sensitivity of 93% and specificity of 73% for detecting serum bilirubin > 222 micromol/litre. At a threshold of 240 micromol/litre, transcutaneous bilirubin had a sensitivity of 90% and specificity of 87% in detecting serum bilirubin levels > 290 micromol/litre. Transcutaneous bilirubin measurements showed similar diagnostic accuracy results (sensitivity and specificity) for detecting hyperbilirubinaemia (serum bilirubin values from HPCL-B method > 290 micromol/litre). [EL Ib]

In the second observational study, from Malaysia,[78] 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 sternum 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/litre) 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 statistically significant for forehead and sternum ($r = 0.80$ and 0.86, respectively; $P < 0.001$ for both). Minor variation was observed in correlation coefficients for the three ethnic groups, with the values ranging between 0.79 and 0.84 at the forehead and 0.86 and 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/litre) had a sensitivity of 100% and specificity of 39% for detecting serum bilirubin levels > 300 micromol/litre, while the values were 76% and 85% at a transcutaneous bilirubin threshold of 260 micromol/litre. For sternum transcutaneous bilirubin, the sensitivity and specificity at a threshold of 200 micromol/litre were 100% and 34%, respectively while at a threshold of 280 micromol/litre 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/litre, especially when transcutaneous bilirubin was measured from the forehead. Moreover, the areas under the curves for different serum bilirubin levels (≥ 250 micromol/litre, ≥ 280 micromol/litre and ≥ 300 micromol/litre) were slightly but consistently larger for the sternum readings compared with the forehead readings. [EL Ib]

In a Danish study,[45] 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 with gestational age < 35 weeks and sick term and near-term babies in the NICU formed Group 1 ($n = 261$, with mean birthweight 2521 g) while Group 2 was made up of healthy term and near-term babies with gestational age ≥ 35 weeks in the maternity ward ($n = 227$, with mean birthweight 3362 g). 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 0.67 for the foot. Based on these results, the forehead was recommended as the preferred site for transcutaneous bilirubin measurement. Although exact data were not given for Bland–Altman analysis, figures from both groups showed that transcutaneous bilirubin from the forehead underestimated 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 (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/litre or 10% of bodyweight in grams for ill babies and 50 micromol/litre 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 III]

The fourth study was conducted in the UK[44] 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/litre. Significant correlation was seen between serum bilirubin levels and transcutaneous bilirubin readings ($r = 0.77$; $P < 0.001$). Although the BiliChek underestimated serum bilirubin levels by a small value (mean difference −10.6 micromol/litre), the confidence intervals of the difference were wide, ranging from −80 to +60 micromol/litre. This discrepancy was not found to increase with rises in bilirubin levels. With a threshold value of > 195 micromol/litre, transcutaneous bilirubin measurements using BiliChek could detect serum bilirubin levels > 250 micromol/litre with a sensitivity of 91% and a specificity of 66%. [EL II]

The fifth study was conducted in Italy[79] to evaluate BiliChek in preterm babies. The study population comprised 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 2145 ± 518 g. 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/litre in 61% of the sample (209/340), with a mean difference of 18.8 micromol/litre. This difference was found to increase at higher levels of bilirubin. The most effective transcutaneous bilirubin threshold values were 111 micromol/litre to detect serum bilirubin levels > 171 micromol/litre (sensitivity 100% and specificity 40%) and 171 micromol/litre to detect serum bilirubin levels > 205 micromol/litre (sensitivity 100% and specificity 72%). [EL Ib]

In the sixth study, from Nigeria,[80] 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% of 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/litre. When the data were segregated according to serum bilirubin, correlation for serum bilirubin ≥ 205 micromol/litre was better compared with serum bilirubin levels < 205 micromol/litre ($r = 0.84$ versus 0.67). At serum bilirubin levels ≥ 205 micromol/litre, transcutaneous bilirubin measurements underestimated serum bilirubin with a mean difference of 21.4 micromol/litre, but overestimated it when serum bilirubin levels were < 205 micromol/litre (mean difference of 35.7 micromol/litre). When the data were analysed on the basis of skin pigmentation, transcutaneous bilirubin measurements correlated strongly with all three degrees of pigmentation. Although the mean difference between transcutaneous bilirubin and serum bilirubin readings was small (8.5 micromol/litre), the imprecision (standard deviation) increased with increasing degree of pigmentation: 92 micromol/litre for light, 133 micromol/litre for medium, and 197 micromol/litre for dark pigmentation. [EL II]

In the last study, from the USA,[81] transcutaneous bilirubin measurements with BiliChek were compared with serum bilirubin levels obtained by the diazo and the VITROS® methods. 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/litre. The BiliChek overestimated diazo serum bilirubin by a mean of 34 micromol/litre and VITROS serum bilirubin by a mean of 22 micromol/litre. There was a moderately positive correlation between transcutaneous bilirubin and serum bilirubin values: diazo ($r^2 = 0.65$) and VITROS ($r^2 = 0.66$) when bias was accounted for. [EL III]

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 a 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/litre. 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. Altough there were differences in the populations studied, in threshold cut-off values of transcutaneous bilirubin and in 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 that 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 of 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.

Recommendations

See the end of Section 5.2.

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 C.

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 bilirubin estimations above a certain threshold. They judged that, under their recommended thresholds for treatment (a relatively high threshold) and further monitoring (a relatively low threshold), 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 estimate 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 fewer than 9200 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 fewer than 9200 meters were required.

Overall GDG translation from evidence (5.2.2)

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 over another.

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/litre and, as few babies with high levels were studied, transcutaneous bilirubin cannot be recommended at levels above 250 micromol/litre. If a transcutaneous bilirubinometer records a bilirubin level above 250 micromol/litre, a serum bilirubin level should be taken to check the bilirubin level accurately. The GDG opinion is that transcutaneous bilirubin should not be used in very preterm babies (gestational age < 35 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 has made research recommendations 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 is 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/CG37). The GDG considers that any healthcare professional can 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 five to seven cases of kernicterus each year in the UK. The GDG is of the opinion that the 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 is 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 gestational age ≥ 35 weeks followed by serum bilirubin in appropriate subgroups.

Depending on the number of bilirubinometers needed, the latter strategy is a more cost-effective option than serum bilirubin in all visibly jaundiced babies. In addition, transcutaneous bilirubin measurement is a less invasive procedure than blood sampling and thus is more acceptable to parents and clinical staff.

Recommendation – 5.2 Devices for measuring bilirubin

When measuring the bilirubin level:

- use a transcutaneous bilirubinometer in babies with a gestational age of 35 weeks or more and postnatal age of more than 24 hours
- 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 babies less than 35 weeks gestational age
- always use serum bilirubin measurement for babies at or above the relevant treatment threshold for their postnatal age, and for all subsequent measurements
- do not use an icterometer.

6 Formal assessment for the causes of neonatal hyperbilirubinaemia

Introduction

Most babies with an elevated serum bilirubin level do not have underlying disease, and the jaundice resolves by 2 weeks of age. However, an important minority have a diagnosis that requires specific treatment. Babies who have haemolysis (rapid breakdown of red cells) because of antibodies or G6PD deficiency can have rapidly rising bilirubin levels that 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 that 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 that 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 predefined 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 G6PD 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 co-morbidity, 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 that 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 is aware of an ongoing RCT in the Netherlands that 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 continuing 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/litre 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/litre (used here as a proxy for 'moderate' hyperbilirubinaemia)
- a group including studies where the serum bilirubin threshold for inclusion was > 400 micromol/litre, the mean serum bilirubin of the entire sample was > 400 micromol/litre 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.

6.1 Tests to detect underlying disease in all babies with hyperbilirubinaemia

Description of included studies (6.1.1–6.1.4)

Overall, 33 articles contributed to this analysis and some have been included in more than one group.* The median sample size was 109 (range 21–3099). For population-based studies, the incidence of jaundice by live births was recorded.

Serum bilirubin > 154 micromol/litre

Nine studies[82-90] with 10 204 participants contributed data to this analysis (Table 6.1). Three studies each were carried out in Nigeria[82;83;85] and India[84;86;87] and one apiece in Australia,[89] Pakistan[88] and China.[90] The entry levels ranged from bilirubin levels > 154 micromol/litre to > 205 micromol/litre. 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.[82;88;89] Where reported, the age of onset of jaundice ranged from 0 to 10 days. Preterm babies were included in all but three studies[82;83;86] 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[85] reported mean birthweight, which was 2.73 ± 0.74 kg. Males accounted for 57.9% of cases in the three studies[83;86;90] that reported gender.

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

Table 6.1 Results of studies investigating the causes of jaundice at various levels of serum bilirubin

Country	Criteria	Preterm (%)	Age (days)	BF (%)	Associated pathology											
					Blood group incompatibility			G6PD deficiency			Infection			Idiopathic/no known cause		
					n	*N*	(%)	*n*	*N*	(%)	*n*	*N*	(%)	*n*	*N*	(%)
Serum bilirubin less than 255 micromol/litre																
Nigeria[82]	> 170		0–10		180	424	42.5	229	424	54	60	424	14.1	39	424	9.2
Nigeria[83]	> 170		0–10		11	40	27.5	13	40	32.5	34	40	85	3	40	7.5
Nigeria[85]	> 205	25.6			43	150	28.7	109	327	33.3	38	217	17.5			
India[86]	> 170				30	100	30	4	100	4						
India[87]	> 205	14			9	50	18	2	50	4	7	50	14			
India[84]	> 205	16.7			102	454	24.5	23	454	5.1						
Pakistan[88]	PT	13			113	869	13	20	869	2.3	165	869	19			
Australia[89]	> 154	36.3			794	6129	12.9	51	6129	0.8	198	6129	3.2			
China[90]	> 170	3.6	0–10		414	1811	22.9	241	1811	13.4	680	1811	37.5			
Serum bilirubin between 255 micromol/litre and 399 micromol/litre																
India[91]	> 255	18.5	0–15	63	24	92	26.1	4	92	4.3	18	92	19.6			
Nigeria[92]	> 170				24	102	23.5	41	102	40.2	57	102	55.9			
Israel[93]	> 306	0	0–10	95.2	0	21	0	2	21	9.5	0	21	0			
Nigeria[94]	> 255	16	0–7		28	125	22.4	49	125	39.2	1	125	0.8	35	125	28
Papua New Guinea[95]	> 255	10		100	12	50	24	11	50	22	8	50	16	19	50	38
Singapore[96]	> 255				78	270	28.9	18	270	6.7						
Singapore[97]	> 221	6.6			43	181	23.8	4	181	2.2						
Taiwan[98]	> 255		0–10		62	196	31.6	43	196	21.9	10	196	5.1	53	196	27
Turkey[99]	359				220	624	35.3	24	624	3.8	36	624	5.7			
Iran[100]	ICD			100	22	376	5.8	8	376	2.1	59	376	15.7			
UAE[101]	Chart	26	0–6		23	85	27	8	85	9.4						
Saudi Arabia[102]	> 255				23	211	10.9	64	211	30.3	4	411	1.9			
Serum bilirubin > 400 micromol/litre or exchange transfusion																
China[90]	ET	3.6	0–10		157	581	27	130	581	22.4						
Singapore[96]	ET				18	46	39.1	2	46	4.3	8	46	17.4	6	46	13
India[84]	ET				39	66	59.1	11	66	16.7						

Country	Criteria	Preterm (%)	Age (days)	BF (%)	Associated pathology											
					Blood group incompatibility			G6PD deficiency			Infection			Idiopathic/no known cause		
					n	*N*	(%)	*n*	*N*	(%)	*n*	*N*	(%)	*n*	*N*	(%)
India[103]	ET				21	141	14.9	24	141	17.2	34	141	24.1	50	141	35.4
Pakistan[88]	ET				11	27	40.1	2	27	7.4	6	27	22.2			
Papua New Guinea[95]	ET	10		100	4	11	36.4	3	11	27.3	2	11	18.2	2	11	18.2
Australia[89]	ET				166	248	66.9	2	248	0.8	2	248	0.8			
Ghana[104]	> 340	0	0–8		15	35	42.9	13	35	37.1				10	35	28.6
Nigeria[94]	ET	16	0–7		16	53	30.2	21	53	39.6	0	53	0	11	53	20.7
Nigeria[105]	> 204				15	109	13.8	67	109	61.5	24	109	22	13	109	11.9
UK[106]	> 510		0–31	87.7	39	106	36.8	5	106	4.7	4	106	3.8	29	106	27.3
Turkey[107]	> 425	0			8	21	38.1	4	21	19.5				10	21	47.5
Turkey[108]	> 428		0–30	100	14	93	15.1	2	39	5.1	7	93	7.5	61	93	65.6
Greece[109]	ET				35	75	46.7	14	75	18.7						
Iran[100]	ET			100	2	14	14.3	0	14	0	9	14	64.3			
Denmark[110]	> 450	8.8	0–28	100	54	113	47.8	1	113	0.9						
Canada[111]	> 425		0–60	81.4	60	258	23.2	20	258	7.75	3	258	1.2			
Kernicterus																
China[90]	K				51	156	32.7	58	156	37.2						
UK[106]	K				4	14	28.6	3	14	21.4	2	14	14.3	1	14	7.1
Nigeria[112]	BE				35	115	30.4	40	115	34.8	16	115	13.9			
Ghana[104]	K				6	17	35.3	8	17	47				3	17	17.6
USA[113]	K				1	14	7.1	3	14	21.4	2	14	14.3	6	14	42.8
USA[20]	K				24	125	19.2	26	125	20.8				44	125	35.2
Singapore[97]	K				4	8	50	0	8	0						
Greece[109]	K				1	6	16.7	3	6	50						
Turkey[108]	K				1	6	16.7	1	6	16.7	3	6	50	1	6	16.7
Turkey[99]	K				3	6	50	1	6	16.7						

BE = bilirubin encephalopathy; BF = breastfeeding; ET = exchange transfusion; ICD = International Classification of Diseases; K = kernicterus; PT = phototherapy.

Serum bilirubin between 255 and 399 micromol/litre

Twelve studies[91-102] with 2333 participants contributed data to this analysis (Table 6.1). Two studies each were carried out in Nigeria[92;94] and Singapore[96;97] and one apiece in India,[91] Israel,[93] Papua New Guinea,[95] Iran,[100] Saudi Arabia,[102] Taiwan,[98] Turkey[99] and the United Arab Emirates.[101] Bilirubin levels at entry ranged from > 170 micromol/litre to > 306 micromol/litre. Jaundice at this level affected 2.2% of all live births in the five population-based studies[92-96] included in this analysis. The percentage of preterm babies (reported in six studies[91;93-95;97;101]) ranged between 0% and 18.6% and the mean serum bilirubin levels (also reported in six studies[91-93;97-99]) ranged between 310 micromol/litre and 376 micromol/litre. Where reported, the age of onset ranged from 0 to 15 days, and breastfeeding rates ranged from 63% to 100%. In one study,[93] the mean gestational age was 39.3 ± 1.2 weeks and not reported in the other 11 studies. The mean birthweight was 3082 ± 530 g and 3206 ± 340 g in two studies[93;99] and was not reported in the other ten studies. Males accounted for 52.2% of cases of moderate jaundice in the six studies[91-93;95;99;100] that reported on gender.

Serum bilirubin > 400 micromol/litre or requiring exchange transfusion

Seventeen studies[84;88-90;94-96;100;103-111] with 1997 participants contributed data to this analysis (Table 6.1). There were three good-quality national surveillance studies from Canada,[111] Denmark[106;110] and the UK, while, of the rest, two studies each were carried out in India,[84;103] Nigeria[94;105] and Turkey[107;108] and one apiece in Australia,[89] China,[90] Ghana,[104] Greece,[109] Iran,[100] Pakistan,[88] Papua New Guinea[95] and Singapore.[96] Bilirubin levels at entry ranged from > 425 micromol/litre to > 510 micromol/litre. Subjects in studies with lower entry levels of serum bilirubin but who received exchange transfusions were also included in this analysis. Six studies[104-108;111] reported mean serum bilirubin levels ranging from 471 micromol/litre to 595 micromol/litre. Hyperbilirubinaemia at these levels affected 0.02% of all live births in the three population-based studies[88;89;95] included in this analysis. Seven studies[90;94;95;104;107;110] 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 to 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 2943 g to 3560 g. Mean birthweight was not reported in five studies.[103-105;108;109] Males accounted for 63.1% of cases of severe jaundice in the eight studies[104-111] that reported on gender.

Kernicterus

Ten studies[20;90;97;99;104;106;108;109;112;113] with 467 participants contributed data to this analysis (Table 6.1). Two studies each were carried out in Turkey[99;108] and the USA[20;113] and one apiece in China,[90] Ghana,[104] Greece,[109] Nigeria,[112] Singapore[97] abd the UK.[106] One population-based study[106] 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.*

Description of included studies (6.1.5–6.1.7)

Overall, six articles contributed to these analyses. One literature review[114] and two case series from India[115] and Canada[116] were included in the review on the Bilirubin/Albumin ratio. The literature review[114]which included six studies was rated EL 1++, while the other two studies [115;116] were rated EL 3. One case series[117] of EL 3 from Brazil was included in the review of free bilirubin. Two case series[118;119] OF EL 3 from the USA were included in the review of conjugated hyperbilirubinaemia.

6.1.1 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/litre, 23.9% at serum bilirubin between 255 micromol/litre and

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

399 micromol/litre and 33.7% serum bilirubin > 400 micromol/litre. 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 at each level of serum bilirubin and in cases of kernicterus. In studies from the Middle East, it was found in 21.9% of cases of serum bilirubin between 255 and 399 micromol/litre, in 29.1% of cases of exchange transfusion or serum bilirubin > 400 micromol/litre 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/litre or exchange transfusions and 18.9% of kernicterus cases.

6.1.2 G6PD deficiency

Review findings

The pooled prevalence rates of G6PD 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/litre, 11.8% at serum bilirubin between 255 micromol/litre and 399 micromol/litre and 16.5% serum bilirubin > 400 micromol/litre. G6PD 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 G6PD deficiency in different world regions. In Africa it accounted for over 35% 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/litre and 9.3% at serum bilirubin between 255 and 399 micromol/litre to 19.6% of cases of exchange transfusion or serum bilirubin > 400 micromol/litre and 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/litre 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/litre or receiving exchange transfusions, and 20.9% of kernicterus cases.

6.1.3 Infection

Review findings

The pooled prevalence rates of infection (as defined in each study; see the evidence tables) varied as serum bilirubin levels rose. This was identified as a cause of hyperbilirubinaemia in 12.4% of cases at serum bilirubin < 254 micromol/litre, 9.7% at serum bilirubin between 255 micromol/litre and 399 micromol/litre and 8.9% at serum bilirubin > 400 micromol/litre. 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% to 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/litre 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/litre or receiving exchange transfusions and in 14.3% of kernicterus cases.

6.1.4 No known cause

Review findings

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

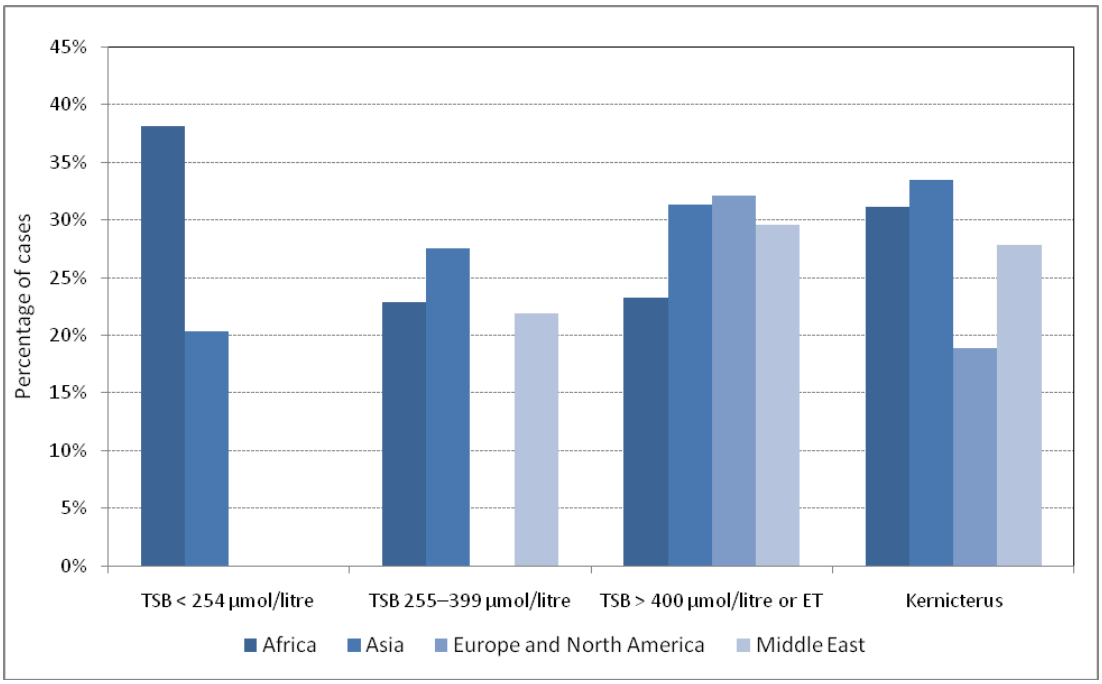


Figure 6.1 Prevalence of blood group incompatibility related to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases; TSB = total serum bilirubin, ET = exchange transfusion

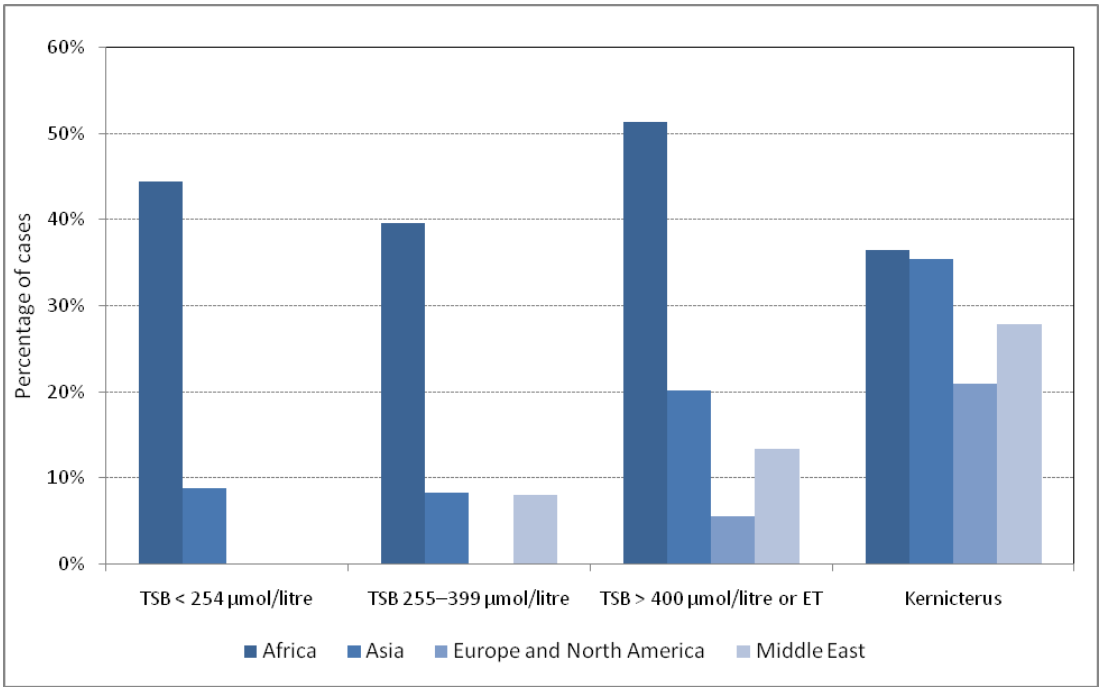


Figure 6.2 Prevalence of G6PD deficiency related to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases; TSB = total serum bilirubin, ET = exchange transfusion

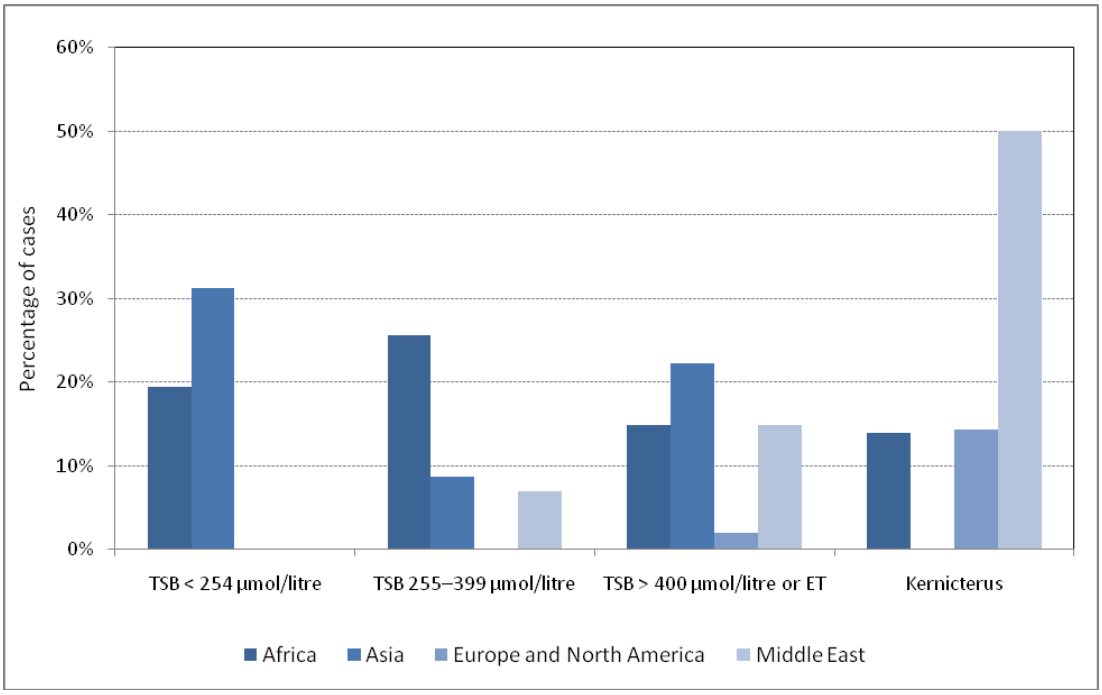


Figure 6.3 Prevalence of infection related to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases; TSB = total serum bilirubin, ET = exchange transfusion

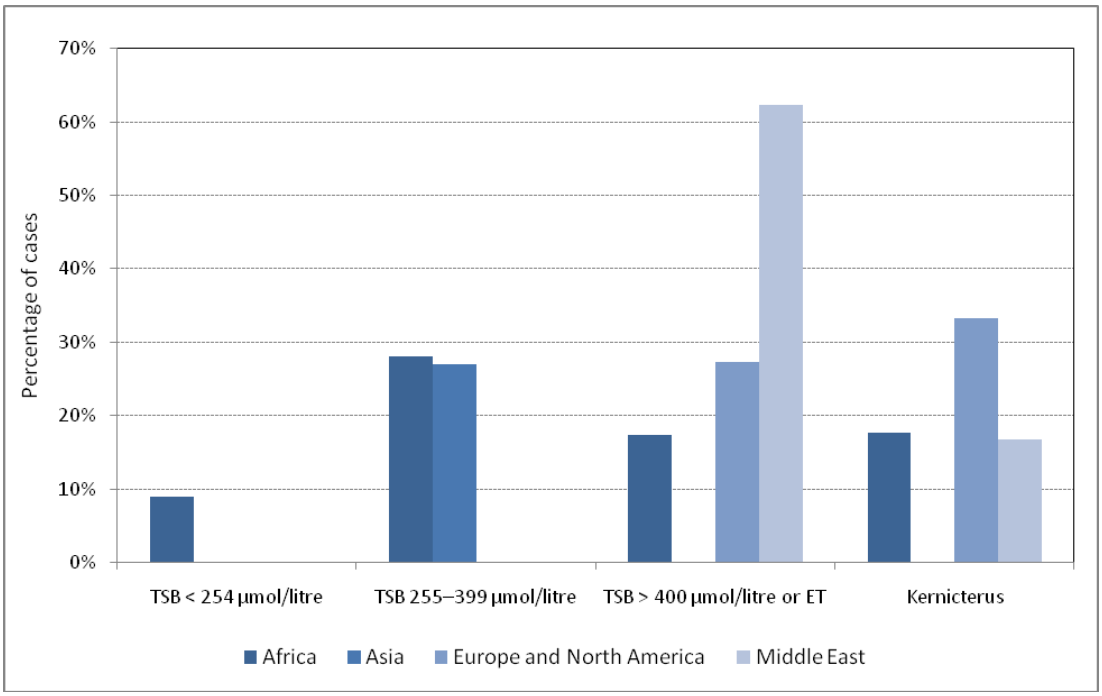


Figure 6.4 Prevalence of 'no cause identified' in relation to severity of hyperbilirubinaemia in different geographical regions expressed as a percentage of cases; TSB = total serum bilirubin, ET = exchange transfusion

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 at each level of serum bilirubin and in cases of kernicterus. In Asia no cause could be found for 27% of cases with serum bilirubin between 255 micromol/litre and 399 micromol/litre and 29.9% of cases of exchange transfusion or serum bilirubin > 400 micromol/litre. In the Middle East no cause was found for 62.3% of cases of serum bilirubin > 400 micromol/litre and 16.7% of cases of kernicterus. In Europe and North America 27.3% of babies with serum bilirubin > 400 micromol/litre and 33.3% of cases of kernicterus had no cause identified.

Overall evidence summary (6.1.1– 6.1.4)

These meta-analyses indicate that blood group incompatibility and G6PD deficiency are the most commonly associated conditions in babies with hyperbilirubinaemia > 255 micromol/litre. 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/litre), whereas G6PD deficiency was more common in kernicterus cases.

G6PD 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 G6PD 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 (6.1.1–6.1.4)

Only poor-quality evidence (EL 2– and EL 3) 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 G6PD 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 (Coombs' test) in healthy babies, this finding emphasises the conclusions reached in Chapter 4 on prediction (see Section 4.2.3), namely that a positive DAT (Coombs' test) 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

See the end of Section 6.1.

6.1.5 Bilirubin/albumin ratio

Review findings

The usefulness of the B/A ratio in predicting bilirubin-induced neurotoxicity in preterm babies (gestational age < 32 weeks) with unconjugated hyperbilirubinaemia was examined in a systematic review.[114] Studies were included if the B/A ratio was measured and outcome data on neurotoxicity or neurodevelopmental outcome were 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 ($P = 0.19$ versus $P = 0.98$) 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 6 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 1++]

A case series in India[115] 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 g. The reported mean serum bilirubin was 227 ± 80 micromol/litre, mean free bilirubin 8.7 ± 5.6 nmol/l and mean albumin levels 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 3]

A Canadian case series[116] examined the relationship between albumin levels and free bilirubin. A total of 55 plasma samples from 46 jaundiced babies were used. Diagnoses included preterm birth, birth asphyxia, respiratory distress syndrome and idiopathic hyperbilirubinaemia. The mean gestational age was 36 ± 4 weeks and the mean birthweight was 2453 ± 813 g. 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 3]

6.1.6 Relationship between circulating free bilirubin and unconjugated bilirubin

Review findings

A case series from Brazil[117] examined the correlation between free bilirubin and unconjugated bilirubin in 43 term babies with non-haemolytic hyperbilirubinaemia. Inclusion criteria were birthweight > 2500 g, negative DAT, gestational age 37–41 weeks, postnatal age < 7 days, and negative maternal history and serology for syphilis. The babies had no history of perinatal hypoxia, had Apgar score > 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 ($P < 0.01$). [EL 3]

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

Review findings

A retrospective case series in the USA[118] looked at the usefulness of measuring conjugated bilirubin in jaundiced term babies. Preterm babies were excluded. Testing rates were different in the two 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/litre while in the second it was > 17 micromol/litre. 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 five (3.6%), congestive heart failure in five (3.6%), multiple anomalies in two (1.3%), pyloric stenosis in two (1.3%), extreme growth restriction (possible rubella) in one (0.7%), hypothyroidism in one (0.7%) and choledochal cyst in one (0.7%). [EL 3]

A retrospective case series in the USA[119] looked at the usefulness of laboratory tests in babies with hyperbilirubinaemia. Only babies ($n = 447$) with a birthweight of > 2500 g were included. The mean birthweight was 3440 ± 485 g. 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 morphological examination, and 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 examination or routine haematocrit (at 4 hours) in 145 (32.4%) cases. Thirteen cases (2.9%) had other causes related to hyperbilirubinaemia that were not identified by the routine tests. Seventy-five cases (16.8%) were diagnosed from the routine tests. These included isoimmunisation alone in 58 cases (12.9%) and isoimmunisation accompanied by preterm birth, bruising, cephalohaematoma, bacterial infection, viral infection or maternal diabetes in 17 cases (3.8%). [EL 3]

Overall evidence summary (6.1.5–6.1.7)

A number of poor-quality studies and one good-quality review were identified. The good-quality review identified six studies that showed a link between the B/A ratio and various indices of bilirubin encephalopathy (abnormal ABR, IQ at 6 years). Two poor-quality studies showed a moderately positive correlation between free bilirubin and both the B/A ratio and the B/A 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, two studies have been carried out to determine the diagnostic 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 from evidence (6.1.5–6.1.7)

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. Furthermore, 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 is 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 agrees with the AAP that this practice should cease, and total bilirubin levels should be used to guide management. The GDG is 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 considers that total serum bilirubin should be used to guide the management of jaundiced babies less than 14 days old.

Recommendations – 6.1 Tests to detect underlying disease in all babies with significant hyperbilirubinaemia

In addition to a full clinical examination by a suitably trained healthcare professional, carry out all of the following tests in babies with significant hyperbilirubinaemia as part of an assessment for underlying disease (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)):

- 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.

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

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

Do not use the albumin/bilirubin ratio when making decisions about the management of hyperbilirubinaemia

Do not subtract conjugated bilirubin from total serum bilirubin when making decisions about the management of hyperbilirubinaemia (see management thresholds in the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).

6.2 Formal assessment of babies with prolonged jaundice

Description of included studies

Three studies of EL 3 from Turkey[120;121] and the UK[122] have been included. Two were case series[120;122] and one was a retrospective chart review.[121] The sample size ranged from 42 to 381.

Review findings

A UK case series[122] examined causes of prolonged jaundice, defined as jaundice persisting beyond day 14. The mean gestational age of the 154 included babies was 39 weeks, the mean birthweight was 3200 g and the mean age at referral was 16 days. Ninety-six (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 nine (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 G6PD deficiency and two cases of urinary tract infection were identified. [EL 3]

A case series from Turkey[120] 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 the study. The mean gestational age was 38 weeks, the mean birthweight was 3194 g, the 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/litre. One baby had conjugated hyperbilirubinaemia and was referred for exclusion of biliary atresia. Seven babies (26.9%) had blood group incompatibility and four (15.4%) had inadequate caloric intake. The remaining 14 (53.8%) had 'breastmilk' jaundice. [EL 3]

Causes of conjugated hyperbilirubinaemia were also reported in another Turkish study,[121] 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/litre and the mean conjugated bilirubin was 130 micromol/litre. The causes of the conjugated hyperbilirubinaemia included culture-proven sepsis in 15 (35.7%) babies, perinatal hypoxia–ischaemia in seven (16.7%), blood group incompatibility in five (11.9%), trisomy 21 in three (7.1%), TPN-associated cholestasis in three (7.1%), neonatal hepatitis in two (4.8%), metabolic liver disease in one (2.4%), biliary atresia in one (2.4%) and portal venous thrombosis in one (2.4%). No cause was identified in four (9.5%) cases. [EL 3]

Evidence summary

First-line investigations for prolonged jaundice resulted in nine (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%) were 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 G6PD deficiency (if appropriate).

The GDG is 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 and liver disease (e.g. 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 is aware of the evidence demonstrating better outcomes for babies with biliary atresia who are offered early surgery and hence stresses the urgency of seeking specialist advice when a high level (greater than 25 micromol/litre) of conjugated bilirubin is found.

The GDG considered that, in the first instance, a consultant neonatologist or a consultant paediatrician should be consulted and cases subsequently referred to a specialist liver disease centre if clinically indicated after appropriate investigation.

Recommendations – 6.2 Formal assessment of babies with prolonged jaundice

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

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

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

7 Treatment

Clinical questions

Phototherapy:

i) How effective is phototherapy?

ii) What is the best modality of giving phototherapy (clinical and cost-effectiveness)?
   a) Conventional phototherapy (single, double or multiple phototherapy)
   b) Sunlight
   c) Fibreoptic phototherapy (biliblankets, bilibeds and other products)

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 versus constant phototherapy on maternal–infant bonding, and parental anxiety)?

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?

7.1 How to manage hyperbilirubinaemia

7.1.1 What are the indications for starting and stopping treatment in babies with neonatal hyperbilirubinaemia?

Description of included studies

No studies were identified.

Review findings

No studies were identified.

Evidence summary

No evidence was identified.

GDG translation from evidence

The GDG recognised that was no reliable evidence to inform the choice of thresholds for commencing therapy – including phototherapy and exchange transfusion – in babies with jaundice. This was not surprising. The ultimate purpose of phototherapy is to prevent kernicterus, and kernicterus is a rare event. Moreover, factors other than the absolute level of total serum bilirubin are important additional risk factors for kernicterus – for example, prematurity or co-existence of illnesses such as sepsis, perinatal asphyxia and acidosis. The GDG recognised that for these reasons it was impossible to devise studies that would accurately determine 'correct' thresholds for treatment. Nevertheless, therapeutic thresholds are important. There is clear evidence that phototherapy is effective and can reduce the need for exchange transfusion (see Section 7.2).

The GDG therefore considered that there was a compelling need to provide specific guidance to clinicians regarding thresholds for treatment. When determining the thresholds, the GDG considered that the primary aim was to choose a threshold with a wide margin of safety, with the threshold for phototherapy well below that for exchange transfusion. The rationale for this was the difference in the safety profile between the two therapies. However, the choice of threshold should not be so low that phototherapy would be used unnecessarily. In choosing the threshold levels, the GDG considered that account should be taken of current common practice while eliminating more extreme threshold strategies.

Phototherapy thresholds for infants of 38 weeks or more gestation

For babies of 38 or more weeks of gestation, the GDG agreed through an informal consensus process that a reasonable threshold for initiation of phototherapy was 350 micromol/litre in infants aged 96 hours or more. The GDG believed that this was consistent with current views on the low risk associated with moderate hyperbilirubinaemia in term babies. The GDG discussed a recent publication that provided data on current practice regarding thresholds for therapy in a large number of units in the UK.[1] That publication did not draw conclusions regarding 'best practice' but did inform the group about the range of policies being used. The GDG noted that their chosen phototherapy threshold was closely comparable with the most commonly reported threshold (340 micromol/litre) currently used by units in the UK.[1] It was also comparable with the threshold proposed by the American Academy of Pediatrics.[123] There was evidence that the publication of the AAP recommendation in 1994 had not been associated with a significant change in the reporting of kernicterus cases in the USA.[124]

For the period from birth to 96 hours, again based on informal consensus, the GDG agreed on a series of bilirubin levels with 6-hourly stepwise increases at which phototherapy is recommended until the 96-hour threshold of 350 micromol/litre is reached. These recommended levels are presented in table form (see the threshold table in Section 1.3).

Phototherapy thresholds for infants less than 38 weeks of gestation

With regard to preterm babies, one longstanding and common approach has been to determine the threshold for phototherapy using the simple formula

$$\text{bilirubin in micromol/litre} = (\text{gestational age} \times 10) - 100$$

This formula has been proposed for use in paediatric textbooks for many years. Based on informal consensus, the GDG agreed that this formula should be used for babies aged 72 hours or older. The GDG noted that use of this simple formula produced a threshold for phototherapy that was either within or close to the middle quartiles for thresholds reported to be in current use by neonatal units in the UK. They were therefore comparable with 'average practice' and would avoid some of the more extreme values being employed in some units. The widespread use of this formula is not likely to change the number of preterm babies treated with phototherapy in most neonatal units.

For all babies aged less than 72 hours, based on informal consensus, the GDG agreed that the threshold should be lower because of the evidence that shows that bilirubin levels are rising for the first few days of life.[34]

It was agreed for babies less than 38 weeks of gestation the threshold for phototherapy was best presented using a series of graphs (see treatment threshold graphs) of total bilirubin versus age in hours, with a separate graph for each gestational age (from 23 weeks to 37 weeks of gestation). The graphs were constructed using the formula for infants of 72 hours of age and older. The threshold levels during the first 72 hours were determined by drawing a straight line from a level of 40 micromol/litre (the upper limit of normal for the umbilical cord blood bilirubin) at birth to the formula-based level at 72 hours. The GDG were aware that Excel spreadsheets originally devised by Dr Giles Kendall and Professor T J Cole at University College London could potentially be used to display the threshold levels in graphic form. The GDG are grateful to them for their kind permission to adapt these spreadsheets.

Exchange transfusion thresholds for babies of 38 weeks or more gestation

Similar considerations were applied to the choice of levels for exchange transfusion. The process was one of informal consensus by the GDG.

For babies of 38 weeks or more gestation, a threshold of 450 micromol/litre from 42 hours of age onward was agreed by informal consensus. This level was chosen based on the GDG's agreement that it was widely accepted that kernicterus would be very unusual in term babies with serum bilirubin levels lower than this. The GDG noted that this was comparable with the American Academy of Paediatrics recommendation of 430 micromol/litre and with reported thresholds currently used in many units in the UK.[1] In the first 42 hours of life, again based on informal consensus, the GDG agreed on a series of bilirubin levels with 6-hourly stepwise increases at which exchange transfusion is recommended until the 42-hour threshold of 450 micromol/litre is reached. These recommended levels are also presented in table form (see the threshold table in Section 1.3).

Exchange transfusion thresholds for babies less than 38 weeks of gestation

For preterm babies, the GDG again agreed to use a simple formula (bilirubin in micromol/litre = gestational age × 10) that has been proposed for use in paediatric textbooks for many years. Based on informal consensus, the GDG agreed that this formula should also be used for babies aged 72 hours or older.

For babies less than 72 hours old, based on informal consensus, the GDG agreed that the threshold should be lower for the reasons outlined above. It was again agreed that for babies less that 38 weeks of gestation the threshold for phototherapy is best presented using a series of graphs (see the treatment threshold graphs) of total bilirubin versus age in hours, with a separate graph for each gestational age (from 23 weeks to 37 weeks of gestation). The graphs were constructed using the formula for the period from 72 hours of age and older. The threshold levels during the first 72 hours were determined by drawing a straight line from a level of 80 micromol/litre at birth to the formula-based level at 72 hours.

The GDG considered that these threshold recommendations for phototherapy and exchange transfusion do not represent a significant departure from mainstream practice in the UK and are similar to those currently in use in the USA, will discourage extreme practices, and will be of practical value for clinicians. Furthermore, by standardising national practice, use of the recommended treatment thresholds will allow meaningful studies of outcome to be performed nationally in the future.

Finally, the RCTs of phototherapy (reviewed in Section 7.2), 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 rising bilirubin (> 8.5 micromol/litre per hour), which may be an indicator of haemolysis.

The GDG considered 50 micromol/litre below the exchange transfusion threshold to be a reasonable level at which to step down from multiple phototherapy to single phototherapy. This would avoid exposing babies to multiple phototherapy, with the restrictions on parental contact and feeding that this entails, for longer than necessary.

The GDG also agreed that 50 micromol/litre below the phototherapy threshold would be a resonable level at which to stop conventional phototherapy. This would avoid keeping babies under phototherapy longer than necessary.

Recommendations

See the end of Section 7.1.

7.1.2 Discharge and monitoring

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.

Description of included studies

Two studies, an RCT[125] of different serum bilirubin levels as criteria for stopping phototherapy and an uncontrolled clinical study[126] 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[125] compared stopping phototherapy at two different levels, one at 17 micromol/litre and the other at 51 micromol/litre below the threshold for phototherapy. The study included 52 term babies (gestational age > 36 weeks) with birthweight > 2500 g 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 g and mean serum bilirubin at entry was 252 ± 36 micromol/litre. Twenty-five (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 statistically significant difference between the groups in either duration of phototherapy or the number of babies requiring a second course of phototherapy. [EL 1 + +]

An uncontrolled clinical study from Israel[126] 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 hours (mean 24 hours) after stopping phototherapy. Babies received phototherapy according to the 2004 AAP guideline.[19] The mean gestational age of the sample was 39 ± 2 weeks, mean birthweight was 3204 ± 445 g, and mean age at onset was 62.2 ± 38.3 hours. The mean bilirubin at initiation of phototherapy was 260 ± 55 micromol/litre. 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 when serum bilirubin had fallen to 205 micromol/litre, or once serum bilirubin stabilised and fell below the 75th centile on the hour-specific nomogram. Rebound jaundice was defined as serum bilirubin > 256 micromol/litre 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/litre. In all, 30 (13.3%) babies had rebound jaundice, with serum bilirubin > 256 micromol/litre. 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 at < 72 hours of age (26 of 154, 16.9%) compared with those in whom phototherapy was initiated at > 72 hours of age (4 of 74, 5.4%). [EL 3]

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 hours after discontinuation of phototherapy but does not specify when phototherapy should be discontinued.[127]

The AAP recommends that, for term and near-term babies (gestational age > 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/litre, and measuring serum bilirubin 24 hours after stopping to check for rebound jaundice is optional.[19]

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/litre. In high-risk babies, serum bilirubin should be measured 12–24 hours after discontinuation of phototherapy.[128]

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 numbers 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/litre), 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 RCTs reviewed in Section 7.2 generally adopted the practice of discontinuing phototherapy once the bilirubin levels were 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 recommends a serum bilirubin level be taken 12–18 hours after stopping phototherapy to check for rebound jaundice, because of their decision (see Section 7.1.1) to stop phototherapy once bilirubin levels at least 50 micromol/l below the age-appropriate threshold are 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.

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

Age (hours)	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 bilirubin measurement in 6–12 hours	↓ Consider phototherapy and repeat bilirubin measurement in 6 hours	↓ Start phototherapy	↓ Perform an exchange transfusion unless the bilirubin level falls below threshold while the treatment is being prepared

Recommendations – 7.1 How to manage hyperbilirubinaemia

Use the bilirubin level to determine the management of hyperbilirubinaemia in all babies (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).

If the serum bilirubin level falls during continuous multiple phototherapy to a level 50 micromol/litre below the threshold for which exchange transfusion is indicated:

- step down to single phototherapy

Starting phototherapy

Use serum bilirubin measurement and the treatment thresholds in the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6) when considering the use of phototherapy.

In babies with a gestational age of 38 weeks or more whose bilirubin is in the 'repeat bilirubin measurement' category in the threshold table (Section 1.3) repeat the bilirubin measurement in 6–12 hours.

In babies with a gestational age of 38 weeks or more whose bilirubin is in the 'consider phototherapy' category in the threshold table (Section 1.3) repeat the bilirubin measurement 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 in the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6).

During phototherapy

During phototherapy:

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

Stopping phototherapy

Stop phototherapy once serum bilirubin has fallen to a level at least 50 micromol/litre below the phototherapy threshold (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).

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

For recommendations on starting and stopping exchange transfusions, see Section 7.3. For recommendations on the use of other treatments, including IVIG, see Section 7.4.

7.2 Phototherapy

As there is a large evidence base for phototherapy, the literature search was restricted to RCTs and meta-analyses. Altogether, 472 records were identified by searches. These were screened and 140 hard-copy articles were requested. Seventy-five 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 RCTs were included. No RCTs dealing with sunlight or environmental light were found.

To evaluate the evidence more clearly, conventional phototherapy was compared initially with no treatment, then with multiple phototherapy and finally with newer forms of phototherapy including fibreoptic and light-emitting diode (LED) phototherapy. Various 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 program RevMan 5 (www.cc-ims.net/revman). Where possible, a distinction was made between term and preterm babies and evidence was evaluated accordingly.

7.2.1 Type of phototherapy to use

Phototherapy in term/normal-birthweight babies

Nineteen of the included studies contributed to the following comparisons:

- conventional phototherapy versus usual care/no treatment (seven studies from six articles)
- conventional phototherapy versus multiple phototherapy (four studies)
- conventional phototherapy versus fibreoptic phototherapy (six studies)
- conventional phototherapy versus LED phototherapy (two studies).

Conventional phototherapy versus no treatment

Description of included studies

Seven studies[129-134] from six articles with 667 participants were included in this comparison. One reference[129] included three separate groups each of which was randomly allocated to treatment or control. Three of the studies were carried out in the USA[129;130;133] and one each in Italy,[132] Taiwan[134] and the UK.[131] The evidence level of the included studies ranged from EL 1– to EL 1++. Three studies specified the method of randomisation used as a random numbers table,[129;131] one study used a computer-generated sequence[133] and one used a coin-toss method.[130] The remaining two studies did not report the method used. Two studies[129] reported using sealed envelopes as allocation concealment.

Where reported, the mean and standard deviation for gestational age of the study participants ranged from 39.0 ± 0.8 weeks to 39.2 ± 0.9 weeks, mean birthweight ranged from 2155 ± 632 g to 3404 ± 361 g, 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/litre to 306 ± 12 micromol/litre. In the studies that reported gender, 377 participants (52%) were male.

Review findings

The results from a meta-analysis of these studies showed that significantly fewer exchange transfusions were carried out in babies treated with conventional phototherapy (RR 0.36, 95% CI 0.22 to 0.59) (Figure 7.1). Heterogeneity was within acceptable limits ($I^2 = 42\%$). The number needed to treat with phototherapy to prevent one exchange transfusion was 10.

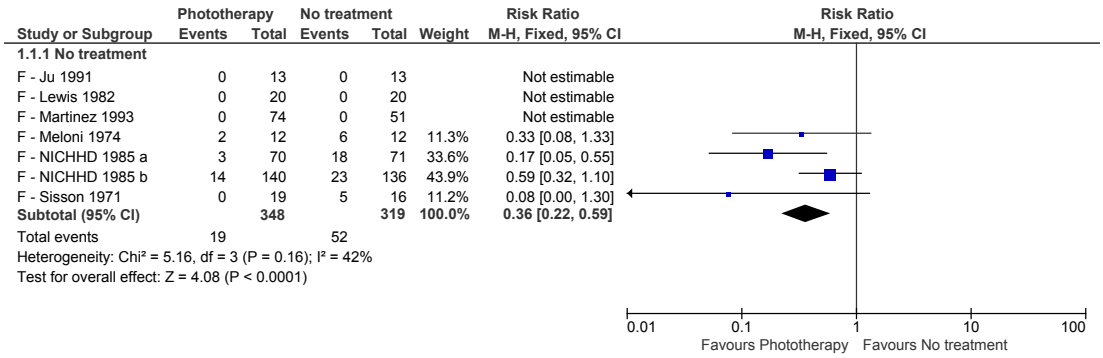


Figure 7.1 Number of exchange transfusions needed when conventional phototherapy is compared with no treatment in term babies

Five studies[129;131;133;134] 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 predefined levels or the need for exchange transfusion. The RR was 0.37 (95% CI 0.24 to 0.58) (Figure 7.2). Heterogeneity was within acceptable limits ($I^2 = 16\%$).

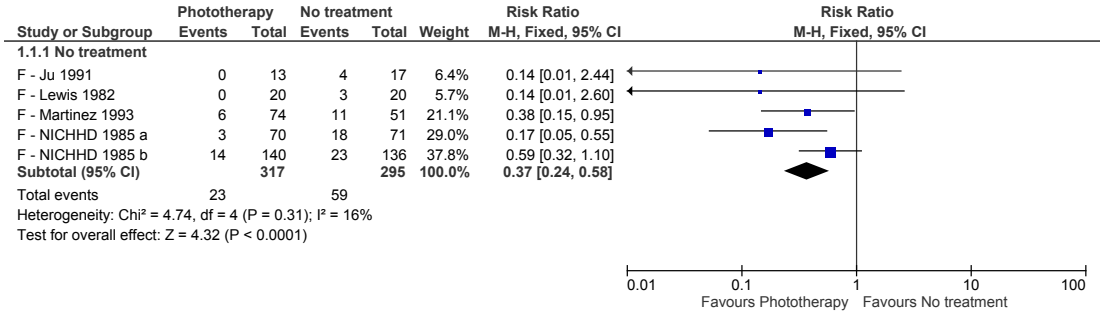


Figure 7. 2 Number of treatment failures when conventional photothearay is compared with no treatment in term babies

Although only two studies[129] contributed data, there was a statistically significantly greater decrease in the mean serum bilirubin levels in the conventional phototherapy group compared with the no treatment group (MD = −45.55 micromol/litre, 95% CI −46.35 to −44.75 micromol/litre) (Figure 7.3). There was significant heterogeneity (I^2 = 100%).

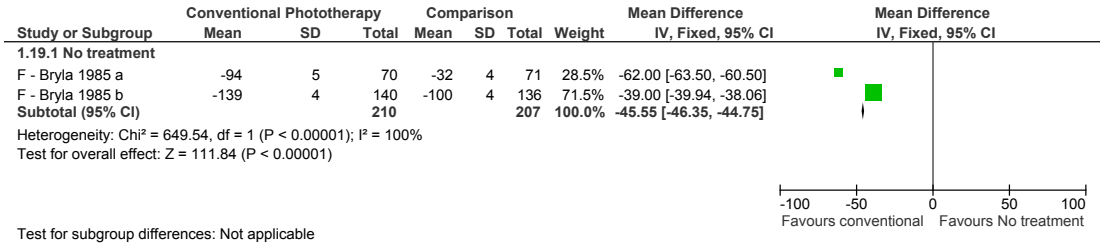


Figure 7.3 Mean decrease in serum bilirubin when conventional phototherapy is compared with no treatment in term babies

See below for the overall evidence summary and GDG translation from evidence for phototherapy in term/normal-birthweight babies.

Conventional phototherapy versus multiple phototherapy

Description of included studies

Four studies[135-138] 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,[136;137] one from Saudi Arabia[135] and one from Singapore.[138] The evidence level of the included studies ranged from EL 1− to EL 1+. One study[138] specified the method of randomisation used as the lottery method while the remaining three studies did not report the method used. One study[135] reported using sealed envelopes as allocation concealment.

The mean gestational age of the study participants ranged from 37.9 ± 2.1 weeks to 38.7 ± 1.3 weeks, the mean birthweight ranged from 2921 ± 696 g to 3130 ± 311 g, 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/litre to 316 ± 47 micromol/litre. In all, 185 (56.4%) of participants were male.

Review findings

In a meta-analysis of these for studies, 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 statistically significant. There was no statistically significant difference between the groups in terms of mean duration of phototherapy.

Three studies[135-137] compared changes in serum bilirubin with each intervention. The mean decrease in serum bilirubin was statistically significantly greater in the multiple phototherapy group (MD = 27.75 micromol/litre, 95% CI 14.50 to 41.00 micromol/litre) (Figure 7.4). Heterogeneity was significant (I^2 = 74%).

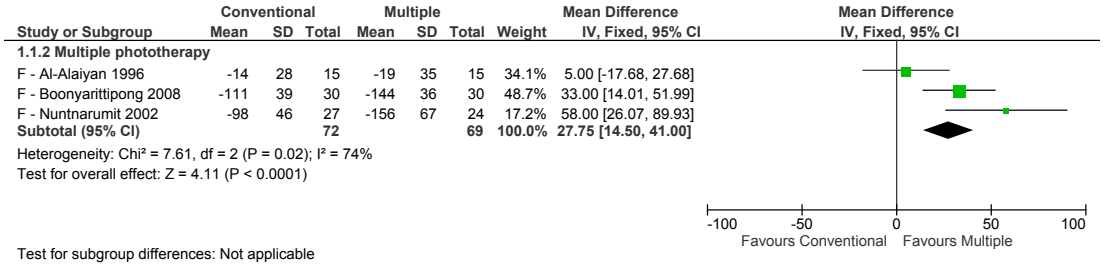


Figure 7. 4 Mean decrease in serum bilirubin when conventional phototherapy is compared with multiple phoptotherapy in term babies

See below for the overall evidence summary and GDG translation from evidence for phototherapy in term/normal-birthweight babies.

Conventional phototherapy versus fibreoptic phototherapy

Description of included studies

Six studies[135;138-142] with 426 participants were included in this comparison. Two of the studies were from the USA[140;141] and there was one apiece from Italy,[142] Saudi Arabia,[135] Singapore[138] and Turkey.[139] The included studies ranged from EL 1– to EL 1+. Three studies specified the method of randomisation used as the lottery method,[138] computer-generated[141] or sequential[139] and the remaining three studies did not report the method used. Two studies[135;142] reported using sealed envelopes as allocation concealment while in one study[139] the nurses who allocated the babies to the groups were blind to the serum bilirubin levels.

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

Review findings

No exchange transfusions were needed with either intervention. Two studies[138;139] reported on treatment failures, defined in one study[139] as having two successive rises in serum bilirubin after initiation of phototherapy, but not defined in the second.[138] Babies who received fibreoptic phototherapy were more likely to be considered as treatment failures (RR 0.12, 95% CI 0.02 to 0.92) (Figure 7.5). There was no heterogeneity (I^2 = 0%).

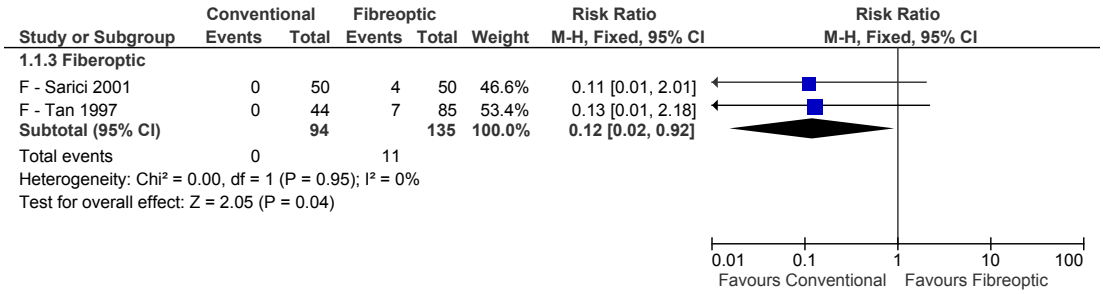


Figure 7.5 Number of treatment failures when conventional phototherapy is compared with fibreoptic phototherapy in term babies

Three studies[135;138;139] reported on rebound jaundice, which was defined as serum bilirubin returning to pre-phototherapy levels. Babies who received fibreoptic phototherapy had fewer cases of rebound jaundice but this was not statistically significant.

All six studies reported the 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/litre, 95% CI −14.03 to −9.99 micromol/litre) (Figure 7.6). Heterogeneity was within acceptable limits (I^2 = 36%).

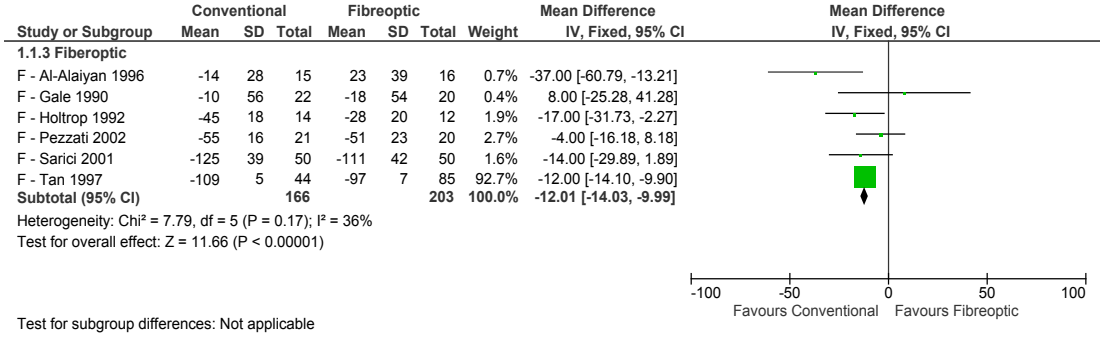


Figure 7.6 Mean decrease in serum bilirubin when conventional phototherapy is compared with fibreoptic phototherapy in term babies

Three studies[135;138;139] reported the mean duration of phototherapy. Babies receiving conventional phototherapy spent statistically significantly less time undergoing phototherapy than babies receiving fibreoptic phototherapy (MD = −12.30 hours, 95% CI −16.97 to −7.63 hours) but heterogeneity was a factor (I^2 = 72%) (Figure 7.7).

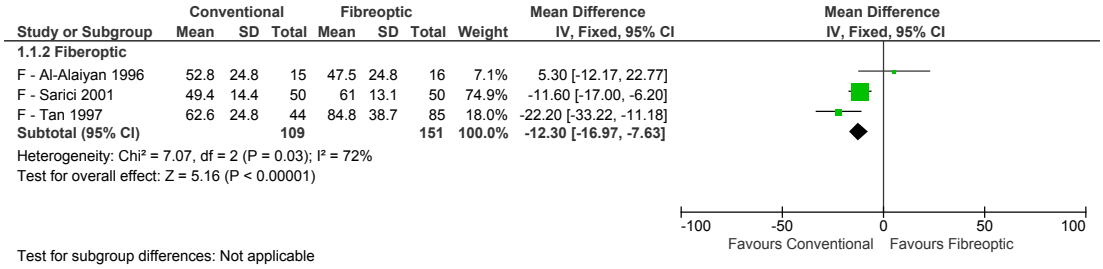


Figure 7.7 Mean duration of phototherapy when conventional phototherapy is compared with fibreoptic phototherapy in term babies

See below for the overall evidence summary and GDG translation from evidence for phototherapy in term/normal-birthweight babies.

Conventional phototherapy versus LED phototherapy

Description of included studies

Two studies from Israel[143;144] with 183 participants were included in this comparison. The evidence level of both studies was EL 1+. Both used computer-generated sequences as the method of randomisation but neither reported on allocation concealment.

The mean gestational age in one study[144] was 39.5 ± 1.5 weeks but was not reported in the second[143] although gestational age > 37 weeks was an inclusion criterion. The mean age in one study[144] was 53.9 ± 37.8 hours and was not reported in the second.[143] Gender and mean birthweight were not reported in either study. The mean baseline serum bilirubin level was 251 ± 74 micromol/litre in one study and 251 ± 77 micromol/litre in the second.

Review findings

There were no reported cases of exchange transfusion, treatment failures or rebound jaundice in either study.

In a meta-analysis, both studies reported the mean decrease in serum bilirubin, which did not differ statistically significantly between the groups (MD = −4.29 micromol/litre, 95% CI −18.95 to 10.36 micromol/litre), with no heterogeneity ($I^2 = 0\%$). Likewise, there was no statistically significant difference in terms of mean duration of phototherapy (MD = 0.64 hours, 95% CI −4.97 to 6.26 hours), with no heterogeneity ($I^2 = 0\%$).

Overall evidence summary for phototherapy in term/normal-birthweight 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 significantly to 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 predefined serum bilirubin levels or the need for exchange transfusion. There was also a statistically significantly greater decrease in the mean serum bilirubin levels with conventional phototherapy compared with no treatment.

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

Compared with fibreoptic phototherapy, treatment failure was statistically significantly less common in babies receiving conventional phototherapy. Similarly, conventional phototherapy was associated with a statistically significantly greater mean reduction in serum bilirubin than fibreoptic phototherapy. Specifically, conventional was statistically 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 with LED phototherapy but this was not statistically significant, and there was no difference between the two types of phototherapy in terms of the mean duration of phototherapy.

Overall GDG translation from evidence for phototherapy in term/normal-birthweight 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 regarding sunlight was reviewed so the GDG cannot recommend sunlight as a treatment option for hyperbilirubinaemia. Fibreoptic phototherapy, which has greater treatment failure, was not deemed a suitable treatment for term babies. While the evidence suggests that multiple phototherapy is more effective than conventional phototherapy, advances in technology have rendered this characterisation less useful because modern phototherapy units are more powerful than those tested in the trials examined. Multiple phototherapy involves exposing a greater area of skin to more powerful irradiance and it is currently believed that this needs to be continuous. However, as a result of this, multiple phototherapy is also accompanied by more fluid balance problems. 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, despite 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 breastfeeding, the GDG considers 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 in cases that require a rapid reduction in serum bilirubin levels.

Recommendations on phototherapy in term/normal-birthweight babies

See the end of Section 7.2.1.

Phototherapy in preterm/low-birthweight babies

Seventeen of the included studies contributed to the following comparisons:

- early phototherapy versus usual care/no treatment (seven studies)
- conventional phototherapy versus multiple phototherapy (two studies)
- conventional phototherapy versus fibreoptic phototherapy (six studies)
- conventional phototherapy versus LED phototherapy (two studies)

Early phototherapy versus no treatment

Description of included studies

Seven studies[129;145-150] with 1238 participants were included in this comparison. Early phototherapy is used for lowering maximum bilirubin levels in babies with low birthweight (< 1500 g) and in preterm babies. Early phototherapy is initiated before serum bilirubin reaches the normal phototherapy threshold.

Six of the studies[129;145-149] were from the USA and one was from Brazil.[150] Babies were included either on the basis of gestational age[148] or birthweight.[129;145-147;149;150] The evidence level of the included studies ranged from EL 1– to EL 1++. One study specified the method of randomisation used as a random numbers table,[129] one study used a computer-generated sequence[145] and one reported using randomised cards,[148] while the remaining four studies did not report the method used. One study[129] used sealed envelopes for allocation concealment.

Where 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 three studies[129;146;150]), mean birthweight ranged from 777 ± 134 g to 1860 ± 344 g (not reported in two studies[129;150]), and mean age at entry to study was reported in one study[129] as 24.2 ± 8.0 hours. In two studies[129;149] phototherapy was initiated within 24 hours of birth, and the mean baseline serum bilirubin levels was 97 ± 33 micromol/litre in the one study[129] that reported. In the studies that reported gender, 1179 participants (51.5%) were male.

Early phototherapy was initiated at varying serum bilirubin levels (e.g. 85.5 micromol/litre) or within 24 ± 12 hours of birth in low-birthweight babies. One study also used postnatal age, with phototherapy being initiated at 85 micromol/litre for the first week of life and at 120 micromol/litre in the second week of life. In three studies[145;149;150] babies in the control groups received phototherapy if their serum bilirubin levels reached an *a priori* cut-off of serum bilirubin.

Review findings

There were statistically 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[129;145;148-150] that reported on these outcomes (Figure 7.8). Most of the exchange transfusions were carried out in one study[129] in which exchange transfusions were conducted at relatively low levels of serum bilirubin based on birthweight and risk profile.[129] The number needed to treat with early phototherapy to prevent one exchange transfusion was 16.

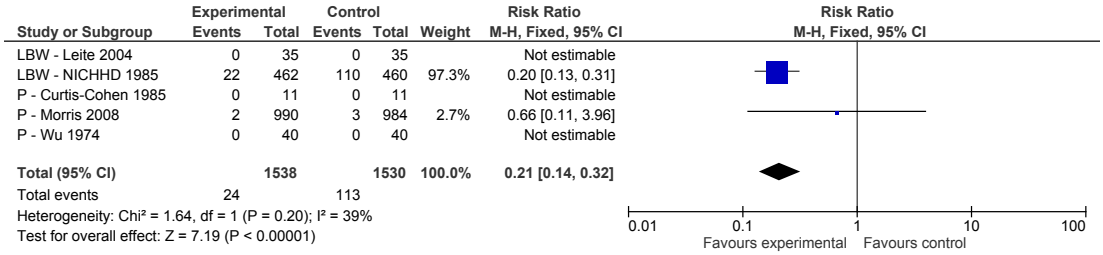


Figure 7.8 Number of exchange transfusions needed when early phototherapy is compared with no treatment in preterm babies

Four studies[129;145;148;150] examined treatment failure as an outcome. Treatment failure was defined as serum bilirubin rising above a predefined level or the need for exchange transfusion. There were statistically significantly fewer treatment failures in babies treated with early phototherapy (RR 0.23, 95% CI 0.17 to 0.32) (Figure 7.9). Heterogeneity was a factor ($I^2 = 53\%$).

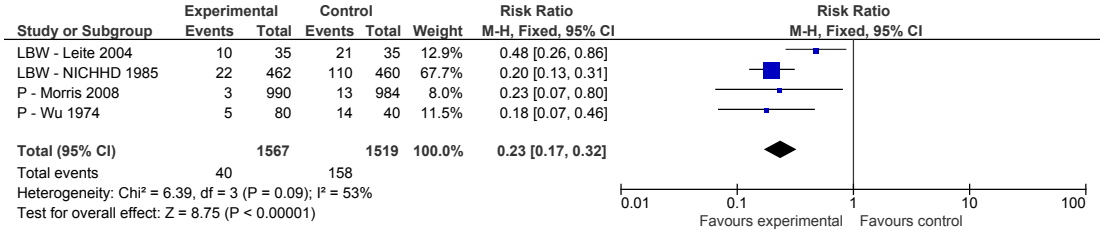


Figure 7.9 Number of treatment failures when early phototherapy is compared with no treatment in preterm babies

The mean peak in serum bilirubin was statistically significantly lower among babies who received early phototherapy (MD = −53.11 micromol/litre, 95% CI −59.44 to −46.78 micromol/litre) (Figure 7.10) but heterogeneity was high ($I^2 = 84\%$).

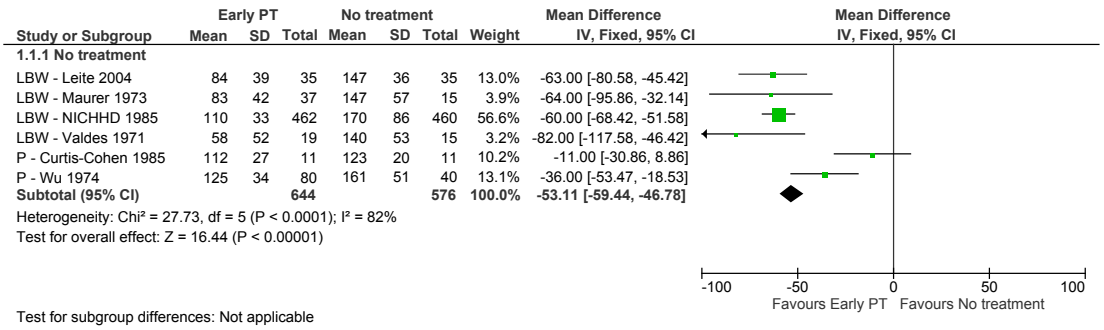


Figure 7.10 Mean peak serum bilirubin when early phototherapy is compared with no treatment in preterm babies

See below for the overall evidence summary and GDG translation from evidence for phototherapy in preterm/low-birthweight babies.

Conventional phototherapy versus multiple phototherapy

Description of included studies

Two studies[151;152] of EL 1+ and with 206 participants were included in this comparison. One study apiece was from Italy[152] and the USA.[151] One study[151] specified the method of

randomisation used as a computer-generated sequence and the other study[152] used sealed envelopes for allocation concealment.

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

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

Review findings

As the two studies used different populations (preterm and very preterm) and different time-points for measuring the change in serum bilirubin, it was not possible to pool the results. One study[151] measured serum bilirubin at 18 hours after initiation of phototherapy and this showed no statistically significant difference between conventional phototherapy and multiple phototherapy. The second study,[152] which measured change in serum bilirubin over 72 hours, found a statistically significant difference in favour of multiple phototherapy (MD = 11.00 micromol/litre, 95% CI 9.01 to 12.99 micromol/litre).

See below for the overall evidence summary and GDG translation from evidence for phototherapy in preterm/low-birthweight babies.

Conventional phototherapy versus fibreoptic phototherapy

Description of included studies

Six studies[152-157] with a total of 398 participants were included in this comparison. Four studies were carried out in Italy[152;153;155;157] and one apiece in Australia[156] and the Netherlands.[154] The evidence level of all included studies was EL 1+. One study[156] specified the method of randomisation used as the lottery method while the remaining five studies[152-155;157] used sealed envelopes.

Where reported, the mean gestational age ranged from 27.9 ± 1.4 weeks to 34.4 ± 1.2 weeks, mean birthweight ranged from 1019 ± 283 g to 2600 ± 382 g, mean age at entry to study ranged from 26.5 ± 15.0 hours to 63.2 ± 17.8 hours, and mean baseline serum bilirubin levels ranged from 94 ± 36 micromol/litre to 241 ± 9 micromol/litre. In the studies that reported gender, 162 (54.1%) participants were male.

Review findings

In a meta-analysis of these six studies, there was no statistically significant difference in the number of exchange transfusions carried out: only five babies who received conventional phototherapy and only seven babies who received fibreoptic phototherapy required exchange transfusions. There were no statistically significant differences for treatment failure (defined as requiring double phototherapy or reaching a predefined 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 statistically significant difference between the groups (MD = −1.17 micromol/litre, 95% CI −3.87 to 1.53 micromol/litre). There was no heterogeneity ($I^2 = 0\%$). Four studies contributed data on the mean duration of phototherapy and there was a statistically significant difference between the groups in favour of fibreoptic phototherapy (MD = 2.63 hours, 95% CI 0.69 to 4.58 hours). There was no heterogeneity ($I^2 = 0\%$).

See below for the overall evidence summary and GDG translation from evidence for phototherapy in preterm/low-birthweight babies.

Conventional phototherapy versus LED phototherapy

Description of included studies

Two studies[158;159] with 119 participants were included in this comparison. One study was carried out in Brazil[158] and the other in Italy.[159] The evidence level in one study[158] was EL 1–

and in the other[159] EL 1+. Neither study reported on the randomisation method. One study[159] reported using sealed envelopes for allocation concealment.

The mean gestational ages were 30.7 ± 2.0 weeks and 33.6 ± 1.9 weeks, the mean ages at time of entry to the study were 64.4 ± 15.2 hours and 68.1 ± 25.5 hours, the mean birthweights were 1192 ± 238 g and 1998 ± 541 g, and the mean baseline serum bilirubin levels were 180 ± 38 micromol/litre and 200 ± 16 micromol/litre. One study[158] reported gender and 58 participants (65.9%) were male.

Review findings

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 (eight versus 12) but this difference was not statistically significant.

Phototherapy in both studies was terminated once a predefined 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 statistically significantly shorter duration of phototherapy (MD = −9.15 hours, 95% CI −3.53 to −14.77) but heterogeneity was high (I^2 = 90%).

Overall evidence summary for phototherapy in preterm/low-birthweight babies

The pooled results of meta-analysis indicate that phototherapy is effective in the treatment of hyperbilirubinaemia in preterm 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 to statistically significantly decrease the risk of exchange transfusion and treatment failure when compared with no treatment. However, in the study that 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 with conventional phototherapy.

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

LED phototherapy was shown to shorten statistically significantly the duration of treatment compared with 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 statistically significant.

Overall GDG translation from evidence for phototherapy in 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 preterm 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 that 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 7.1.1.

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 fact that parents can hold and feed the baby, and that 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 despite phototherapy some babies require further medical interventions.

Recommendations

See the end of Section 7.2.1.

Bulb colour for conventional phototherapy

Description of included studies

Six studies[160-165] with a total of 674 participants were included in this comparison. Two of the studies were from Denmark[160;161] and one apiece were from Greece,[162] Italy,[164] Switzerland[163] and the USA.[165] The included studies ranged from EL 1– to EL 1+. One study[163] used a random numbers table and one study[160] used sealed envelopes for allocation concealment.

One study dealt with term[163] and three with preterm[160;161;164] babies and as there were no statistically significant differences in outcome these were analysed together. Where 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 1930 g to 3395 ± 547 g, and the mean baseline serum bilirubin levels ranged from 190 micromol/litre to 292 ± 35 micromol/litre. In all, 142 participants (55.5%) were male.

Review findings

Regarding duration of treatment, green phototherapy was statistically significantly shorter than blue phototherapy (MD = 7.03 hours, 95% CI 6.23 to 7.83 hours), which in turn was statistically significantly shorter than white phototherapy (MD = −32.00 hours (95% CI −44.72 to −19.28 hours) (Figure 7.11).

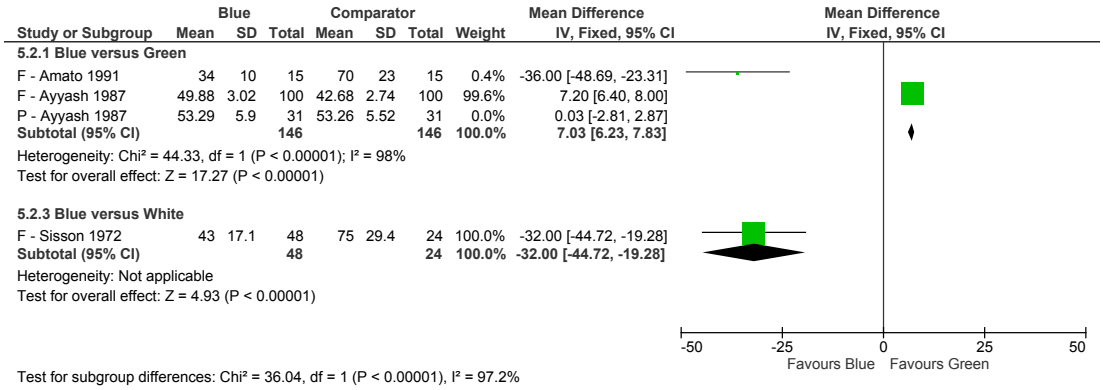


Figure 7.11 Mean duration of treatment when blue lamps are compared with green lamps and with white lamps

Compared with blue phototherapy, there was a statistically significantly greater decrease in serum bilirubin levels among babies treated with green phototherapy (MD = 3.98 micromol/litre, 95% CI 3.43 to 4.52 micromol/litre), both in term and preterm babies (Figure 7.12). Turquoise phototherapy also resulted in a statistically significantly greater decrease in serum bilirubin levels (MD = 14.00 micromol/litre, 95% CI 3.76 to 24.24 micromol/litre).

Evidence summary for bulb colour for conventional phototherapy

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

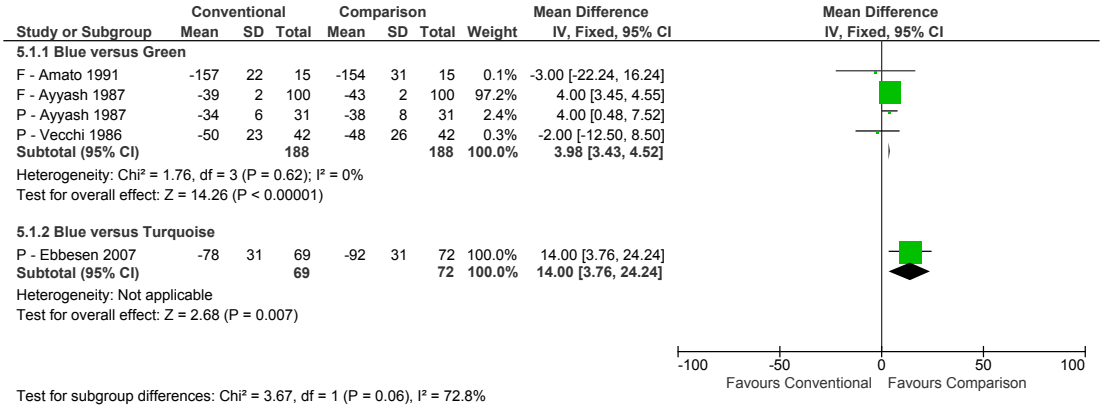


Figure 7.12 Mean decrease in serum bilirubin when blue lamps are compared with green lamps and with white lamps

GDG translation from evidence for 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 – 7.2.1 Type of phototherapy to use

Do not use sunlight as phototherapy for hyperbilirubinaemia.

Single phototherapy treatment for term babies

Use conventional 'blue light' phototherapy as treatment for significant hyperbilirubinaemia in babies with a gestational age of 37 weeks or more unless:

- the serum bilirubin level is rising rapidly (more than 8.5 micromol/litre per hour)
- the serum bilirubin is at a level that is within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours (see the threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).

Do not use fibreoptic phototherapy as first-line treatment for hyperbilirubinaemia for babies with a gestational age of 37 weeks or more.

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

Single phototherapy treatment for preterm babies

Use either fibreoptic phototherapy or conventional 'blue light' phototherapy as treatment for significant hyperbilirubinaemia in babies less than 37 weeks unless:

- the serum bilirubin level is rising rapidly (more than 8.5 micromol/litre per hour)
- the serum bilirubin is at a level that is within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours (see treatment threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).

Continuous multiple phototherapy treatment for term and preterm babies

Initiate continuous multiple phototherapy to treat all babies if any of the following apply:

- the serum bilirubin level is rising rapidly (more than 8.5 micromol/litre per hour)
- the serum bilirubin is at a level within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6)).
- the bilirubin level fails to respond to single phototherapy (that is, the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting single phototherapy)

Research recommendations

What is the clinical and cost-effectiveness of:

- **LED phototherapy compared to conventional phototherapy in term and preterm babies with significant 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 the need for additional fluids. New randomised controlled trials are needed to examine LED phototherapy. Population: Term and preterm babies with significant hyperbilirubinaemia 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 significant hyperbilirubinaemia?**

Why this is important

Existing research has demonstrated the effectiveness of fiberoptic phototherapy in preterm 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 randomised controlled trials are needed to examine fiberoptic phototherapy which uses larger pads. Population: Term babies with significant 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

7.2.2 General care of the baby during phototherapy

Fixed position versus changing positions

Description of included studies

Three studies[166-168] with 133 participants were included in this comparison but not all studies contributed data to each analysis. One study apiece was from Iran,[168] [EL 1−] Israel[166] [EL 1+] and Taiwan.[167] [EL 1+] No study reported the method of randomisation although two studies[166;167] used sealed envelopes for allocation concealment.

All three studies included only term babies. Where 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 3137 ± 384 g to 3500 ± 478 g, and the mean baseline serum bilirubin levels ranged from 320 ± 17 micromol/litre to 321 ± 39 micromol/litre. For the two studies[166;167] that reported gender, 27 of 81 participants (33.3%) were male.

Review findings

There was a trend (not statistically significant) 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 hours) (Figure 7.13).

A similar trend was also reported for mean change in serum bilirubin (MD = −5.98 micromol/litre, 95% CI −14.79 to 2.82 micromol/litre) (Figure 7.14).

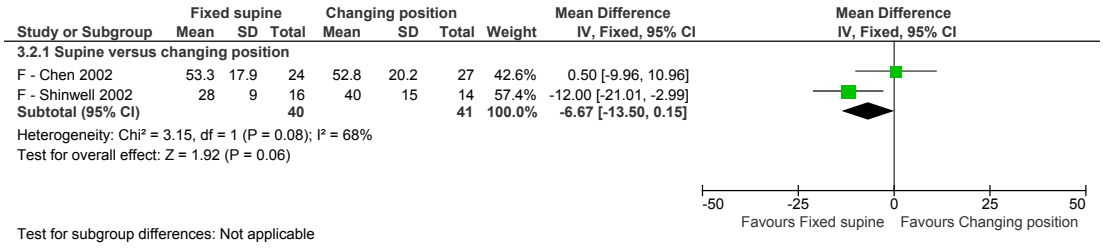


Figure 7.13 Mean duration of treatment when fixed supine position is compared with changing the baby's position

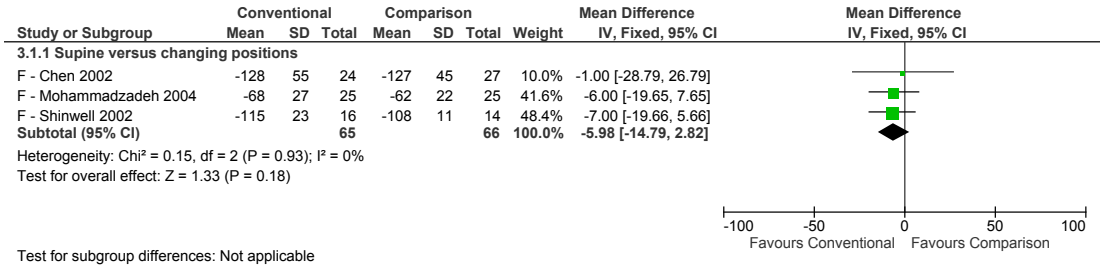


Figure 7.14 Mean change in serum bilirubin when fixed supine position is compared with changing the baby's position

Evidence summary

There was a trend (not statistically significant) 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 on 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.

Recommendations

See the end of Section 7.2.2.

Eye coverings

Description of included studies

Two studies, reported in three publications,[169-171] with 241 participants were eligible for this comparison but only one[170] (comparing eye patches with a tinted headbox) contributed outcome data. One study[169;170] was from Hong Kong and the other was from Italy.[171] The evidence level of one study[169;170] was EL 1+ as a computer-generated sequence was used to allocate babies into the two groups. The second study[171] was rated EL 1– as neither the method of randomisation or allocation concealment was reported.

The mean gestational age from this study[169;170] was 38.6 ± 2.6 weeks, the mean age at entry to study was 89.5 ± 27.6 hours, the mean birthweight was 3087 ± 611 g, and the mean baseline serum bilirubin level was 258 ± 27 micromol/litre. In this study, 106 participants (52.2%) were male.

Review findings

There were statistically significantly more cases of purulent eye discharge among the eye patches group compared with the headbox group (RR 2.53, 95% CI 1.23 to 5.20) (Figure 7.15).

Similarly, there were more features of conjunctivitis among the eyepatch group (RR 6.44, 95% CI 1.49 to 27.80). (Figure 7.16)

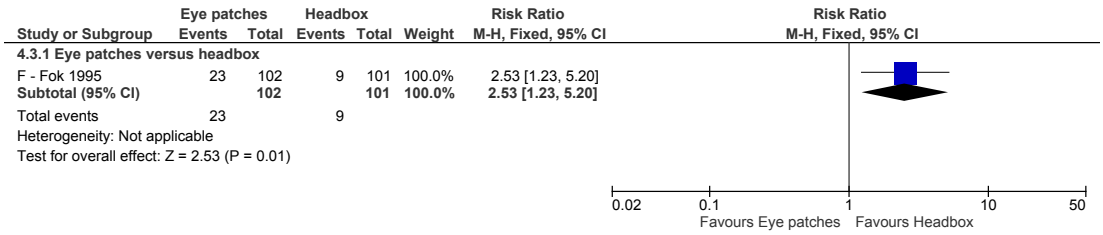


Figure 7.15 Purulent eye discharge when the use of eye patches is compared with headboxes

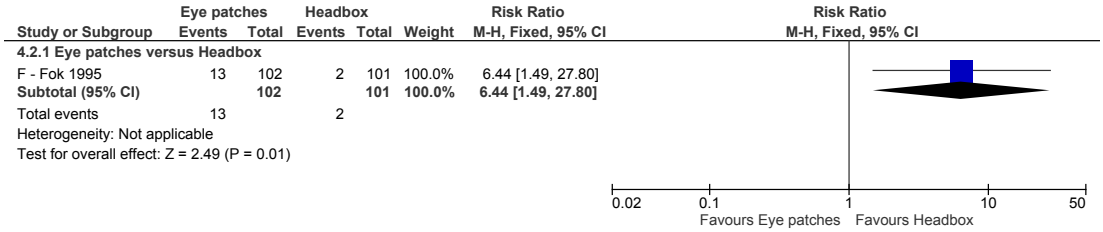


Figure 7.16 Features of conjunctivitis when the use of eye patches is compared with headboxes

Evidence summary

One RCT reported fewer cases of purulent eye discharge and conjunctivitis among babies nursed in a headbox while receiving phototherapy compared with 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 concluded 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 – 7.2.2 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 environment that will minimise energy expenditure (thermoneutral environment)
- monitor hydration by daily weighing of the baby and assessing wet nappies
- support parents and carers and encourage them to interact with the baby

Give the baby eye protection and routine eye care during phototherapy.

Use tinted headboxes as an alternative to eye protection in babies with a gestational age of 37 weeks or more undergoing conventional 'blue light' phototherapy.

7.2.3 Feeding and hydration during phototherapy

Interupting phototherapy for feeding – intermittent versus continuous phototherapy

Description of included studies

Two studies[172;173] ($n = 110$) contributed to this analysis, each comparing continuous phototherapy with various intermittent regimens. One study[172] was from Hong Kong and one[173] from the USA. The evidence level of both studies was EL 1–. Neither study reported the method of randomisation or allocation concealment.

Data from the various intermittent regimens were combined. Respectively the mean gestational ages were 34.7 ± 2.0 weeks[173] and 39.9 ± 1.5 weeks,[172] the mean age at entry to study was 56.8 ± 10.8 hours in one study[173] and not reported in the second, the mean birthweight was 1836 ± 299 g[173] and 3229 ± 394 g,[172] and the mean baseline serum bilirubin levels were 150 ± 19 micromol/litre[173] and 198 ± 25 micromol/litre.[172] Gender was not reported. One study each dealt with term[172] and preterm[173] babies.

Review findings

There was a difference (not statistically significant) between the two groups in favour of continuous phototherapy (MD = −6.97 hours, 95% CI −26.31 to 12.38 hours) (Figure 7.17).

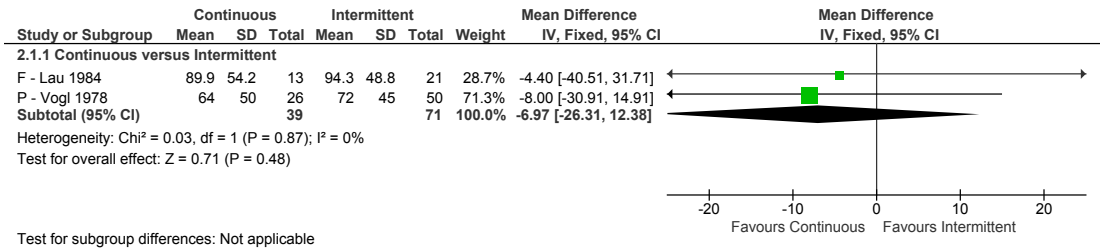


Figure 7.17 Mean duration of treatment when continuous phototherapy is compared with intermittent phototherapy

Evidence summary

Two RCTs, 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 statistically 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 and 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 used by healthcare 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 Sections 7.1.1 and 7.1.2.)

Recommendations

See the end of Section 7.2.3.

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 up milk feeds by bottle/cup/spoon or other liquids (water/juice)
- parenteral feeds

The electronic searches (which were not restricted by study methodology) identified 1831 references although 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, four were included and 16 were excluded for the following reasons: babies were not jaundiced (five studies), not randomised (five studies), no clear intervention (four studies), comparison of phototherapy with interruption of breastfeeding (one study), and the comparison of hospital routines which included feeding (one study).

The included studies were divided into two groups: one group dealt with fluids or feeds given in combination with phototherapy and the other dealt 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 RCTs ($n = 278$) dealt with additional fluids or feeds alongside phototherapy for the treatment of hyperbilirubinaemia. Two studies used computer-generated[133] or block randomisation[174] and two studies[174;175] used sealed envelopes to conceal allocation. Where reported, the mean birthweight of the samples ranged from 2936 ± 473 g to 3404 ± 361 g, the mean gestational age ranged from 37.6 ± 0.9 weeks to 39.4 ± 0.9 weeks, the mean age at entry to the study ranged from 95 ± 17.7 hours to 139 ± 47 hours, and the mean serum bilirubin levels ranged from 254 ± 22 micromol/litre to 377 ± 66 micromol/litre. Of the combined sample, 188 participants (67.6%) were male.

Review findings

The first RCT($n = 74$), from India,[174] 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 30 ml/kg per 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. Statistically significantly more exchange transfusions were needed among babies receiving standard hydration (RR 3.3, 95% CI 1.51 to 7.35). The 'extra fluids' group also showed a statistically significantly greater mean reduction in serum bilirubin (MD = 26 micromol/litre, 95% CI 10.60 to 41.40 micromol/litre) over 24 hours and a shorter duration of phototherapy (MD = 21 hours, 95% CI 9.45 to 32.55 hours). [EL 1 + +]

The second RCT($n = 54$), from Malaysia,[175] 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 per day 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 eight divided feeds at 3-hour intervals. Breastfed babies were fed on demand. In addition, the breastfed 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 statistically significant. There was a greater decrease in serum bilirubin in the babies given supplemental intravenous fluids, but again this difference was not statistically significant. [EL 1+]

An RCT(n = 125) carried out in Argentina[133] 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 although subjects were randomised using a computer-generated sequence of numbers. There was no statistically significant difference between the two groups in mean decrease in serum bilirubin over the 48 hours of phototherapy. [EL 1+]

The final RCT(n = 25), from Thailand,[176] compared the effect on serum bilirubin of different types of formula feeds in combination with phototherapy. The formula feed Enfamil® was compared with the lactose-free formula Enfamil ProSobee®. These feeds have compatible energy, carbohydrate, fat and mineral content: Enfamil ProSobee has a slightly higher protein content that Enfamil. Babies were fed with 3 ounces of formula eight times a day over 72 hours of conventional phototherapy. Blinding and randomisation methods were not reported. There was no statistically significant difference between the types of formula in 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 showed that fewer babies given additional intravenous fluids during phototherapy needed exchange transfusion, they have a greater reduction in mean serum bilirubin, and need shorter duration of phototherapy compared with babies given only enteral feeds. The second study did not confirm these findings.

In one EL I− RCT, formula feeds was no more effective than breastfeeding 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 preterm 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/CG37). 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 the end of Section 7.2.3.

Adverse effects of phototherapy

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

Description of included studies

Thirteen studies[177-189] of varying quality (EL 2 – to EL 1 + +) from France,[181;182] Israel,[186;189] the Netherlands,[187] Sweden,[180] Thailand,[185;188] Turkey [178;179;183] and the USA[177;184] were identified.

Review findings

DNA damage

A non-systematic review of *in vivo* studies[177] demonstrated that phototherapy had DNA-modifying properties that could induce genetic and carcinogenic effects. [EL 1 +].

A second study from Turkey[178] examined the effects on DNA in 33 term babies who received phototherapy for jaundice compared with 14 otherwise healthy controls with jaundice who did not receive phototherapy. There were no significant differences between the groups at entry. The mean gestational age was 39.3 ± 0.9 weeks, the mean birthweight was 3021 ± 450 g, and the mean age at entry was 113 ± 46 hours. Twenty-nine (61.7%) of the sample were male. Phototherapy was applied using a standard Air-Shields unit with four 18 W blue-fluorescent tubes and two 18 W white fluorescent tubes. The light range was between 480 and 520 nm and the irradiance was 12 microwatt/cm² per 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 (which is 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 or 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 statistically 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[179] 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 otherwise healthy controls with jaundice who did not receive phototherapy. The gestational age ranged from 38 to 41 weeks and age at entry was between 3 and 10 days. No other demographic details were reported. Phototherapy was applied using a standard BiliCrystal® unit with either six 20 W white fluorescent tubes placed 45 cm above the baby or, for intensive phototherapy, twelve 20 W white fluorescent tubes placed 20 cm above the baby. The irradiance was 12–16 microwatt/cm² per nm for conventional phototherapy and 30–34 microwatt/cm² per 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 statistically 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[180] 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 statistically significant risk of developing childhood malignant melanoma after phototherapy of babies with hyperbilirubinaemia was found. [EL 2 –]

A second study[181] examined data from an RCT of photoprotection educational programmes for 8- to 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 < 2 mm, 2–5 mm or > 5 mm. Children who had received phototherapy showed no statistically significant difference in naevus counts than those who had not. [EL 1 +]

A small case–control study from France[182] assessed the role of blue light phototherapy used to treat hyperbilirubinaemia on naevus acquisition in children aged 8–9 years. 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 < 2 mm, 2–5 mm or > 5 mm.

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 2 mm or larger was statistically significant ($P = 0.003$). [EL 2 –]

Trans-epidermal water loss

A case–control study from Thailand[185] examined trans-epidermal water loss (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 the mean birthweight was 3166 ± 435 g. The mean serum bilirubin of the babies receiving phototherapy was 248 ± 15 micromol/litre. In all, 44 (55%) 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 statistically significantly higher than the rate of loss in control babies not requiring phototherapy. [EL 2 –]

Another case series, from Israel,[186] examined TEWL during phototherapy in preterm babies. The study included 31 babies, of whom 15 (48%) were males, with a mean gestational age of 31.2 weeks and a mean birthweight of 1447 g. 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%. [EL 3]

A second case series, from the Netherlands,[187] 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 g 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 55 cm above the baby with an irradiance of 12.5 microwatt/cm² per nm. There was an increase of 21.3% in TEWL after 1 hour of phototherapy with halogen lamps. [EL 3]

An RCT in Thailand[188] evaluated the effect of application of a clear topical ointment on TEWL in preterm babies receiving phototherapy. In this study, 40 babies (22 (55%) were male) with a mean gestational age of 33.1 ± 2.6 weeks, a mean birthweight of 1443 ± 196 g and a mean serum bilirubin of 171 ± 39 micromol/litre 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 statistically significant difference between the groups in pre- and post-phototherapy serum bilirubin levels. [EL 1 –]

Heart-rate variability

A controlled before and after study from Israel[189] examined the effects of phototherapy on cardiovascular function. Thirty term babies with Apgar score > 7 at 1 minute and > 8 at 5 minutes who required phototherapy for jaundice were included. Babies with haemolysis, G6PD 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 the mean birthweight was 3116 ± 392 g. The mean age at entry to study was 53 ± 31 hours and the mean serum bilirubin was 238 ± 43 micromol/litre. Sixteen participants (53%) were male. While there were no statistically significant changes in heart rate during phototherapy, significant changes in heart-rate variability were observed. Mean SD1 measurements before and during phototherapy were 12 ± 8 ms 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, respectively ($P < 0.02$). [EL 3]

Vasodilator effects

An RCT[183] 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 preterm babies. The mean gestational age of the term babies was 38.7 ± 1.2 weeks and the mean birthweight was 3361 ± 449 g while for preterm babies the mean gestational age and mean birthweight were 33.5 ± 2.8 weeks and

2088 ± 604 g, respectively. No statistically 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. [EL 1 –]

Patent ductus arteriosus

An RCT[184] 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 the mean birthweight was 1035 g. 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 statistically significantly lower frequency of patent ductus arteriosus ($P < 0.009$) but with a non-statistically significant trend to increased later mortality (up to 167 days), with ten versus four deaths ($P = 0.056$). The majority of deaths were due to complication of preterm birth or sepsis and were not related to the course of therapy in the first 4 weeks. [EL 1 +]

Evidence summary

Studies of mixed quality reported that TEWL increased significantly (by up to 25%) in babies receiving conventional phototherapy. An RCT [EL 1 –] of close and distant phototherapy found no statistically significant differences in clinical variables, including body temperature, heart rate and blood pressure, during phototherapy. Three studies, one EL 1+ and two EL 2 –, examined the association between history of exposure to phototherapy and later naevus acquisition in primary-school children. No statistically significant association was identified. One small study reported a statistically 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 TEWL, whereas halogen lights do increase such water losses. Conventional phototherapy should be interrupted to facilitate breastfeeding, and mothers should be offered lactation support. Breastfeeding 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, 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 – 7.2.3 Feeding and hydration during phototherapy

During conventional 'blue light' phototherapy:

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

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

During multiple phototherapy:

- do not interrupt phototherapy for feeding but continue administering intravenous/enteral 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

7.2.4 Additional equipment

White curtains

Description of included studies

Three RCTs[190-192] ($n = 285$) were eligible for this comparison. One study apiece was from Germany,[191] India[192] and Malaysia.[190] One study[190] was rated EL 1+ as block randomisation was used and investigators were blind to the allocation, the second[192] was rated EL 1+ as sealed opaque envelopes were used as allocation concealment while the third study[191] did not report on either the randomisation method or the allocation concealment and so was rated EL 1–. In one study[190] the four outer walls of the incubator were draped in white cloth while in the other[191;192] two a white cloth was hung from both sides of the phototherapy unit.

The mean gestational 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 2856 ± 345 g and not reported in the other two studies. The mean age at entry to study was 69 ± 36 hours and 105 ± 35 hours in two studies and was not reported in the third study. The mean serum bilirubin ranged from 243 ± 28 micromol/litre to 280 ± 39 micromol/litre. In all, 165 participants (58.3%) were male.

Review findings

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 statistically 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 micromol/litre (95% CI –33.75 to –14.25 micromol/litre) and at 24 hours the mean difference was –20.36 micromol/litre (95% CI –31.52 to –9.19 micromol/litre) (Figure 7.18).

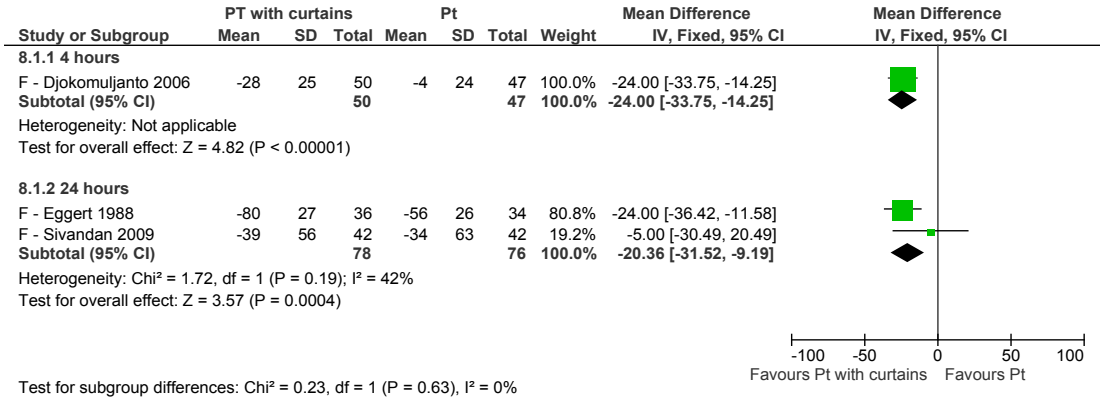


Figure 7.18 Mean change in serum bilirubin when white curtains are used compared with not using white curtains

One study reported that white curtains made no statistically significant difference to the mean duration of phototherapy.[192] Another study, using Cox proportional hazards regression analysis, reported that the median duration of phototherapy was statistically significantly shorter (22 hours) in the phototherapy with curtains group compared with the control.[190]

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 reported 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.

Using incubators or bassinets

Description of included studies

No studies were identified.

Review findings

No studies were identified.

Evidence summary

No evidence was identified.

GDG translation from evidence

As no evidence was identified, the GDG cannot recommend the use of incubators or bassinets for the treatment of hyperbilirubinaemia and considers that clinical considerations and availability should determine whether either of these 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 that minimises their energy expenditure on keeping warm or cool.

Recommendations – 7.2.4 Additional equipment

Use incubators or bassinets according to clinical need and availability.

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

7.3 Exchange transfusion

Clinical question

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

Description of included studies

Following electronic searches, 103 records were identified and 17 hard-copy articles were requested. Following expert advice, five more hard-copy articles were ordered so a total of 22 studies were included. 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.

Review findings

Double-volume exchange transfusion

In six RCTs,[193-199] 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 75–170 ml/kg body weight. Exchange transfusions were initiated at varying serum bilirubin levels, the lowest being 256.5 micromol/litre in preterm babies and 307.8 micromol/litre in term babies. In one RCT[194;195] reported in two articles, 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[193] carried out in the USA compared exchange transfusion with no treatment in 100 babies with indirect serum bilirubin > 307.8 micromol/litre. Babies were less than 1 week old. Demographic details and method of randomisation were not reported although 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 the control group had kernicterus confirmed by autopsy. Seven of the exchange transfusion group had an abnormal neurological examination at 12–24 months compared with six in the control group. [EL 1+]

DVET versus simple transfusion

This RCT[194;195] 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 although sealed envelopes were used to conceal allocation to intervention groups. There were statistically significantly fewer deaths in the exchange transfusion group (RR 0.26, 95% CI 0.11 to 0.60) and also statistically significantly fewer cases of kernicterus (RR 0.38, 95% CI 0.17 to 0.87). [EL 1+]

DVET versus single-volume exchange transfusion

This RCT,[196] carried out in Switzerland, compared DVET with single-volume exchange transfusion (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, the mean birthweight was 3305 ± 392 g, the mean age at entry to study was 17.9 ± 6.1 hours, and the mean serum bilirubin was 207 ± 45 micromol/litre. 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.[200] There was no statistically 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,[197] carried out in Singapore, compared DVET with phototherapy for the management of non-haemolytic hyperbilirubinaemia. In all, 52 babies were included, of whom 28 (54%) were male. The mean gestational age of the sample was 37.0 ± 2.78 weeks, the mean birthweight was 2501 ± 576 g, the mean age at entry to study was 84 ± 12 hours, and the mean serum bilirubin was 297 ± 25 micromol/litre. Both interventions were initiated at serum bilirubin > 256.5 micromol/litre in preterm babies and > 307.8 micromol/litre in term babies. Neither the method of randomisation nor allocation concealment was reported but there were no significant differences between the groups on any baseline variable. There was a statistically significantly greater reduction in mean serum bilirubin 24 hours after initiation of treatment in the phototherapy group (MD = 51 micromol/litre, 95% CI 39.7 to 62.3 micromol/litre). 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 eight babies requiring repeat exchange transfusion, while no babies in the phototherapy group required additional treatment. The RR of treatment failure in the exchange transfusion group was statistically significant, although confidence intervals were wide, at 17.00 (95% CI 1.03 to 280.07). There were no cases of kernicterus in either group. [EL 1–]

Alternative methods for DVET

The fifth RCT,[198] carried out in Canada, compared conventional DVET with albumin-enriched DVET. A total of 42 babies were included, of whom 25 (60%) were male, and 27 (64%) had Rhesus or ABO incompatibility. The mean gestational age of the sample was 36.0 ± 0.7 weeks, the mean birthweight was 2455 ± 153 g, and the mean serum bilirubin was 263 ± 82 micromol/litre. Neither the method of randomisation nor allocation concealment was reported but there were no significant differences between the groups on any baseline variable. There was no statistically 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,[199] carried out in the USA, compared DVET with exchange transfusion with frozen erythrocytes diluted in plasma. The sample was divided into low-birthweight (< 2500 g) and appropriate-birthweight (> 2500 g) groups, 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, the mean birthweight was 1670 ± 434 g, and the mean serum bilirubin was 304 ± 48 micromol/litre, while in the appropriate-birthweight group the mean gestational age of the sample was 39.1 ± 1.8 weeks, the mean birthweight was 3234 ± 494 g, and the mean serum bilirubin was 328 ± 25 micromol/litre There was no statistically significant difference between DVET and frozen erythrocytes in mean reduction of serum bilirubin or in the number of treatment failures or deaths. There were no cases of kernicterus or reported adverse effects in either group. [EL 1 –]

Side effects of DVET

A non-randomised controlled study from India[201] 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 intravenously for every 100 ml 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. [EL 1 –]

A study from India,[202] 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 3]

Another retrospective chart review from the USA[203] 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 the mean birthweight was 2388 ± 973 g. Thirty (55%) of the sample were male. The mean serum bilirubin was 307.8 ± 136.8 micromol/litre. An adverse event was attributed if it occurred within 7 days of exchange transfusion. One baby died and another suffered seizures. The most common adverse effects were thrombocytopenia (22 babies), hypocalcaemia (19), catheter malfunction (six), hypotension (five), venous thrombosis (two), hypokalaemia (two) and hypoglycaemia (two). One baby each suffered from bradycardia, acute renal failure and omphalitis. [EL 3]

A third retrospective chart review in the USA[204] 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 the mean body weight was 2846 ± 806 g. 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 (one death and 26 requiring treatment) and thrombocytopenia (two deaths and 15 requiring treatment). Twelve babies experienced catheter malfunctions (due to clotting) requiring a replacement catheter and/or discontinuation of treatment. [EL 3]

The National Institute of Child Health and Human Development (NICHHD) study in the USA[129] 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/litre for high-risk low-birthweight babies to 342 micromol/litre for babies with birthweight > 2500 g. The mean reduction in serum bilirubin was 139 ± 30 micromol/litre. Adverse effects related to exchange transfusions were transient bradycardia in eight babies (4.2%) – six after receiving calcium – transient cyanosis in three (1.6%), transient vasospasm in two (1.0%), vasospasm with thrombosis in two (1.0%) and apnoea and/or bradycardia requiring treatment in seven babies (3.7%). Three babies died within 24 hours (one within 6 hours) of exchange transfusion. [EL 1 + +]

Evidence summary

Most of the included RCTs 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 with 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 statistically 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 thrombocytopenia, hypocalcaemia, catheter malfunction, hypotension, venous thrombosis, hypokalaemia and hypoglycaemia.

GDG translation from evidence

The GDG considered the potential adverse side effects of DVET when carried out by experienced healthcare professionals and concluded that this procedure is relatively safe and effective for babies at risk of kernicterus from severe hyperbilirubinaemia.

The GDG noted that a single study reported no difference between SVET and DVET 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 absence of evidence to support these practices they should not be recommended.

Blood used for exchange transfusions should comply with the current guidance from the British Committee for Standards in Haematology (www.bcshguidelines.com). The GDG noted that babies whose parents object to the use of blood transfusions for religious or cultural reasons should be treated with the same standard of care as all babies, with the best interests of the child paramount. Local procedures should be in place to support communication with parents in this situation.

As stated in Section 3.2, acute bilirubin encephalopathy is a risk factor for kernicterus, and as such the GDG concluded that there is no reason to change 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.

As bilirubin levels may not fall and may continue to rise, even after an exchange transfusion, it is considered 'best' practice to estimate bilirubin levels within 2 hours to assess whether another exchange transfusion is needed.

Recommendations – 7.3 Exchange transfusion

Use a double-volume exchange transfusion to treat babies:

- whose serum bilirubin level indicates its necessity (see threshold table (Section 1.3) and treatment threshold graphs (Section 1.6))
  and/or
- with clinical features and signs of acute bilirubin encephalopathy.

During exchange transfusion do not:

- stop continuous multiple phototherapy
- perform a single-volume exchange
- use albumin priming
- routinely administer intravenous calcium.

Following exchange transfusion:

- maintain continuous multiple phototherapy
- measure serum bilirubin level within 2 hours and manage according to threshold table (Section 1.3) and treatment thresholds graphs (Section 1.6).

7.4 Other treatments

Clinical questions

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 such as Yin-chen)

Following electronic searches, which were 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 hard-copy articles were obtained. For some interventions, no RCTs were identified so other study types were used in these analyses.

7.4.1 Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) acts by preventing the destruction of sensitised erythrocytes. IVIG contains pooled IgG immunoglobulins extracted from the plasma of over 1000 blood donors. The Department of Health has recently updated their guidance on the use of IVIG (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085235).

Description of included studies

Eleven articles were obtained, including reports of five RCTs[205-209] carried out in Argentina,[205] Germany,[207] Iran,[209] Saudi Arabia[206] and Turkey[208] 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 (two studies), compared different dosages of IVIG (one), examined IVIG as prophylaxis to prevent the need for phototherapy (one), non-English language (one) and conference abstract (one).

One study[208] reported using random numbers to allocate the babies into the treatment groups and using sealed envelopes to conceal the treatment allocation and so was rated EL 1++. None of the other studies reported the method of randomisation or allocation concealment and so

were rated EL 1– . IVIG was administered as a single dose (500 mg/kg body weight) over 2 hours in one study,[207] as a single dose (500 mg/kg body weight) over 4 hours in the second,[206] as a single dose (500 mg/kg body weight) as soon as possible after birth in the third study,[208] as three doses (500 mg/kg body weight each) over 4 hours every 12 hours in the fourth study,[209] and as 800 mg/kg body weight per day for 3 days in the final study.[205]

Two studies[205;208] included both term and preterm babies while the other three[206;207;209] included only term babies. Three of the studies[205;207;208] included only babies with Rhesus haemolytic disease, one[206] included only babies with ABO haemolytic disease and the fifth[209] included babies with either Rhesus or ABO haemolytic disease and presented the results for both groups. The mean birthweight ranged from 2683 ± 292 g to 2834 ± 569 g in four studies[205;206;208;209] and was not reported in the other study.[207] The mean age at entry to study was 20.2 ± 9.5 hours in the one study[209] that reported this. The mean serum bilirubin was 254 ± 57 micromol/litre in the one study[209] that reported this. The mean gestational age ranged from 36.1 ± 2 weeks to 38 weeks in three studies[205;206;208] and another[209] included only term babies. In the three studies[206;208;209] that reported on gender, 109 participants (58.3%) were male.

Review findings

Dichotomous outcomes

Indications for exchange transfusion in the studies included serum bilirubin ≥ 340 micromol/litre (two studies), serum bilirubin ≥ 307.8 micromol/litre in babies over 2000 g, serum bilirubin above the Polacek criteria,[210;211] and serum bilirubin rising by 8.5 or 17.1 micromol/litre per hour. Babies randomised to receive IVIG needed statistically significantly fewer exchange transfusions than controls (RR 0.31, 95% CI 0.20 to 0.47) (Figure 7.19). Heterogeneity was not significant at $I^2 = 37\%$.

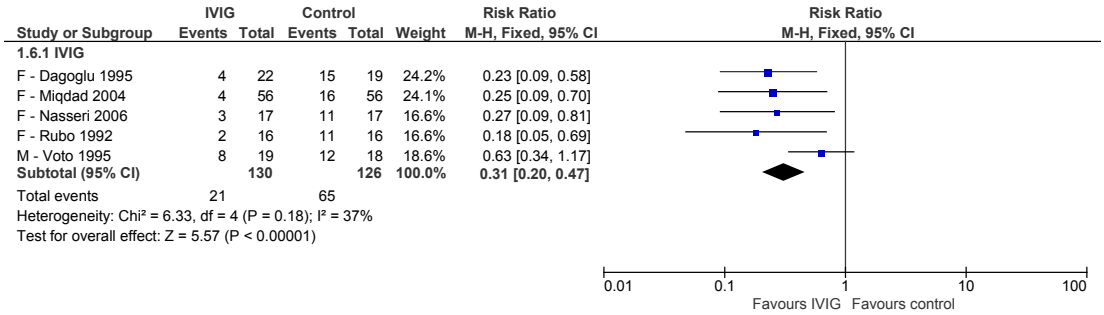


Figure 7.19 Number of exchange transfusions needed when IVIG combined with phototherapy is compared with phototherapy alone

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

The RR was similar in both Rhesus and ABO haemolytic disease: RR 0.33 (95% CI 0.20 to 0.52) and RR 0.29 (95% CI 0.13 to 0.68), respectively (Figure 7.20). 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 two while in ABO disease the NNT was five.

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

Continuous outcomes

Only three studies[205;206;209] reported the duration of adjunctive phototherapy. This was statistically significantly shorter in babies receiving IVIG (MD = −16.46 hours, 95% CI −26.13 to −6.79 hours) (Figure 7.21). Heterogeneity was not a significant factor at $I^2 = 27\%$.

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

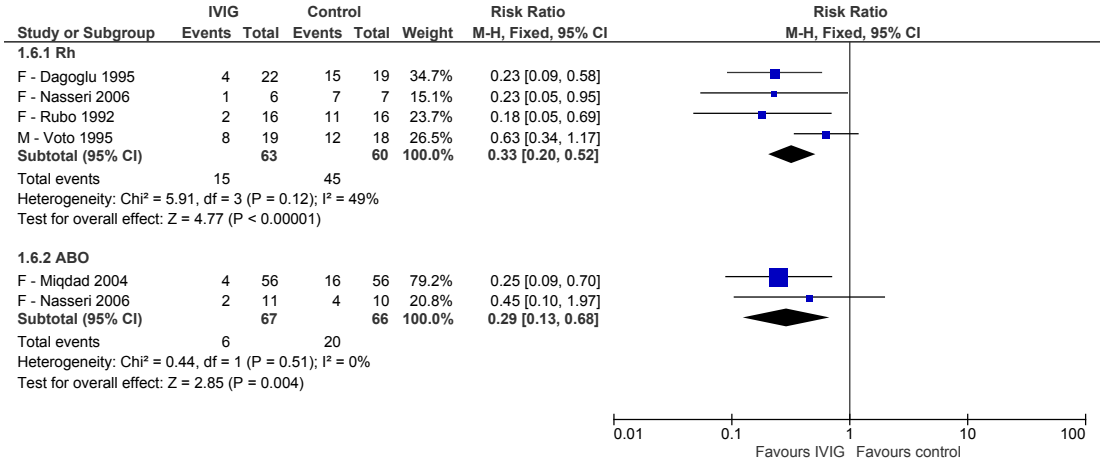


Figure 7.20 Number of exchange transfusions needed when IVIG combined with phototherapy is compared with phototherapy alone – sensitivity analysis based on ABO or Rh haemolysis

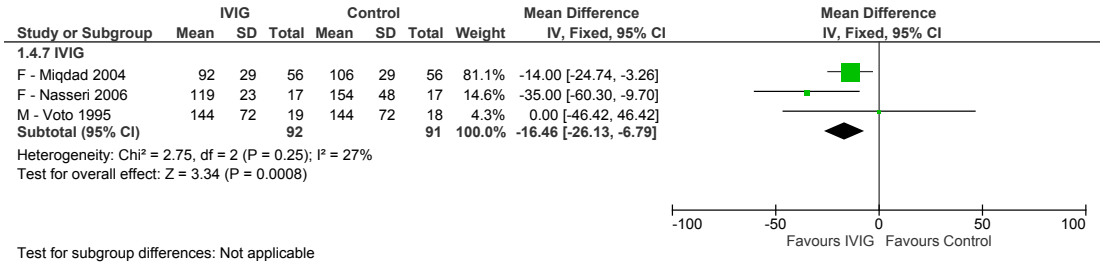


Figure 7.21 Mean duration of phototherapy when IVIG combined with phototherapy is compared with phototherapy alone

7.4.2 Other therapies

Clofibrate

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

Description of included studies

From the six articles obtained, one was excluded as the trial was not randomised. Five RCTs carried out in Iran[212-216] examined clofibrate combined with phototherapy against phototherapy alone for the treatment of non-haemolytic hyperbilirubinaemia. The evidence level of the included studies ranged from EL 1– to EL 1++. Three studies[212-214] reported using random numbers tables as the method of randomisation.

In four studies[213-216] clofibrate was administered in a single oral dose of 100 mg/kg body weight while in the fifth study[212] it was given in either a low dose of 25 mg/kg body weight or a moderate dose of 50 mg/kg body weight. This study reported results after the first 24 hours of treatment while the other RCTs reported up to 96 hours of treatment. This study[212] 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, the mean birthweight ranged from 2542 ± 547 g to 3259 ± 481 g, the mean age at entry to study ranged from 123 ± 55 hours to 216 ± 94.8 hours, the mean serum bilirubin ranged from 301 ± 23.4 micromol/litre to 395 ± 58 micromol/litre, and 145 (53.7%) of the sample were male.

Review findings

Dichotomous outcomes

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

Continuous outcomes

All five studies ($n = 310$) contributed to the analysis on the mean decrease in serum bilirubin. There was a statistically significantly greater decrease in serum bilirubin among those treated with clofibrate (MD = −63.62 micromol/litre, 95% CI −68.59 to −58.66 micromol/litre) (Figure 7.22). Heterogeneity was very high at $I^2 = 95\%$.

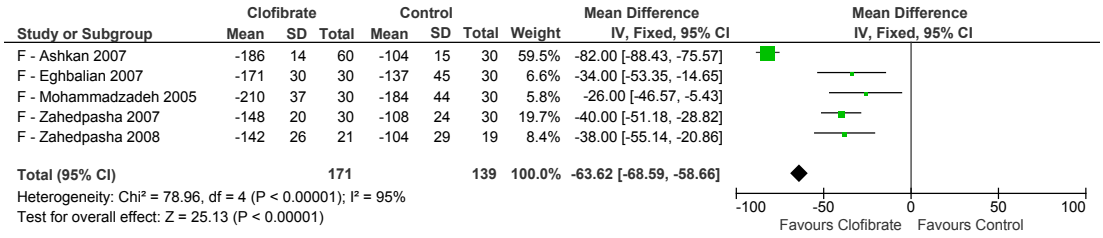


Figure 7.22 Mean decrease in serum bilirubin when clofibrate combined with phototherapy is compared with phototherapy alone

The *post hoc* sensitivity analysis excluding the low/moderate dose study showed an MD of −36.60 micromol/litre (95% CI −44.40 to −28.80 micromol/litre) and heterogeneity was non-existent at $I^2 = 0\%$ (Figure 7.23).

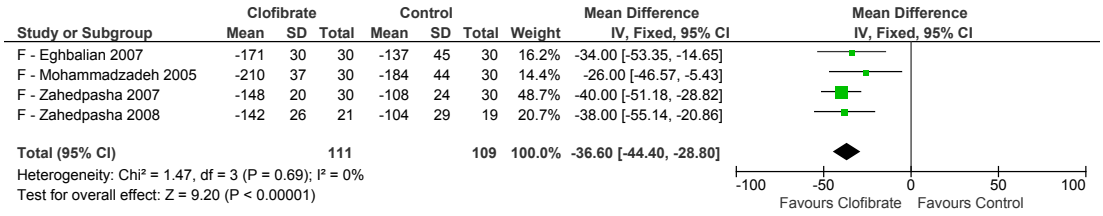


Figure 7.23 Mean decrease in serum bilirubin when clofibrate combined with phototherapy is compared with phototherapy alone – sensitivity analysis based on dosage used

Three studies[212-214] ($n = 210$) contributed data on duration of phototherapy. Babies who received clofibrate required a statistically significantly shorter time under phototherapy (MD = −9.58 hours, 95% CI −11.14 to −8.02 hours) (Figure 7.24). There was a high level of heterogeneity at $I^2 = 86\%$.

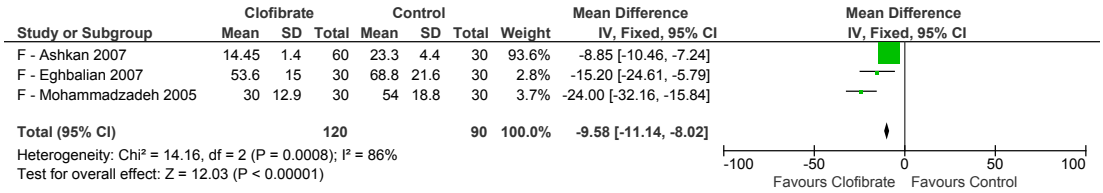


Figure 7.24 Mean duration of phototherapy when clofibrate combined with phototherapy is compared with phototherapy alone

The *post hoc* sensitivity analysis excluding the low/moderate dose study showed an MD of −20.22 hours (95% CI −26.39 to −14.06 hours) with I^2 still relatively high at 48% (Figure 7.25).

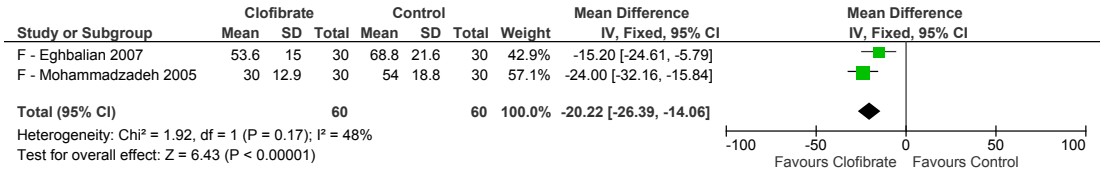


Figure 7.25 Mean duration of phototherapy when clofibrate combined with phototherapy is compared with phototherapy alone – sensitivity analysis based on dosage

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Riboflavin

Description of included studies

From the four articles obtained, one was excluded as the study reported was not randomised. Three RCTs[217-219] from Hungary,[218] Turkey[219] and the USA[217] compared riboflavin in combination with phototherapy with phototherapy alone for the treatment of hyperbilirubinaemia. One study[217] used random numbers to allocate treatment but did not report on allocation concealment and so was rated EL 1+. Neither of the other two studies[218;219] reported either randomisation method or allocation concealment and so were rated EL 1–.

Where reported, the mean birthweight ranged from 3230 ± 502 g to 3338 ± 425 g, the mean age at entry to study ranged from 50.2 ± 27.2 hours to 71.3 ± 24.1 hours, and the mean serum bilirubin was 358 ± 71 micromol/litre. In one study[217] that reported gender, 12 participants (50%) were male. The mean gestational age was not reported.

Review findings

Dichotomous outcomes

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

Continuous outcomes

In one RCT[217] (*n* = 24) from the USA, riboflavin (sodium phosphate 1.5 mg/kg body weight 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 mean reduction (not statistically significant) in serum bilirubin after 24 hours (MD = −17.00 micromol/litre, 95% CI −35.81 to 1.81 micromol/litre). [EL 1+]

In the second RCT[219] (*n* = 124), from Turkey, riboflavin was given as a single oral dose of 3 mg/kg body weight within 30 minutes of starting phototherapy in the treatment of term babies with non-haemolytic hyperbilirubinaemia. Babies receiving riboflavin showed a statistically significant reduction in mean serum bilirubin after 24 hours (MD = −30.00 micromol/litre, 95% CI −49.20 to −10.80 micromol/litre). There was no statistically significant difference regarding mean duration of phototherapy. [EL 1–]

The third RCT[218] (*n* = 28), from Hungary, evaluated riboflavin given as an intravenous dose of 10 mg/kg body weight 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 statistically significantly greater difference between the groups in serum bilirubin after 3 hours (MD = −119.00 micromol/litre, 95% CI −154.62 to −83.38 micromol/litre). [EL 1–].

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Metalloporphyrins

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

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Albumin infusions

Three articles were obtained and two were excluded because one study compared two preparations of human serum albumin and the other study was a non-randomised controlled trial. The first study[198] has been included in the section on exchange transfusions. There was no statistically significant difference between DVET and albumin-enriched DVET in terms of mean reduction of serum bilirubin, the mean duration of adjunctive phototherapy or the level of rebound jaundice. There were no cases of kernicterus or reported adverse effects in either group.

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Cholestyramine

Three articles were obtained but no RCTs were identified and one article was a duplicate publication.

Description of included studies

Two controlled clinical trials[220;221] [EL 2–], from Greece[220] and Singapore,[221] 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 both studies received 1.5 g/kg per day of cholestyramine powder mixed in milk.

In the second study,[220] for the preterm sample ($n = 20$) the mean gestational age was 33.4 ± 0.3 weeks, the mean birthweight was 2077 ± 88 g, the mean age at entry to study was 76 ± 2.9 hours, and the mean serum bilirubin was 198 ± 5 micromol/litre. Nine participants (45%) were male. Among the term babies in the two studies, the mean gestational ages were 38.9 ± 0.2 and 39.1 ± 0.3 weeks, the mean birthweights were 3154 ± 139 and 3286 ± 39 g, the mean ages at entry to study were 84 ± 2.9 and 90 ± 1.5 hours, and the mean serum bilirubin levels were 298 ± 5 micromol/litre in both studies. Gender was reported in one study[220] and 15 participants (37.5%) were male.

Review findings

In the first study[221] (conducted in babies with non-haemolytic hyperbilirubinaemia), control babies showed a statistically significantly greater reduction in mean serum bilirubin than those receiving cholestyramine (MD = 18.00 micromol/litre, 95% CI 8.55 to 27.45 micromol/litre).

In the second study[220] (conducted in babies with both haemolytic and non-haemolytic jaundice), there was a statistically 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 to –34.62 hours) and for preterm babies the MD was –26.30 hours (95% CI –33.00 to –19.60 hours).

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Agar

A total of 11 articles were obtained. Two studies,[222;223] from Denmark[223] and the USA[222], were included. These were non-randomised controlled trials [EL 2–] that compared phototherapy alone with agar combined with phototherapy.

Description of included studies

Babies in both studies were allocated to treatment according to their hospital numbers, and thus allocation concealment was not possible.

Agar was given in 250 mg 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 g and 2729 ± 538 g, 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/litre and 274 ± 51 micromol/litre. One study[223] reported the mean gestational age of 36.8 ± 2.5 weeks. Of the combined sample, 57 participants (56.4%) were male.

Review findings

When both studies were pooled in a meta-analysis, there was no statistically significant difference between treatment and control groups in mean reduction in serum bilirubin (MD = −2.00 micromol/litre, 95% CI −24.13 to 20.13 micromol/litre). Also there there was no statistically significant difference in the mean duration of phototherapy (MD = −6.57 hours, 95% CI −16.06 to 2.92 hours). Heterogeneity was low at $I^2 = 21\%$.

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Barbiturates

Eighteen articles were obtained, including one controlled clinical trial from New Zealand[224] concerning phenobarbitone treatment of hyperbilirubinaemia. Seventeen papers were excluded for the following reasons: phototherapy not evaluated concurrently (two studies), phenobarbitone evaluated for prophylaxis, not treatment, of jaundice (12), maternal treatment with phenobarbitone evaluated (two) and no jaundice-related outcomes included (one).

Description of included studies

In one controlled clinical trial [EL 2−] the mean gestational age of the sample was 34.8 ± 2.7 weeks, the mean birthweight was 2155 ± 632 g, the mean age at entry to study was 48.1 ± 14.7 hours, and the mean serum bilirubin was 174 ± 40 micromol/litre. Forty-nine (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 g received 8 mg of phenobarbitone three times daily while those babies with birthweight < 3000 g received 2 mg/kg of phenobarbitone three time daily.

Review findings

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).

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

D-penicillamine

Three articles were obtained and all were excluded. Two were historical control studies and one was a controlled clinical trial examining D-penicillamine as prophylaxis for hyperbilirubinaemia in preterm babies.

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Glycerin

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

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Charcoal

Two articles were obtained and were excluded: one was a non-randomised controlled study and the other a historical control study. The controlled clinical trial 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 erythropoietic rotoporphyria who were treated with this preparation.

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Pojark Manna

One article was obtained and included.

Description of included studies

This RCT from Iran[225] 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 g of Shirkhest, and control babies received a starch solution with caramel added so as to appear identical to the Shirkhest solution. The mean serum bilirubin in the study was 401 ± 53 micromol/litre. No other demographic details were provided.

Review findings

Phototherapy was discontinued when serum bilirubin fell below 256.5 micromol/litre. The mean duration of phototherapy was similar in the treatment and the control groups. [EL 1 –]

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

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,[226] 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.

See the end of Section 7.4 for the overall Evidence summary and GDG translation from evidence.

Other interventions

Only case reports were identified for homeopathy and acupuncture.

Overall evidence summary for other treatments

The included RCTs 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 (100 mg/kg body weight) led to statistically significant reductions in mean serum bilirubin levels and duration of phototherapy compared with 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 10 mg/kg body weight 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, traditional Chinese medicine, homeopathy or acupuncture.

Cost-effectiveness of other treatments

The clinical evidence suggests that babies with Rhesus and ABO haemolytic disease receiving IVIG are less likely to require exchange transfusion, which is an expensive procedure with associated morbidity and mortality. However, IVIG is also a relatively expensive therapeutic intervention and there is a shortage of global supply. Therefore an economic evaluation was undertaken to help guide GDG recommendations. Full details of this analysis can be found in Appendix D. The analysis compared giving IVIG as an adjunct to phototherapy in babies with Rhesus haemolytic disease and ABO haemolytic disease where serum bilirubin is continuing to rise at more than 8.5 micromol/litre per hour against not giving IVIG to these babies.

In the base-case analysis, the NNT with IVIG to avoid an exchange transfusion was two for babies with Rhesus haemolytic disease and five for babies with ABO haemolytic disease. The model assumed a mortality rate of 2% for exchange transfusion for the base case but did not consider other complications arising from an exchange transfusion or IVIG. This was partly to simplify the analysis but also because any impact on quality-adjusted life years (QALYs) would be small relative to the impact from assuming causation between exchange transfusion and mortality. In the base-case analysis, IVIG appears to be a cost-effective treatment for Rhesus haemolytic disease and ABO haemolytic disease, with incremental cost-effectiveness ratios of £2,248 per QALY and £11,944 per QALY, respectively. However, there is important uncertainty in the model, in particular in relation to the exact number needed to treat with IVIG to avoid an exchange transfusion and the mortality attributable to exchange transfusion. Therefore, to test the robustness of the base-case cost-effective finding, a 'worst-case' sensitivity analysis was undertaken. This used the upper 95% confidence interval for NNT (three for Rhesus disease and 13 for ABO disease) and a much lower 0.3% mortality due to exchange transfusion. For Rhesus haemolytic disease this gave a cost per QALY of £34,379, which is only just outside the upper bound of what NICE would accept as cost-effective treatment. The incremental cost-effectiveness ratio for ABO haemolytic disease in this 'worst-case' sensitivity analysis was £243,381 per QALY. These results suggest that IVIG for Rhesus disease is likely to be cost-effective as it remains borderline cost-effective even in a 'worst-case' scenario. However, the cost-effectiveness of IVIG in ABO disease is less clear-cut and further research would be needed to more accurately establish its cost-effectiveness in this population.

Overall GDG translation for other treatments

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 (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085235). 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/litre per hour despite multiple phototherapy. While 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 believes that further research could better inform cost-effective practice. The GDG noted that babies whose parents object to the use of blood products for religious or cultural reasons should be treated with the same standard of care as all babies, with

the best interests of the child paramount. Local procedures should be in place to support communication with parents in this situation.

The evidence for effectiveness of clofibrate in neonatal jaundice is strong but is confined to one population. The GDG notes that studies of clofibrate in adults reported significant adverse effects.[227] 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 – 7.4 Other treatments

Use intravenous immunoglobulin (IVIG) (500 mg/kg over 4 hours) 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 per hour.

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.

7.5 Satisfaction with treatment

Description of included studies

No studies were identified.

Review findings

No studies were identified.

Evidence summary

No evidence has been identified.

Research recommendations

What is the effectiveness, cost-effectiveness and safety of Clofibrate alongside phototherapy versus phototherapy alone for non-haemolytic significant 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 breastfeeding and mother-baby bonding. However no studies have been carried out in a UK population. New placebo-controlled double-blind randomised controlled trials in a UK population are needed. Population: Term and preterm babies with significant hyperbilirubinaemia in the first 28 days of life. Interventions: Clofibrate (a single 100mg/kg dose) combined with phototherapy versus phototherapy with a placebo. 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 when used to prevent exchange transfusion in newborns with haemolytic disease and rising bilirubin?

Why this is important.

Existing research has demonstrated that IVIG is effective in preventing the need for an exchange transfusion in babies with Rhesus haemolysis. New placebo-controlled double-blind randomised controlled trials are needed to examine if IVIG is effective in sub-groups of babies with ABO haemolysis, ie preterm babies, babies with bilirubin rising greater than 10 micromol/litre per hour or babies with co-morbid illnesses such as infections. Population: Term and preterm babies with significant hyperbilirubinaemia in the first 28 days of life. Interventions: IVIG (500mg/kg over 4 hours) 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

Description of included studies

Two studies[228-230] of EL 3 were included. One[228] examined barriers to follow-up in the first week of life and the other[229;230] (reported in two publications) investigated maternal concerns about jaundice

Review findings

A qualitative study in the USA[228] examined barriers to first-week follow-up for jaundice. Four focus groups, one each for physicians and nurses and two for parents, comprising seven to nine 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, nine physicians, eight nurses and 14 parents attended the focus groups. Tapes of each session were transcribed and summarised. 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 Table 8.1.

Table 8.1 Problems and solutions regarding information about jaundice

Experiences	Reported by	Solutions	Reported by
Communication gaps during hand-over	MD, RN	Notify community healthcare provider when baby born	MD, RN
Missing key information, e.g. 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 risks to near-terms	MD, RN
Poor understanding of risks to near-terms	MD		

MD = medical doctor; RN = registered nurse; P = parent.

An ethnographic study from the USA[229;230] examined maternal concerns about neonatal jaundice. In all, 47 mothers of healthy breastfeeding babies with jaundice were interviewed. The mean maternal age was 27 years. Over half of multiparous mothers had had a previous baby with jaundice and three-quarters had breastfed a previous baby. Hyperbilirubinaemia was defined as serum bilirubin > 170 micromol/litre. The interviews were held between 2.5 and

14.5 weeks postpartum. Regarding causes of jaundice, 26 mothers (55%) 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%) 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%) 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
- prolonged jaundice.

Of the 20 mothers who were not concerned, ten 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, five of their babies had breast milk jaundice and five had had blood tests but did not require treatment. The remaining ten 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. [EL III]

Evidence summary

The focus-group studies from the USA, both EL III, 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 from evidence

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 is needed regarding causes of jaundice,

information that addresses 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 prenatal 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.

Recommendations – 8 Informaton

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

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

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

- anticipated duration of treatment
- reassurance that breastfeeding, nappy-changing and cuddles 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 phototherapy including all of the following:

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

Offer parents or carers information on exchange transfusion including:

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

Offer parents or carers information on IVIG including:

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

Appendix A

Scope

1 Guideline title

Neonatal jaundice

1.1 Short title

Neonatal jaundice

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Women's and Children's Health to develop a clinical guideline on the recognition and treatment of infants with neonatal jaundice for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost-effectiveness.
b) The Institute's clinical guidelines support the implementation of National Service Frameworks (NSFs) in aspects of care for which a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by NICE after an NSF has been issued will have the effect of updating the Framework.
c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, if appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) 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 1st week of life, and about 10% of breastfed babies are still jaundiced at 1 month of age. In most infants with jaundice there is no underlying disease, and this early jaundice (termed 'physiological jaundice') is generally harmless.
b) Neonatal jaundice refers to the yellow colouration of the skin and the sclera 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 body, a condition known as hyperbilirubinaemia.
c) Bilirubin is a breakdown product of the red cells in the blood. Red cell breakdown produces unconjugated (or 'indirect') bilirubin, which is partly bound to albumin. Normally this is metabolised in the liver to produce conjugated (or 'direct') bilirubin, which then circulates through the gut and is excreted in the urine and the stool.
d) Newborn babies have more circulating red cells and a shortened red cell lifespan, so the bilirubin levels are higher than they are later in life. The breakdown and excretion of bilirubin is also slower. Thus degrees of hyperbilirubinaemia occurring as a result of this normal physiological mechanism are common in newborn babies and usually benign (harmless) compared with adult levels.

e) Breastfed infants are more likely to develop physiological jaundice within the 1st week of life. 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.

f) Jaundice may also have other, non-physiological, causes, including blood group incompatibility (Rhesus, ABO or similar problems), other causes of haemolysis, sepsis, bruising and metabolic disorders. Gilbert's and Crigler–Najjar syndromes are rare causes of neonatal jaundice. Deficiency of a particular enzyme, glucose-6-phosphate-dehydrogenase (G6PD), can cause severe neonatal jaundice. G6PD deficiency is more common in certain ethnic groups and runs in families. Congenital obstruction and deformities affecting the biliary system, such as in the condition known as biliary atresia, cause an obstructive jaundice associated with conjugated hyperbilirubinaemia. This condition needs specialist management and surgical treatment.

g) In young babies, unconjugated bilirubin can penetrate across 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) because it acts as a 'cell poison' slowing essential processes. Entry of unconjugated bilirubin into the brain can cause both short-term and long-term neurological dysfunction. Acute problems include lethargy, abnormal muscle tone, irritability, temporary cessation of breathing (apnoea) and convulsions. This presentation is known as acute bilirubin encephalopathy. This deposition of bilirubin causes a yellow staining of a particular part of the deep neural tissue (the deep grey matter) within the brain; this staining is referred to as 'kernicterus'. The term kernicterus is also used to denote a group of signs typical of chronic bilirubin encephalopathy. These signs 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 that probably include acidosis, postnatal age, rate of rise of bilirubin level, serum albumin concentration, and whether the baby has another illness at the time (including infection).

h) Although neonatal jaundice is very common, kernicterus is very rare. There is a poor correlation between levels of bilirubin in the body and the clinical features 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 dehydration, preterm birth, respiratory distress, 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 G6PD deficiency or Rhesus haemolytic disease.

i) The correlation between actual bilirubin levels and kernicterus is poor for the various reasons discussed above in 3 g and h. Kernicterus in healthy term babies with none of the factors (as described above) is virtually unknown below a threshold level of 425 micromoles of bilirubin per litre of serum, but the number of cases rises above this threshold level and the risk of kernicterus is greatly increased in full term newborns with bilirubin levels above 515 micromol/litre. Kernicterus is also known to occur at lower levels of bilirubin in full term babies who have any of the factors described in 3 h.

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

k) Clinical recognition and assessment of jaundice can be difficult. This is particularly the case in babies with darker skin. Once the diagnosis is made, there is uncertainty about when to treat raised bilirubin levels and there are variations in the use of phototherapy, exchange transfusion and other treatments. There is a need for more uniform, evidence-based practice, and for more widespread consensus-based practice in areas lacking evidence.

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.
b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).
c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) All newborn infants (both term and preterm) from birth to 28 days.
b) Special attention will be given to the recognition and management of neonatal jaundice in babies with darker skin.

4.1.2 Groups that will not be covered

a) Babies with jaundice that lasts beyond the first 28 days.
b) Babies with jaundice that requires surgical treatment to correct the underlying cause.
c) Management of babies with conjugated hyperbilirubinaemia.

4.2 Healthcare setting

a) The guideline will cover management in primary (including community care) and secondary care. Guidance regarding tertiary referral will also be included.

4.3 Clinical management

a) Identification of factors that increase the risk of kernicterus in a baby with jaundice
b) Recognition and management in primary care (includes community care).
- Role and timing of assessment in primary care.
- Estimation of hyperbilirubinaemia and its management.
- Management at home, in the community and after discharge.
- Indications for referral to secondary care

c) Recognition and management in secondary care.
- Assessment in secondary care.
- Investigations including:
  - bilirubin – components and methods of estimation
  - other relevant haematological and biochemical tests
  - urine tests
  - screening for metabolic disorders
  - end tidal carbon monoxide concentration
- Timing of lab investigations including point of care testing. Indications for referral to tertiary care.

d) Treatment of hyperbilirubinaemia.
- Interpretation of bilirubin levels and use of nomograms.
- Phototherapy (various modalities).
- Blood exchange transfusion.
- Other treatment modalities.
- Role of nutritional support and rehydration.

e) Outcomes that will be considered:
- major outcomes:
  - mortality
  - morbidity, seizures
  - neurological complications (immediate, short-term and long-term)
  - impact on resource use and costs
- other outcomes:

  - auditory, visual and other non-neurological complications
  - hospital admission (duration, frequency, acquired infections)
  - effect on maternal infant bonding, breastfeeding and family bonding

f) Information and support that should be given to parents and carers:
   - at the time of initial presentation
   - after diagnosis and during management
   - about long-term effects, including significant morbidities and functional outcome.

g) Note that guideline recommendations will normally fall within licensed indications; exceptionally and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the summary of product characteristics to inform their decisions for individual patients.

h) The guideline development group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

4.4 Status

4.4.1 Scope

This is the final scope.

Related NICE guidance

- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63. Available from www.nice.org.uk/CG063
- Intrapartum care: care of healthy women and their babies during childbirth. NICE clinical guideline 55. Available from www.nice.org.uk/CG055
- Routine postnatal care of women and their babies. NICE clinical guideline 37. Available from www.nice.org.uk/CG037
- Antenatal care: routine care for the healthy pregnant woman. NICE clinical guideline 6. Available from www.nice.org.uk/CG006

4.4.2 Guideline

The development of the guideline recommendations will begin in April 2008.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

These are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Appendix: Referral from the Department of Health

The Department of Health asked NICE:

'To prepare a clinical guideline on the recognition and treatment decisions of babies who are jaundiced.'

Appendix B

Declarations of interest

This appendix includes all interests declared on or before 28 January 2010.

A.1 GDG members

Cristiana Aride

No interests declared

Jeffery Barron

No interests declared

Yvonne Benjamin

No interests declared

Sally Cottrell

No interests declared

Karen Ford

No interests declared

Kevin Ives

Personal pecuniary interest

Receives medico-legal instructions from solicitors acting for Claimants and Defendants to write expert reports in cases of litigation involving jaundice mediated brain injury in the newborn (kernicterus).

Personal non-pecuniary interest

Member of the Neonatal Society; Member of the British Association of Perinatal Medicine; Fellow of the Royal College of Paediatrics and Child Health; Published on Neonatal Jaundice, including a chapter in Rennie and Roberton's Textbook of Neonatology, Third and Fourth Editions, Churchill Livingstone, 1999, 2005.

Maria Jenkins

No interests declared

Alison Johns

No interests declared

Donal Manning

Personal non-pecuniary interest

Published a peer-reviewed perspective in Archives of Disease in Childhood 2009, in which the opinions expressed were formed by personal knowledge of, and evidence review of, neonatal jaundice.

Farrah Pradhan

No interests declared

Janet Rennie

Personal pecuniary interest

Payment received from the Legal Aid Board and the National Health Service Litigation Authority for independent expert medico legal reports for civil proceedings in cases of kernicterus. This work is undertaken outside of NHS time.

Personal non-pecuniary interest

Conducted research survey on the management of neonatal jaundice in the UK (work was done and submitted before accepting the post of Chair) published in the Archives of Disease in Childhood 2009. No funding or grant was received for this work.

Debra Teasdale

No interests declared

A.2 NCC-WCH staff and contractors

M Qutayba Almerie

No interests declared

Shona Burman-Roy

No interests declared

Katherine Cullen

No interests declared

Rajesh Khanna

No interests declared

Hannah Rose Douglas

No interests declared

Paul Jacklin

No interests declared

Juliet Kenny

No interests declared

Rosalind Lai

No interests declared

Hugh McGuire

No interests declared

Kristina Pedersen

No interests declared

Edmund Peston

No interests declared

Stephen Murphy

No interests declared

Manveet Patel

No interests declared

Itrat Iqbal

No interests declared

Jay Bannerjee
No interests declared

Carolina Ortega
No interests declared

Anuradha Sekhri
No interests declared

Martin Whittle
Personal pecuniary interests
Adviser to National Screening Committee in relation to obstetric ultrasound services

A.3 External advisers

None

Appendix C

Economic evaluation of alternative testing strategies in the detection of hyperbilirubinaemia

C.1 Introduction

Jaundice (a yellow colouration of the skin) is caused by hyperbilirubinaemia and is common in the newborn baby. Rarely, if bilirubin levels are sufficiently high, bilirubin can cross the blood–brain barrier and cause a brain-damaging condition called kernicterus, a lifelong disabling neurological problem with manifestations of cerebral palsy and deafness with high costs of care. Hyperbilirubinaemia can also cause deafness without cerebral palsy, and other adverse outcomes have been described. Levels of bilirubin can be controlled with phototherapy, but the only way to reduce very high levels in an emergency is with an exchange transfusion. This is a costly intensive care procedure that carries a mortality risk. Phototherapy is generally effective in controlling bilirubin levels, preventing them from rising to a level at which kernicterus occurs, and hence some clinicians have called for kernicterus to be classified as a 'never event'.[231] There is some evidence to show that cases of kernicterus have risen recently, probably as a result of earlier discharge following childbirth.[232;233]

Current practice in England and Wales is varied but the GDG estimates that fewer than 10% of babies undergo specific testing of their bilirubin levels following visual examination. At present, babies who develop kernicterus often present late and with bilirubin levels already in the toxic range. The key to prevention of kernicterus is early detection of cases at a time when phototherapy can be effective. Any guideline recommendation that requires more widespread testing will have important resource implications for the NHS as well as require a change in practice in many places. Therefore the guideline recommendation regarding identification of cases by testing for hyperbilirubinaemia was highlighted by the GDG as an important priority for economic analysis. The NHS operates within resource constraints and a more intensive testing and treatment strategy can only be justified if it represents a better use of scarce resources than could be obtained in some alternative use of those resources.

C.2 Literature review

A literature search was undertaken to assess the economic evidence base for strategies to prevent kernicterus in newborn babies. This initial search yielded 33 papers and the abstracts of these papers were read to exclude papers that were clearly not relevant. As a result of this initial screen, five papers were retrieved, of which only one was identified as a relevant economic evaluation.

This was a US study that compared the cost-effectiveness of four strategies against current practice to prevent kernicterus in newborn infants.[234] An incremental cost-effectiveness analysis was undertaken using a decision-analytic framework. The strategies were modelled for a population of healthy term infants who were being discharged within 48 hours of an uncomplicated vaginal birth. The strategies were:

1. current practice – physicians and nurses assess the need for serum bilirubin testing after delivery and prior to discharge based on a review of clinical history and physical examination, including visual inspection of skin colour; clinical judgement and assessment of risk are used to determine the timing of follow-up
2. universal follow-up 1–2 days after early discharge, but in other respects similar to the first strategy

3. routine serum bilirubin testing prior to discharge with follow-up within 2 days of discharge if the bilirubin measurement is greater than the 40th percentile value on the nomogram
4. routine transcutaneous bilirubin testing prior to discharge with the percentile value on the nomogram developed by Bhuthani *et al*.[34] guiding decisions about the need for serum bilirubin testing before discharge and subsequent follow-up.

In strategies 2–4 the threshold for laboratory testing is lowered in recognition of the unreliability of visual estimation of bilirubin.

The authors estimated that with current practice 2.3% of infants would receive phototherapy compared with 8.1%, 5.6%, and 7.8% for strategies 2–4, respectively. The savings from an averted kernicterus case were assumed to be $921,000 (at 2003 prices). The authors assumed that strategies 2–4 would be equally effective at preventing kernicterus cases and their primary outcome was to estimate the cost per kernicterus case averted in each of those strategies, with a relative risk reduction of 0.7, an assumption made in the absence of data.

The results suggested that routine serum bilirubin was the cheapest strategy at $5.75 million per case averted. Using transcutaneous bilirubin meters prior to discharge gave a cost per averted kernicterus case of $9.19 million. Universal screening was the most expensive strategy, with a cost per case averted of $10.32 million. One-way sensitivity analysis suggested that the magnitude of these costs were sensitive to incidence of kernicterus although this did not alter the ranking of the strategies in terms of costs. The authors concluded that their data suggested that it would be premature to implement large-scale routine bilirubin screening.

However, there are often difficulties in generalising the result of an economic evaluation from one setting to another. In particular, the US hospital charges seem unlikely to accurately reflect NHS costs and the costs of a kernicterus case may have been understated. Furthermore, the GDGs remit did not cover screening. Therefore, a *de novo* economic model was developed to reflect the UK context and to enable the GDG to consider cost-effectiveness issues in making their recommendations.

C.3 Background to the economic evaluation

Kernicterus is a largely preventable disease if severe hyperbilirubinaemia is identified early and promptly treated (using phototherapy or, for more acute cases, exchange transfusion). Therefore, early identification of raised (or rapidly rising) bilirubin levels is the key to reducing severe morbidity.

There are studies which demonstrate that more intensive monitoring reduces the need for exchange transfusions. Evidence from the USA reports that during the 1970s kernicterus was practically eradicated, which was probably due to the liberal use of phototherapy.[235] The disease re-emerged in the 1990s, largely among babies cared for in the home environment in the neonatal period, often with limited medical supervision during the first week after birth.[235] Kernicterus has fallen again in the USA since the adoption of the 1994 American Academy of Pediatrics (AAP) guidelines;[123] estimates are that the rate has fallen from 5.1 per 100 000 in 1988 to 1.5 per 100 000.[124]

In the UK, babies are discharged earlier and are monitored less often than in previous decades.[236] Reduced contact with experienced midwives and reliance on intermittent visual examination to assess bilirubin levels may be one of the reasons for the failure to detect babies with significantly elevated serum bilirubin levels. A newborn baby might only be visited once by a midwife in the postnatal period if there are no risk factors, although the norm is currently around two or three visits in the first week. Visual examination by a midwife to assess for jaundice during these postnatal visits is currently the standard of care, with a small proportion of these jaundiced children being subjected to a total serum bilirubin (TSB) blood test based on clinical visual assessment of the level of bilirubin. This is known to be unreliable. There is strong evidence that visual examination alone cannot be used to assess the level of bilirubin in a baby (see Chapter 5 on recognition). The inaccuracy of visual assessment for the detection of bilirubin levels, particularly in babies with dark skin tones, is likely to be a major factor responsible for the late presentation of babies with significant hyperbilirubinaemia. Therefore a

more reliable strategy for the detection of babies who require treatment with phototherapy may be required if it is cost-effective.

The cost of the care of a person with kernicterus throughout their life runs to millions of pounds. If resources were invested in a testing strategy that is effective in reducing the number of cases of kernicterus annually by one case per year, it would be cost saving if the total annual cost of the strategy were less than the discounted lifetime cost of caring for one individual with the disease. Since kernicterus is a lifetime condition with poor quality of life, the value that the NHS places on preventing a case of kernicterus is not only calculated as the cost saved by preventing the downstream costs but also the £20,000 per quality-adjusted life year (QALY) over the lifetime of the condition. Clearly, if the intervention were more successful in preventing kernicterus, then more NHS resources could be used to identify hyperbilirubinaemia and still be cost-effective.

It seems plausible that a more intensive testing strategy could be clinically effective if it overcomes the limitations of visual examination alone, thereby leading to better detection and treatment. Currently, there are two methods of testing: a TSB and a transcutaneous bilirubinometer (TCB), which is a non-invasive test on the surface of the skin. TCB is probably not accurate above a threshold level of 250 micromol/litre of bilirubin so that TSB testing is required in babies whose TCB is above this threshold level. Hence a strategy involving more bilirubin measurements could be based on TSB alone or TCB with TSB only required for those babies whose TCB level was higher than the threshold value. Current evidence does not favour one strategy over the other for the detection of babies with bilirubin levels under 250 micromols/litre. That is, even though TSB is the gold standard test, both strategies, when used correctly as part of an assessment and management process to test babies who are visibly jaundiced, would be equally effective at detecting hyperbilirubinaemia and preventing kernicterus. Both methods are in use in the NHS. The TSB can be analysed in hospital laboratories without the need for additional equipment. The TCB requires the purchase of hand-held devices, sufficient for one to be available for each community midwife undertaking postnatal visits on any particular day.

The economic evaluation was undertaken to determine the conditions under which increased testing would be cost-effective, and to explore which testing strategy would be cost-effective under different circumstances.

C.4 Method

In this analysis we evaluate the cost-effectiveness of moving from current practice to a more intensive test strategy in England and Wales subject to the limitations of the published evidence.

The following strategies are compared:

1. 'Current practice' – a visual examination followed by TSB in 10% of visually jaundiced babies
2. TSB – a TSB on all babies with a positive visual examination
3. TCB followed by TSB if positive TCB – a TCB on all babies with a positive visual examination, with a TSB on those babies with a positive TCB.

Visual examination has a high negative predictive value, which means that babies who do not appear visually jaundiced are very unlikely to have clinically significant jaundice. However, visual examination has been shown to be unreliable in detecting the severity of hyperbilirubinaemia. Therefore, visual examination alone as a basis for detecting jaundice requiring phototherapy has poor sensitivity, which may put jaundiced babies at a higher risk of developing kernicterus.

Detection of hyperbilirubinaemia requiring treatment or further monitoring can be better assessed using a TCB or a blood test to measure the TSB. The TCB is done with a hand-held device (such as the Minolta JM-103 or the BiliChek) that is simple to use and is placed on the baby's skin. The TSB is the gold standard test but is more invasive and distressing to the baby since it requires a blood sample. Both tests can be carried out by the midwife during the home visit or in hospital if the baby has not been discharged.

Diagnostic tests are usually evaluated according to their sensitivity and specificity and these characteristics can be used to generate probabilities in decision-analytic models. Initially, we intended to compare the alternative strategies using such an approach. However, the decision-making process in this context is far more complicated than that implied by the outcomes for a 'two by two table'. Rather than the test result dividing the patient population neatly into positives and negatives for hyperbilirubinaemia, 'raised bilirubin level' is measured on a continuum from normal to severe disease and different test thresholds are used to stratify patients into groups requiring immediate treatment, further monitoring or transfer back to routine care. Decision-making is affected implicitly in a Bayesian manner by the impact of the bilirubin level on the post-test probability of disease. The decision-making is complicated further as a number of other factors, such as family history of jaundice, will also be taken into account. Furthermore, monitoring can occur at many points in time and this temporal aspect is important because thresholds for clinically significant jaundice change and the evidence base to track changes in diagnostic accuracy over the relevant time periods is lacking. Therefore, it was ultimately decided that there was not sufficient published evidence to populate such a decision model. Furthermore, it was felt that the GDG would not be able to estimate the vast array of model parameters to reflect the actual micro decision-making process that occurs in actual clinical practice.

The GDG has set a higher bilirubin threshold as a basis for treatment and a lower bilirubin threshold for further monitoring. The rationale for this is to avoid unnecessary phototherapy (i.e. a high specificity or false positive rate in terms of treatment) while avoiding missed cases by continued monitoring in babies who have an intermediate bilirubin level (i.e. a high sensitivity or false negative rate in terms of monitoring). While the TCB is not thought to be reliable at high bilirubin levels (hence the need for TSB if TCB is positive), it is nevertheless thought to be accurate at the more intermediate levels.

The GDG opinion is that, using the thresholds defined in this guideline, either method of testing would be effective in detecting hyperbilirubinaemia and avoiding new cases of kernicterus. Therefore, the cost-effective strategy was estimated using a cost-minimisation approach that assumes no difference in effectiveness between testing strategies. As noted earlier, there is insufficient evidence to estimate the incremental benefit of moving from 'current practice' to a more intensive testing regime, although evidence on the limitations of visual examination suggests that some benefit is likely. Therefore, threshold analyses were undertaken to determine the number of kernicterus cases that a more intensive testing approach would have to avert in order for this to be considered cost-effective.

C.5 Model parameters and assumptions

The cost analysis was undertaken from the perspective of the NHS and personal social services, which is in accordance with the NICE guidelines manual (www.nice.org.uk/guidelinesmanual).[237] The costs were estimated using a bottom-up or 'ingredients' approach, which involves detailing the physical quantity of resources used in providing treatment alongside the unit cost of those resources. From this it is possible to estimate the total cost of treatment.

It was assumed that visual examination is undertaken in the first instance in all strategies. In the 'current practice' strategy, it was additionally assumed that visual examination is used to determine the severity of hyperbilirubinaemia with a proportion of these having a TSB blood test as a precursor to possible phototherapy. No cost has been applied to the visual examination as it is assumed this would occur as part of the standard home visit carried out by a midwife or as part of standard hospital care if the baby had not been discharged.

The population characteristics for this analysis are shown in Table C.1. Economic parameters used in the assessment of cost benefit (other than the costs of the test strategies) are shown in Table C.2. It should be noted that the base-case values for the cost and QALY loss of a kernicterus case should not be considered point estimates in a conventional sense. Considerable uncertainty surrounds both values and therefore, as part of sensitivity analysis, both are varied simultaneously to derive a cost-effectiveness threshold across a wide combination of values.

The base-case estimate of the lifetime cost of kernicterus is based on a legal settlement and, as such, may include costs over and above those which are deemed relevant for the perspective used by NICE in economic evaluation. A US study[234] used mean lifetime direct and indirect costs of cerebral palsy as a proxy for kernicterus costs and as a result used a cost of $921,000 (at 2003 prices). However, this method may underestimate the costs as kernicterus is associated with severe cerebral palsy. Also, untreated hyperbilirubinaemia can also cause hearing loss without cerebral palsy with a need for cochlear implants and the potential cost savings from averting these complications are not explicitly considered within the model. The base-case QALY loss of a kernicterus case can be considered as an upper bound estimate as it is based on assuming a health state that is as bad as death.

Table C.1 Population characteristics

Item	Value	Source	Notes
Births	690 000	Office for National Statistics (2008)[238]	Based on 2007 births
Babies identified as jaundiced on visual examination	60%	GDG	
Babies currently tested for jaundice on basis of visual examination	10%	GDG	Testing is assumed to be with TSB
Mean number of tests per baby tested[a]	1.33	Kuzniewicz *et al*. (2008)[11]	Pre-universal screening this US study estimated 0.8 tests per baby. We assumed that this was based on 60% of babies being tested, on the basis of the GDG's estimate of babies identified as visually jaundiced in the UK. A weighted average was then used to estimate the tests per baby in the 60% tested that would give an average of 0.8 tests per baby overall. In addition, the GDG considered this a reasonable estimate.

[a] A TCB positive followed by a TSB is considered as a single test for the purposes of this analysis.

Table C.2 Cost–benefit parameters

Item	Value	Sensitivity analysis range	Source	
Kernicterus case	£5.5 million	£0–10 million	JMW Clinical Negligence Solicitors	www.jmw.co.uk/kernicterus_bilirubinaemia
Discount rate	3.5%		NICE guidelines manual (2009)[237]	Both costs and QALYs are discounted
QALY gained per kernicterus case avoided	25	0–25	Calculation	This is an approximation, based on an assumption that the quality of life with kernicterus is not much better than death
Willingness to pay for a QALY	£20,000		NICE guidelines manual (2009)[237]	An advisory threshold

The resource 'ingredients' and their unit costs for TSB and TCB are shown in Table C.3 and Table C.4, respectively. The resource items include any of the additional staff time required to undertake a test as part of a routine postnatal visit. It also includes equipment costs and consumables, those resources that are used up in the provision of the test that cannot be reused.

Table C.3 TSB resources and costs

Resources	Unit cost	Source	Notes
Clinical nurse specialist	£69.00	PSSRU (2008)[239] (www.pssru.ac.uk/pdf/uc/uc2008/uc2008.pdf)	It is assumed that it would take 10 minutes to perform this test
Venous blood test	£7.00	GDG estimate	One per test
Gloves	£0.06	medisave.co.uk, accessed 16 July 2009	£6.27 per 100; one pair per test

Table C.4 TCB resources and costs

Resources	Unit cost	Source	Notes
Clinical nurse specialist	£69.00	PSSRU (2008)[239]	It is assumed that it would take 1 minute to perform this test
TCB meter	£3,400 £3,600	Manufacturer, JM-103 Manufacturer, BiliChek	No consumables required
Calibration tips	£5.50	Manufacturer, BiliChek	
TSB	£18.56	Marginal cost of TSB (see Table C.3)	It is estimated that 25% of TCB tests would be positive leading to a TSB

The purchase of medical equipment, TCB meters in this case, carries an opportunity cost that differs from operating costs such as labour and consumables in certain respects. The purchase of TCB meters involves an upfront payment before use. However, that cost is fixed as it does not vary with the quantity of treatment provided. The equipment can often be used over a number of years before it needs to be replaced.

The equipment costs have two facets:

- opportunity cost – the money spent on the equipment could have been invested in some other venture yielding positive benefits; it is calculated by applying an interest rate to the sum invested in the equipment
- depreciation cost – the equipment has a certain lifespan and depreciates over time; eventually, the equipment has to be replaced.

In economic evaluation, the usual practice is to annuitise the initial capital outlay over the expected life of the equipment to give an 'equivalent annual cost'. Calculating the equivalent annual cost means making an allowance for the differential timing of costs, using discounting.

The formula for calculating the equivalent annual cost is given below:

$$E = \frac{K - S/(1+r)^n}{A(n,r)}$$

where:

E = equivalent annual cost
K = purchase price of equipment
S = resale value
r = discount (interest rate)
n = equipment lifespan
$A(n,r)$ = annuity factor* (n years at interest rate r)

To calculate the equivalent annual cost we have assumed that the meters last 5 years and have no resale value. However, the total annual equivalent cost would depend on the actual number of meters that were necessary to deliver the strategy. This is not known and service delivery is not generally part of the remit of NICE guidelines. Therefore, the results are presented as a threshold analysis, with the threshold being the number of meters at which the TSB strategy (Strategy 2) would be equivalent in cost to the TCB strategy (Strategy 3).

* An annuity factor converts a present valueinto an annuity, a series of equal annual payments.

C.6 Results

The marginal cost per test (excluding equipment) was estimated to be £18.56 for TSB and £5.87 for TCB for a test requiring no consumables and £11.37 for a test requiring calibration tips.* Using these figures the cost per strategy was calculated as follows for the model's default input values:

Calculation of total costs per annum of each strategy

1. *Current practice*
   Population: 690 000
   Tested with TSB: 690 000 × 0.1 × 0.6 = 41 400
   TSB tests: 41 400 × 1.33 = 55 062
   Cost: 55 062 × £18.56 = £1.02 million
2. *Strategy 2 (TSB to all visually jaundiced babies)*
   Population: 690 000
   Visibly jaundiced: 690 000 × 0.6 = 414 000
   TSB tests: 414 000 × 1.33 = 550 620
   Cost: 550 620 x £18.56 = £10.22 million
3. *Strategy 3 (TCB to all visually jaundiced babies followed by TSB if TCB is positive)*
   Population: 690 000
   Visibly jaundiced: 690 000 × 0.6 = 414 000
   TCB tests: 414 000 × 1.33 = 550 620
   TSB tests: 550 620 × 0.25 = 137 655
   Cost (BiliChek): 550 620 × £11.37 = £6.26 million plus annual equivalent equipment cost
   Cost (Minolta): 550 620 × £5.87 = £3.23 million plus annual equivalent equipment cost

Figure C.1 shows how the incremental costs of the TCB strategy (for two different types of meter) relative to the TSB strategy vary according to the number of meters that would be necessary to deliver a strategy of TCB testing. The point where the lines plotting the incremental costs of TCB cross the horizontal axis gives the threshold number of meters for cost neutrality between TCB and TSB. If the TCB strategy can be delivered with fewer meters than implied by this threshold then it would be cheaper than the TSB strategy. With the other model values held constant at their default values, Figure C.1 suggests that a TCB strategy using the cheaper meter will cost less than the TSB strategy providing that it can be delivered with fewer than 9200 meters.

Figure C.2 strongly suggests that both the TSB and TCB strategies are more expensive than current practice in terms of test costs. This would be the case even if a much fewer than 9200 TCB meters were required. The cost-effectiveness of this additional testing ultimately depends on any offsetting savings and health gains derived as a result of improved outcomes, that is averted kernicterus cases. This is an unknown but the 'what-if' analysis presented in Figure C.3 shows the minimum number of kernicterus cases that would need to be averted for cost-effectiveness using the model's default input values and varying the number of TCB meters.

Figure C.2 shows the test costs of all three strategies in a scenario where 9200 meters are needed to deliver the TCB strategy.

Figure C.3 shows the total additional cost to the NHS of more intensive testing between a minimum of 1000 TCB meters and a maximum of 9200. The cost on the *x*-axis is the incremental cost difference between 'current practice' and more intensive testing. In this figure, the comparator with current practice is always TCB. If 9200 meters or fewer are purchased, the cheaper option is always TCB. If more meters are required, then the TSB strategy should be preferred on cost-effectiveness grounds. The figure shows that the total cost of using 9200 meters would require an additional £9.14 million per year. The number of kernicterus cases to be averted would have to be at least 1.52 per year for this additional cost of testing to be cost-effective compared with current practice. Buying only an additional 1000 meters, the total additional cost would be £2.96 million per year and 0.49 cases of kernicterus would need to be averted per year for TCB to be more cost-effective than current practice.

* The marginal cost of TCB reflects that 25% of tests will be followed by TSB.

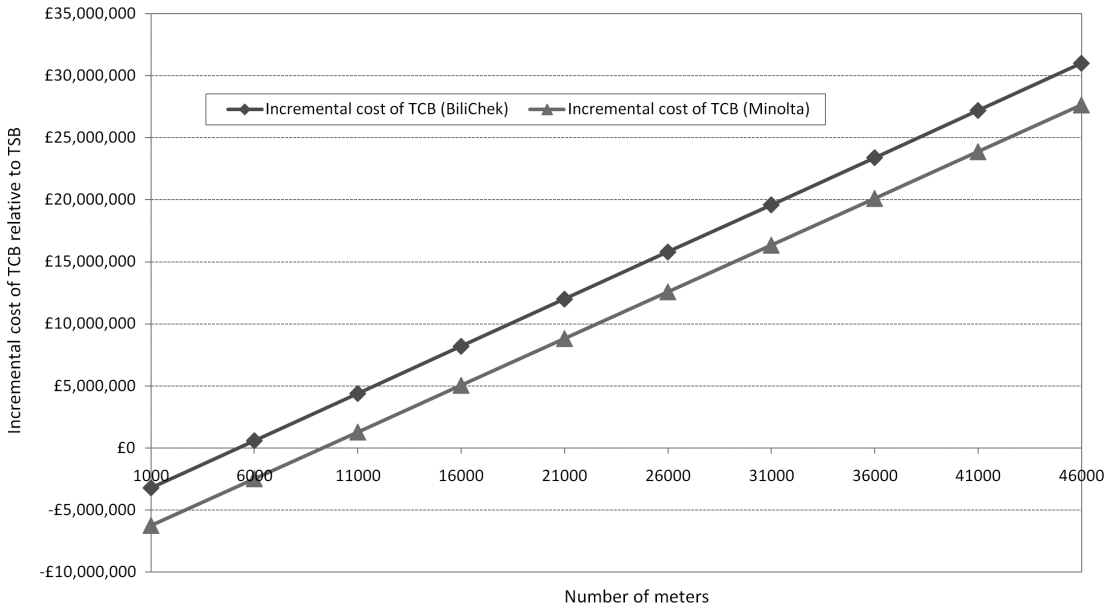


Figure C.1 Comparing the incremental costs of TCB with TSB, varying the number of TCB meters needed to deliver the strategy

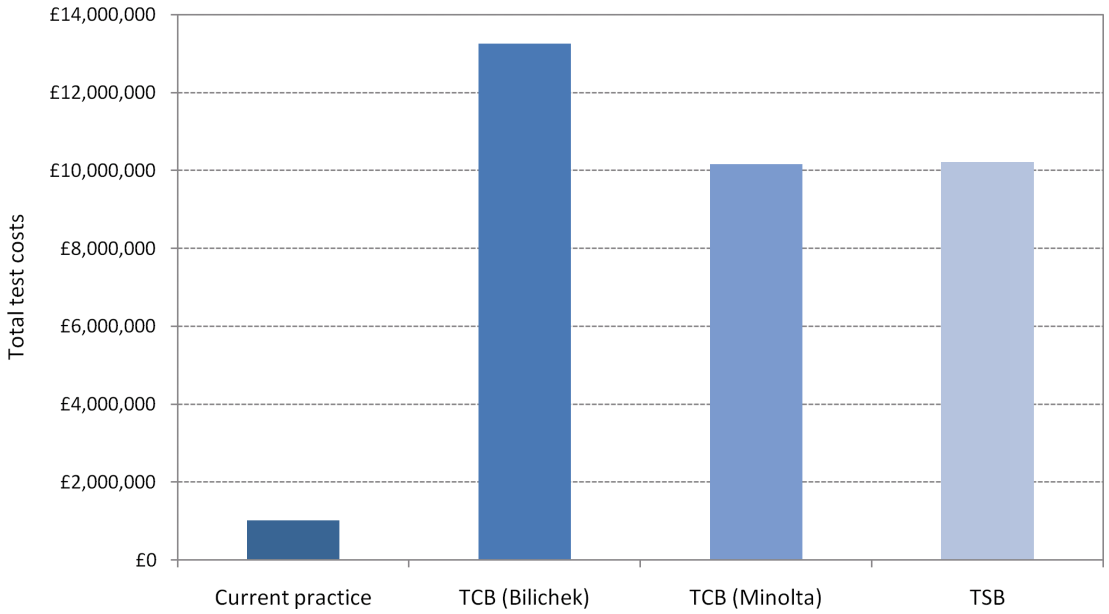


Figure C.2 Total test costs of the different strategies with the model's default input values and assuming 9200 TCB meters

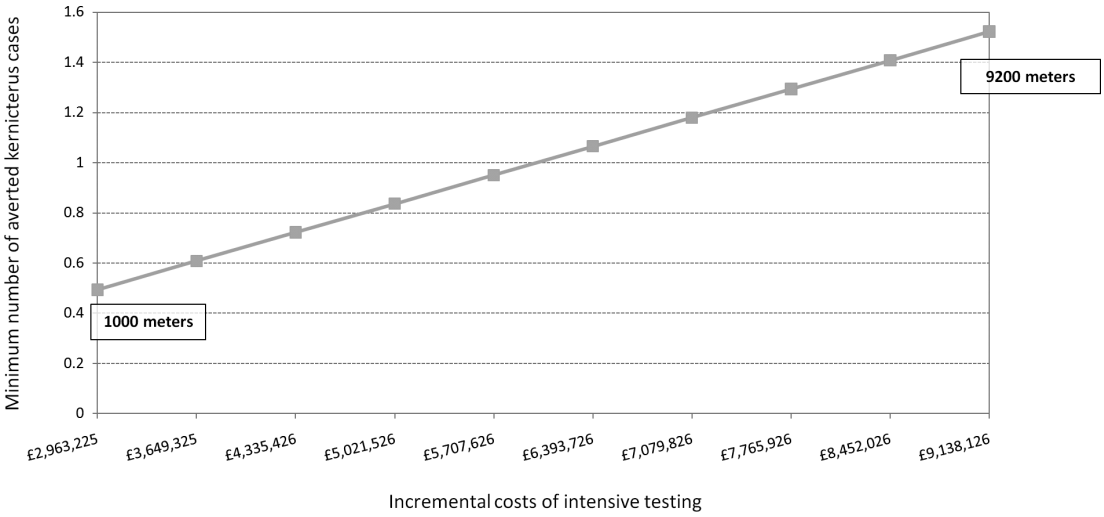


Figure C.3 The minimum number of kernicterus cases to be averted at different incremental costs of more intensive testing

C.7 Sensitivity analysis

Sensitivity analysis is used in economic evaluation to assess how sensitive the results of the model are to the assumptions made about the model parameters, particularly those parameters where considerable uncertainty exists as to their actual value. One-way sensitivity analysis involves altering the value of a single parameter, holding all the others constant, to determine how sensitive the cost-effectiveness conclusion is to the assumptions made about that particular parameter.

The base-case results above were presented as threshold analyses reflecting uncertainty about the number of meters that would be needed for the TCB strategy and the number of kernicterus cases that would need to be averted in order for the additional costs of more intensive costing to be deemed an efficient use of scarce NHS resources. However, the sensitivity analyses below explore how changes in other model parameters would affect results.

C.7.1 Varying the cost of meters

In this sensitivity analysis the cost of the meters is varied between £600 and £3,600. It is assumed that the meter is a Minolta and does not therefore require a new calibration tip for each test. The analysis additionally considers how this is affected by the number of meters needed to deliver the TCB testing strategy.

Figure C.4 shows that the cost of meters is likely to be an important determinant of the cost-effectiveness of TCB relative to TSB. As the cost of meters falls, the number of meters has far less impact in determining the incremental costs of the TCB strategy.

C.7.2 Varying the mean number of tests per baby tested

In this sensitivity analysis the mean number of tests per baby tested is varied between one and two tests. The analysis is repeated for different numbers of TCB meters.

Figure C.5 shows that the incremental costs of the TCB test strategy relative to the TSB test strategy fall as the average number of tests per baby increase. This simply reflects that TSB test has the higher marginal cost. If just one test per baby were required then the threshold number of meters for cost neutrality would be approximately 7000. However, if babies were tested twice on average then that cost neutrality threshold would rise to approximately 14 000 meters. It should be noted that whilst more testing improves the cost-effectiveness of TCB relative to TSB the opposite is the case with respect to current practice.

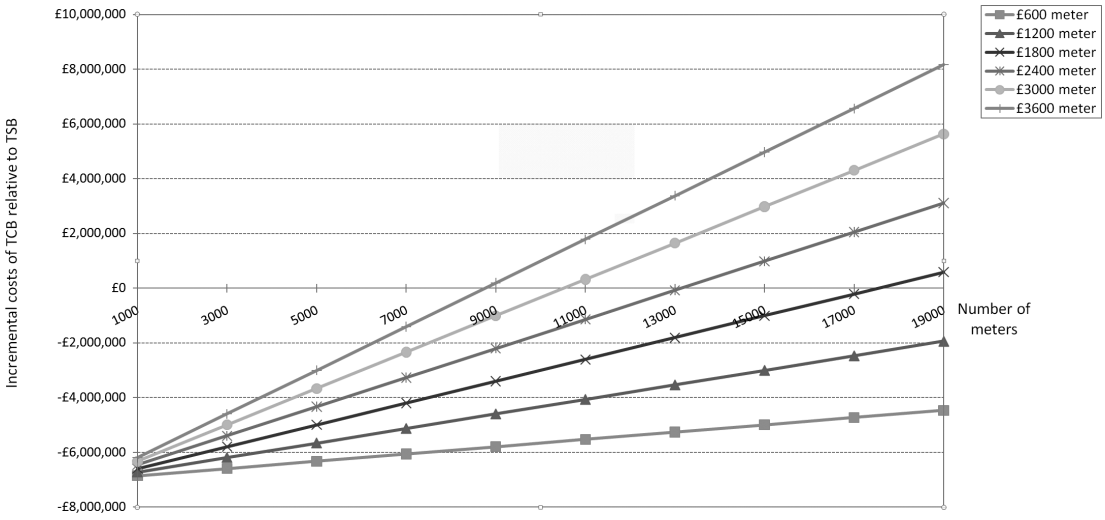


Figure C.4 Comparing the incremental costs of TCB with TSB, varying the number of TCB meters needed to deliver the strategy and the cost of the TCB meter

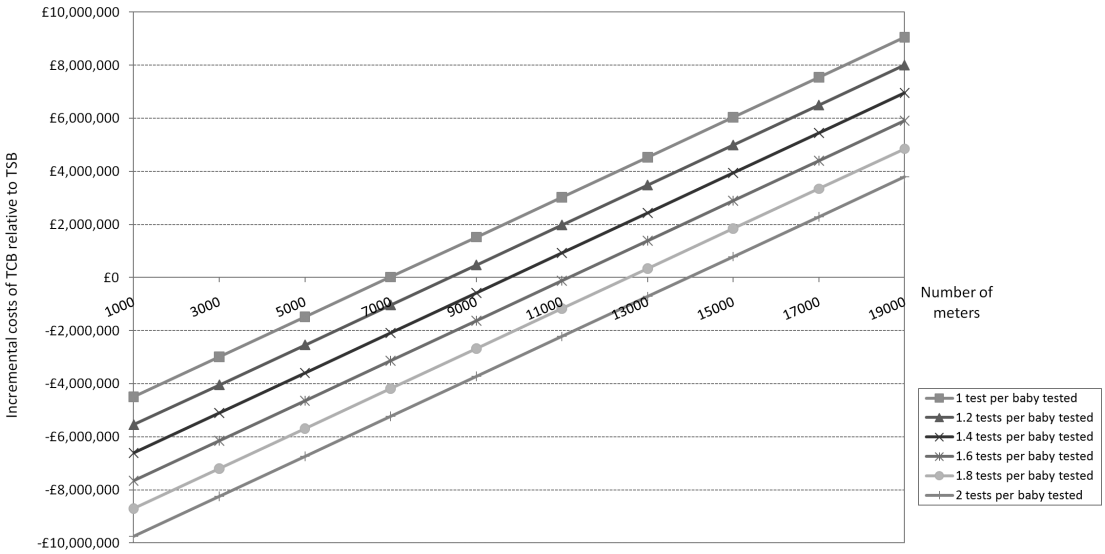


Figure C.5 Comparing the incremental costs of TCB with TSB, varying the number of TCB meters needed to deliver the strategy and the mean number of tests per baby tested

C.7.3 Simultaneously varying the QALY gain and cost averted of a kernicterus case

These are important unknowns because together with effect size they are fundamental determinants of whether increased testing costs represent a good use of scarce NHS resources. The greater the QALY gain associated with an averted kernicterus case, the greater the NHS would be willing to pay for such a gain. The greater the saving from an averted kernicterus case, the more the additional costs of testing will be offset by a reduction in 'downstream' treatment costs.

Figures C.6 and C.7 show that the number of kernicterus cases that would need to be averted for the TCB strategy to be considered cost-effective is very sensitive to the costs of a kernicterus case. A high cost of kernicterus implies that a much lower number of cases would need to be averted in order to meet NICE criteria for cost-effectiveness. By comparison, increasing the QALY gain associated with an averted case has only a relatively small impact on the threshold

cost saving from averted kernicterus cases that would be necessary for cost-effectiveness at any given number of averted cases. These two figures together also show the large impact the number of meters has on these cost-effectiveness thresholds. For a given number of averted cases, a much higher saving and QALY gain is necessary for cost-effectiveness when the TSB strategy requires 9200 meters compared with when 2000 meters are required.

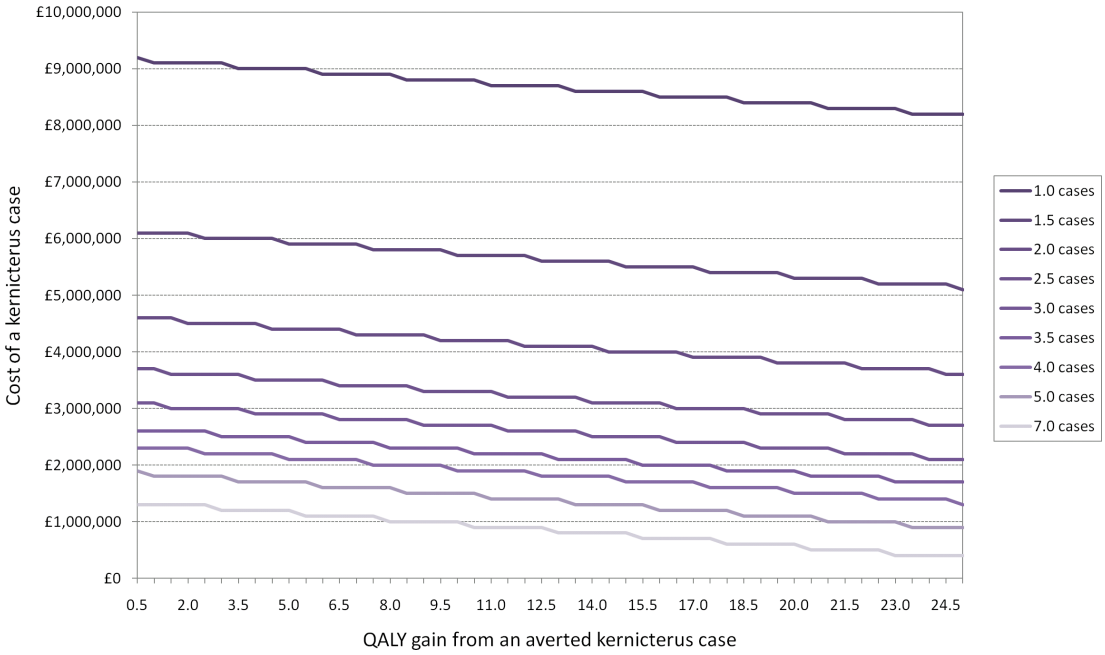


Figure C.6 Thresholds for cost-effectiveness according to the number of kernicterus cases averted and the savings and QALY gain from an averted kernicterus case based on 9200 TCB meters

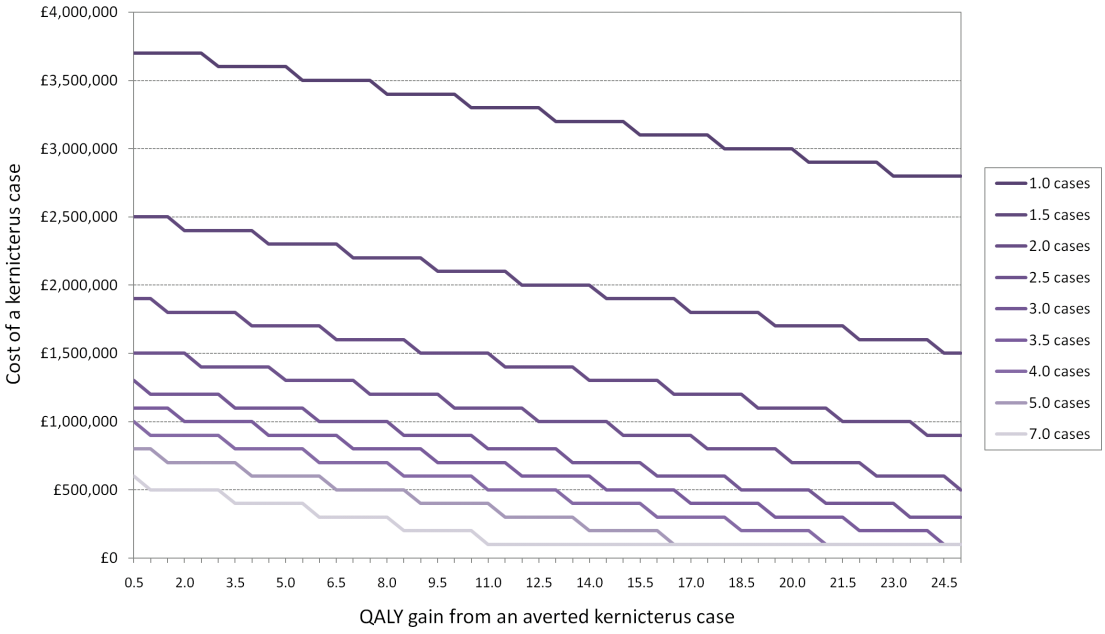


Figure C.7 Thresholds for cost-effectiveness according to the number of kernicterus cases averted and the savings and QALY gain from an averted kernicterus case based on 2000 TCB meters

C.8 Discussion

The analysis compared the current testing strategy with an uplift in testing using alternative strategies. In the base-case analysis, the current strategy of testing only 10% of babies using TSB was £1.02 million per year. The next cheapest strategy was to use Strategy 3 (TCB to all visually jaundiced babies followed by TSB if TCB is positive) using a meter that does not require calibration tips which cost £10.16 million, or £13.25 million using a meter requiring a calibration tip. Using the TSB more intensively (on 60% of babies who are visibly jaundiced) would cost £10.22 million per year. The cost difference between TSB and TCB is mainly due to the increased time to do a blood test compared with a skin test.

An important question is whether any change from current practice can be justified on cost-effectiveness grounds. In part this depends on the fixed costs, that is, the number of TCB meters needed to deliver Strategy 3. This determines the incremental costs of increased testing if the TCB strategy is deemed more cost-effective than TSB, that is, the strategy with the lowest cost since this is a cost-minimisation analysis. In the base-case analysis, the results estimate that the maximum incremental cost of more intensive testing is around £9.14 million, which is the incremental cost of an enhanced testing strategy using TSB alone relative to current practice. If the strategy using the TCB could be delivered with the purchase of only 1000 additional bilirubinometers (which would be a highly conservative estimate) then the incremental cost would be £2.96 million. Figure C.3 suggests that 1.52 cases of kernicterus would have to be averted for more intensive testing to be considered cost-effective if the incremental testing costs were £9.14 million. If fewer resources were required (fewer bilirubinometers purchased) then fewer cases would need to be averted. This assumes a threshold QALY value of £20,000. At a higher threshold, say £30,000 per QALY, the number of cases of kernicterus averted in order for more intensive testing to be cost-effective would be fewer.

Figure C.3 shows how this threshold of kernicterus cases that need to be averted for cost-effectiveness falls as the incremental costs of more intensive testing fall, as is the case with a smaller number of TCB meters. The evidence base is currently not sufficiently robust to assess whether more intensive testing would achieve such an incremental gain – there are approximately five to seven new kernicterus cases per year in England and Wales. However, given the evidence about the limitations of visual examination, the GDG is opposed to relying on observations that have been demonstrated to be unreliable in the detection of severe hyperbilirubinaemia. It does seem plausible that a more intensive testing strategy using tests that are known to have greater reliability in detection of severe hyperbilirubinaemia would lead to more appropriate and timely intervention with a concomitant reduction in adverse outcomes.

The costs of the TCB testing strategy vary according to the cost of the meter used. In the absence of evidence that health outcomes are different between types of meter used, the cheaper Minolta meter should be preferred. The base-case results (see Figure C.2) suggest that, at current prices, the Minolta meter would be about £3 million cheaper, assuming that the meters themselves are similarly priced. Therefore, in the remainder of the discussion it will be assumed that the analysis is based on the cheaper Minolta TCB meter.

Figures C.1, C.3, C.4 and C.5 all show that the number of meters necessary to deliver the TCB strategy is important in determining the relative cost-effectiveness of the TCB strategy (Strategy 3) to the TSB strategy (Strategy 2). In the base-case analysis, TCB is cheaper than TSB providing the number of TCB meters is less than 9200.

If it is decided that more intensive testing is likely to be cost-effective then a secondary decision is whether initial testing should be done using TCB or TSB. Factors such as convenience to the nurse and discomfort to the baby are not irrelevant to the decision but have not been included explicitly in this analysis because they are difficult to quantify and probably of a relatively small magnitude. This analysis suggests that the choice between TCB and TSB would depend on the number of meters that would be required. The NHS staff census as reported on the NHS Information Centre website (www.ic.nhs.uk/statistics-and-data-collections/workforce/nhs-staff-numbers, accessed August 2009) reports the 'head count' figure for practising midwives as 25 000 with 19 500 full-time equivalents. The base-case analyses suggest that were all midwives required to have a TCB meter in order to implement a TCB strategy then TSB would be the cost-

effective option. However, not all midwives do postnatal checks. It may be more useful to consider the number of postnatal checks undertaken per day.

If we assume that each birth has, on average, three postnatal visits then this amounts to:

$(690\,000 \times 3) \div 365 = 5670$ postnatal visits per day

Community midwives would typically do 6–10 postnatal visits per day, which suggests that the postnatal workload is managed by approximately 1000 midwives on any given day, which might suggest that the service could actually be delivered with fewer than 9200 meters.

In interpreting this analysis, there are a number of caveats to be considered in addition to the most important ones already highlighted concerning the lack of evidence. The analysis assumes that 25% of infants will require a confirmatory TSB before consideration of phototherapy. If this estimate were higher, then the total cost of the TCB strategy would be higher and the cost threshold at which TSB would be the preferred option would consequently be lower. The analysis also assumes that a move to more intensive testing does not lead to increased phototherapy. This might seem a counter-intuitive assumption as the efficacy of more intensive testing is ultimately predicated on not missing cases that could benefit from treatment. However, intervention rates may also be influenced by recommendations on thresholds for commencing treatment, where current practice varies. In some settings this might lead to lower, but more targeted, intervention than currently occurs.

The analysis also assumes that the varous test strategies will not differ in terms of the amount of testing undertaken and the number of follow-up home visits undertaken. Of course, it is possible that the convenience of TCB could lead to additional 'downstream' costs not considered here.

An important assumption in this analysis is that phototherapy rates would not change if a more intensive testing strategy were adopted. This is a strong assumption in the model since we do not know how many more cases of hyperbilirubinaemia would be correctly identified by a change in testing strategy.

C.9 Conclusion

Based on the published limitations of visual examination, the GDG strongly believes that a more intensive testing strategy is required in order to improve outcomes in neonatal jaundice. This will require more resources but, if this reduces the incidence of kernicterus by sufficient numbers, it would be cost-effective to implement in the NHS. While the analysis presented here is unable to demonstrate that this would be cost-effective, it does suggest that the actual number of kernicterus cases needed for more intensive testing to be cost-effective is relatively small, for example 0.49 cases per year if the TCB strategy could be delivered with 1000 meters up to 1.52 cases per year if 9200 meters are required. This is the cut-off above which the total cost of TSB strategy is cheaper than TCB. It is important to remember that these values are based on strong assumptions (for the lifetime QALYs lost through kernicterus and the lifetime cost of kernicterus) that are supported by the GDG but are not based on externally verifiable evidence. The number of cases of kernicterus that could be prevented is the critical unknown. However, reports from the USA[240] have shown a reduction of four cases per 100 000 births after the mid 1990s.

Determining which intensive testing strategy is cost-effective depends crucially on the number of meters that would have to be purchased in order to deliver TCB. The number of community midwives involved in home visits on any one day is far smaller than the total number working in the NHS at any one time. Therefore it seems plausible that the TCB strategy could be delivered with a number of transcutaneous meters that is sufficiently low to meet the threshold for cost-effectiveness. However, service delivery is not within the remit of this NICE guideline and local commissioners may want to opt for the strategy they believe can be delivered most cost-effectively in their area.

Appendix D

Cost-effectiveness of intravenous immunoglobulin (IVIG)

D.1 Introduction

The clinical evidence suggests that babies with Rhesus and ABO haemolytic disease receiving IVIG are less likely to require exchange transfusion, an expensive procedure with associated morbidity and mortality.[241] However, IVIG is also a relatively expensive therapeutic intervention and there is a shortage of global supply. Therefore an economic evaluation was undertaken to help guide GDG recommendations. The analysis compared giving IVIG as an adjunct to phototherapy in babies with Rhesus haemolytic disease and ABO haemolytic disease where serum bilirubin is continuing to rise at more than 8.5 micromol/litre per hour against not giving IVIG to these babies.

D.2 Method

A simple decision-analytic model was used to assess the cost-effectiveness of IVIG as an adjunct to multiple phototherapy in babies with haemolytic disease where bilirubin levels continue to rise. The structure of this model is shown in Figure D.1. Costs were taken from the perspective of the NHS and personal social services, which is in accordance with the NICE guidelines manual (www.nice.org.uk/guidelinesmanual).[237] The cost of multiple phototherapy was not included in the analysis as it common to both treatment alternatives. However, the costs of exchange transfusion are important as the rationale for IVIG is that the rates of exchange transfusion will vary according to treatment. Naturally, the costs of IVIG are also an important cost input, as this is the treatment evaluated.

Health outcomes are measured in quality-adjusted life years (QALYs). Exchange transfusion is associated with mortality and morbidity[241] and in this model the difference between the treatment alternatives in QALYs is assumed to only be a consequence of mortality arising from exchange transfusion. This was partly to simplify the analysis but also because any impact on QALYs from morbidity would be small relative to that from assuming causation between exchange transfusion and mortality. We assume that IVIG would have no adverse effects that would have important long-term morbidity.

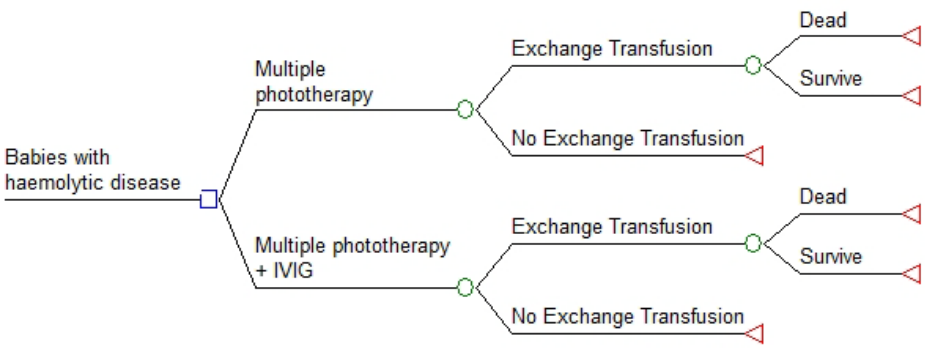


Figure D.1 Decision tree for the IVIG cost-effectiveness model

D.3 Model parameters

The treatment cost of IVIG was estimated using the unit costs in Table D.1.

Table D.1 Unit costs for IVIG

Resource	Unit cost	Source	Notes
IVIG	£1,000	GDG estimate	
Specialty doctor per hour	£54	PSSRU (2008)[239] (www.pssru.ac.uk/pdf/uc/uc2008/uc2008.pdf)	15 minutes set-up time
Nurse, day ward, per hour of patient contact	£43	PSSRU (2008)[239]	4 hours of nurse time
Non-elective inpatient bed day	£430	NHS Reference Costs 2007/08[242] (currency code PB01Z)	Inpatient cost estimated as an excess bed day for non-elective patient with a major neonatal diagnosis

It takes 4 hours to administer IVIG and it was assumed that the drip was set up by a specialist registrar but that a nurse would supervise the treatment for the 4 hours. The treatment is provided as an inpatient procedure and therefore treatment also includes the resources involved in the occupation of a hospital bed. This was estimated by using the 2007/08 NHS Reference Costs[242] excess bed-day cost for a non-elective inpatient with a major neonatal diagnosis.

The cost of an exchange transfusion was estimated using the 2007/08 NHS Reference Costs and the category of non-elective inpatient with a major neonatal diagnosis. The costs of treatment are summarised in Table D.2.

Table D.2 Treatment costs

Resource	Unit cost	Source	Notes
Exchange transfusion	£2,108	NHS Reference Costs 2007/08[242] (currency code PB01Z)	Non-elective inpatient, with a major neonatal diagnosis
IVIG	£1,616		Based on the unit costs in Table D.1

The efficacy of treatment relates to the number needed to treat (NNT) with IVIG to avoid an exchange transfusion. This in turn influences the number of babies who avoid an exchange transfusion and its associated mortality. The clinical parameters used in the model are given in Table D.3.

Table D.3 Clinical parameters

Parameter	Value	Range (sensitivity analysis)	Source
NNT Rhesus disease	2	2 to 3	See Chapter 7
NNT ABO Disease	5	5 to 13	See Chapter 7
Exchange transfusion mortality	2%	0.3% to 2%	Jackson (1997)[204]; Ip *et al.* (2004)[243]

Finally, there is a range of cost–benefit inputs which reflect NICE methodology. These inputs are shown in Table D.4. The QALY gain of an averted exchange transfusion death is an approximation of the discounted QALY gain from a life lived in perfect health and for an average life expectancy.

Table D.4 Cost–benefit parameters

Parameter	Value	Source	Notes
QALY gain from averted exchange transfusion mortality	25		Approximately 75 to 80 years of life lived in full health
Willingness to pay for a QALY	£20,000	NICE guidelines manual (2009)[237]	An advisory threshold of £20,000 to £30,000 is suggested in the manual
Discount rate	3.5%	NICE guidelines manual (2009)[237]	

D.4 Results

The results with base-case values are shown in Tables D.5 and D.6 for Rhesus haemolytic disease and ABO haemolytic disease, respectively.

Table D.5 Cost-effectiveness of IVIG for babies with Rhesus haemolytic disease with base-case model values

Treatment	Cost	Mortality	QALY loss	ICER
No IVIG	£2,108	0.02	0.5	–
IVIG	£2,670	0.01	0.25	£2,248 per QALY

Table D.6 Cost-effectiveness of IVIG for babies with ABO haemolytic disease with base case model values

Treatment	Cost	Mortality	QALY loss	ICER
No IVIG	£2,108	0.02	0.5	–
IVIG	£3,302	0.016	0.4	£11,944 per QALY

With base-case values, IVIG appears to be cost-effective in babies with Rhesus and ABO haemolytic disease with incremental cost-effectiveness ratios (ICERs) of less than £20,000 per QALY. The treatment appears to be most cost-effective in babies with Rhesus haemolytic disease, which is because the data suggest a lower NNT to avoid an exchange transfusion. If more exchange transfusions are avoided, that has a beneficial effect on both 'downstream' costs and averted mortality.

D.5 Sensitivity analysis

The results for the base-case analysis are only as reliable as the base-case inputs that produce them. There is important uncertainty in some of these inputs, especially with respect to exchange transfusion mortality and the NNT to avoid exchange transfusion. The 95% confidence intervals for the NNT were as follows:

- Rhesus haemolytic disease: 1.6 to 3
- ABO haemolytic disease: 3 to 13

In exploring this uncertainty, there is limited value in exploring scenarios where exchange transfusion mortality is higher than the base case, the NNT is lower than the base case and the cost differential between exchange transfusion and IVIG is bigger than the base case. That is not to say that such scenarios are implausible but rather they would simply reinforce the observed cost-effectiveness of treatment. Rather, we are more interested in subjecting the cost-effectiveness finding to scrutiny by observing the extent to which the cost-effectiveness would still hold with the least propitious but still plausible scenarios. Therefore, the sensitivity analyses take a 'worst-case' scenario with respect to clinical parameters and a threshold approach to costs.

Analysis 1 – varying clinical parameters

In this analysis it was assumed that the mortality rate for an exchange transfusion was 3 per 1000.[243] Furthermore, we took the upper limit of the 95% confidence intervals for the NNT. In this analysis the ICER for Rhesus haemolytic disease was £34,379. For ABO haemolytic disease the ICER was £243,381.

Analysis 2 – varying treatment costs

In this sensitivity analysis the clinical parameters were maintained at their base-case value. The costs of IVIG were then increased to determine the value at which IVIG treatment would no longer be cost-effective. For ABO haemolytic disease IVIG treatment remained cost-effective for all IVIG treatment costs less than £2,421. For Rhesus haemolytic disease IVIG treatment would have to exceed £6,054 for it to no longer be considered cost-effective.

D.6 Discussion

This analysis strongly suggests that IVIG is a cost-effective treatment in babies with Rhesus haemolytic disease as an adjunct to phototherapy where bilirubin levels are still rising. This finding seems reasonably robust with respect to uncertainty in model inputs. Even when the NNT was taken from the upper limit of the 95% confidence interval and much lower exchange transfusion mortality than the base case was assumed, the ICER was only just outside what would be considered cost-effective by NICE criteria. Also, with base-case clinical inputs the cost-effectiveness of IVIG in Rhesus disease babies was not sensitive to the costs of IVIG.

For patients with ABO haemolytic disease the cost-effectiveness of IVIG is less certain because of the higher NNT. The cost-effectiveness in this group is very sensitive to exchange transfusion mortality and the NNT within plausible ranges. While cost-effective in the base-case analysis, the ICER in the 'worst-case' scenario would not be considered to be a cost-effective use of scarce NHS resources.

While the sensitivity analysis did not suggest that the results were particularly sensitive to changes in IVIG cost, it should be remembered that if the true clinical inputs conferred a lower benefit with IVIG treatment then the importance of treatment costs as a determinant of cost-effectiveness would increase.

D.7 Conclusion

The model seems to provide good evidence that IVIG treatment in babies with Rhesus haemolytic disease can be considered cost-effective and it therefore supports the GDG recommendation. IVIG treatment in babies with ABO haemolytic disease may also be cost-effective, as indicated by the base-case results. However, sensitivity analysis suggested this finding is subject to considerable uncertainty. Nevertheless, IVIG treatment in this group of patients is consistent with recent Department of Health guidance and is also likely to have a relatively small cost impact given the number of babies affected and therefore the GDG recommendation seems reasonable. Research to ascertain the cost-effectiveness of IVIG, especially in babies with ABO haemolytic disease, could be useful given the current evidence base.

Appendix E

Implementation tools

BiliWheel

Currently jaundice is recognised by visual inspections of the baby. The evidence reviewed in this guideline demonstrated that inspection of a baby by the parent, health visitor or midwife can determine the presence of jaundice in most cases, but it is not an accurate method for determining the severity of jaundice. Severity of jaundice is assessed by measurement of the bilirubin level (using a serum sample or a transcutaneous bilirubinometer). The clinical significance of the bilirubin level must be interpreted taking into account the baby's age (in hours). Errors are easily made when calculating a baby's age and this could lead to failure to recognise the need for treatment. For example, it is difficult to quickly and accurately mentally calculate the postnatal age of a baby whose bilirubin has just been measured at 6.30 am on a Monday and who was born at 7.45 pm on the previous Friday.

The BiliWheel was inspired by discussions within the Guideline Development Group. It is a handy pocket-sized device (diameter 115 mm) comprised of three concentric wheels designed to help health visitors and community midwives determine the clinical significance of the bilirubin level by calculating a baby's age in hours and relating this to the bilirubin level. It is similar in concept to the gestation wheel, with which midwives and community health visitors are familiar.

Using the BiliWheel, the community health visitor or community midwife will be able to position the '0' hour mark of the outer disk (which is 0–168 hours) at the time/day of birth on the inner disk (divided into days and hours) and will then read the age in hours at the current time.

Once the baby's age has been determined, the health visitor or community midwife will interpret the baby's bilirubin level using the data on the reverse side of the BiliWheel. The pointer on the second outer disk is rotated to the age (in hours) on the inner wheel. A window shows four threshold bilirubin levels corresponding to four stepped intervention based on treatment threshold adopted by the GDG:

1. Repeat transcutaneous bilirubin/serum bilirubin measurement (6 – 12 hours)
2. Consider phototherapy
3. Phototherapy
4. Exchange transfusion

The GDG anticipates that the BiliWheel will:

- prevent delays in treatment
- reduce readmission rates for mothers and babies
- raise awareness of key issues relating to the management of jaundice with community-based healthcare professionals
- support implementation of the guideline.

A prototype of the BiliWheel has been developed and a validation study is underway. The validation study will recruit practising and student midwives at two centres.. The primary outcome will be the accuracy of the BiliWheel in determining age in hours and correct intervention using six case vignettes. An iterative development and testing process will be used enabling feedback from each round of testing to inform the final design and additional content of the BiliWheel.

If validated, a printable version of the BiliWheel will be available in pdf format for downloading from www.ncc-wch.org.uk following publication of the guideline.

Parent Information Factsheet

The GDG have developed this parent information factsheet to accompany the guideline. The information included in this appendix is also being used by NICE as the basis for an implementation tool.

Neonatal Jaundice Parent Information Factsheet

What is jaundice?

Jaundice is a common condition in newborn babies. Jaundice is caused by a build-up of a chemical in the blood called bilirubin. Newborn babies' bodies are not developed enough to process bilirubin and remove it from the blood. Because of this more than half of all newborn babies become slightly jaundiced for a few days. Jaundice is usually noticeable to the eye because the build up of bilirubin causes the skin and the whites of the eyes and gums to appear yellow. In most babies jaundice is mild, causes no harm and clears up by itself. Nevertheless it is still important to contact your midwife or another health care professional if you think that your baby might have jaundice.

How can I check my baby for jaundice?

It is important to check your baby for any signs of yellow colouring particularly during the first week of life. The yellow colouring will usually appear around the face and forehead first and then spread to the body arms and legs. A good time to check your baby for jaundice is when you are changing their nappy or clothes. From time to time gently press your baby's skin to see if you can see a yellow tinge developing. Check the whites of the eyes if they are open and when your baby cries have a look inside their mouth and see if the sides of the gums or roof of the mouth look yellow. Ask your midwife to show you how to check your baby for jaundice if you are not sure.

What should I do if I think my baby has jaundice?

- If you believe that your baby's skin, gums or eyes are yellow on the first day of life, contact your midwife, on-call midwife or another healthcare professional urgently as this could be a sign of another medical problem.
- If your baby is more than 24 hours old and you think that your baby's skin, gums or eyes are yellow, contact your midwife, on-call midwife or another healthcare professional on the same day.

It is also important to let your midwife, on-call midwife or another healthcare professional know:

- If any of your other children needed treatment for jaundice as babies
- If your baby was born at less than 38 weeks
- How you are feeding or intending to feed your baby (breast/bottle/both)
- If your baby passes pale, chalky coloured stools (poo) or dark urine (wee) that stains the nappy.

How is jaundice diagnosed?

If you or your midwife thinks your baby has jaundice then the level of bilirubin should be measured by a healthcare professional. The levels can be measured either by using a simple device (known as a transcutaneous bilirubinometer) that is placed on the baby's forehead or chest and gives a reading, or by taking a blood sample, usually from the baby's heel. It is important to monitor the level of bilirubin so a repeat test will often be required 6–12 hours later.

How is jaundice treated?

Slightly elevated levels of bilirubin are not harmful but you may need additional support to establish breastfeeding. Ask your midwife to assist with this.

If the level of bilirubin in your baby's blood is found to be unusually high or continues to rise, then your baby may need to receive treatment in hospital. This treatment usually consists of light therapy or 'phototherapy'. Phototherapy involves placing the baby under a lamp which shines a special type of light (light in the blue spectrum) onto the skin. This light helps to break down the bilirubin so it can be removed from the body in urine. Phototherapy does not involve giving the baby medicine.

Your baby will be placed under the light naked apart from a nappy. This is to make sure that the light can shine on as much of the skin as possible. During phototherapy your baby's bilirubin levels will need to be measured every six hours.

Your baby's eyes will be protected from the light with eye pads or a Perspex eye shield. If the doctor is confident that the treatment is working and the bilirubin level is not too high, you will be encouraged to take your baby out for short breaks for feeds.

If your baby's bilirubin level is very high then more than one lamp will be used at the same time. In this situation the baby will need to remain under the light without breaks until the bilirubin level has dropped.

Are there any complications of jaundice?

Jaundice does not cause any problems in the majority of babies. In some rare cases the bilirubin level may become very high and this could result in a serious condition called kernicterus which can cause long term problems such as hearing loss and cerebral palsy.

If your baby is at risk of kernicterus they will need to have a different type of emergency treatment in an intensive care unit. This emergency treatment is called an exchange transfusion. An exchange transfusion involves replacing the baby's blood with new blood from a donor. Though neonatal jaundice is very common, kernicterus is extremely rare.

What if my baby remains jaundiced?

In most babies jaundice clears up within a few days. However if jaundice lasts more than two weeks (or more than three weeks in babies that were born premature) then it is called prolonged jaundice. If your baby has prolonged jaundice contact your midwife or another healthcare professional straight away because your baby may need some additional blood tests to ensure that there are no liver problems.

Will my baby recover from jaundice?

The outcome for a baby with jaundice is extremely good, as long as the jaundice is recognised before the levels get too high and it is treated appropriately.

Where can I find out more information?

NICE website: www.nice.org.uk

Yellow Alert website: www.childliverdisease.org/education/yellowalert

Appendix F

Registered stakeholder organisations

This appendix includes a list of all registered stakeholders at the time of submission for factual accuracy check (2 February 2010.). The most current list of registered stakeholders is available on the NICE website.

Abbott Laboratories Limited
Alder Hey Children's NHS Foundation Trust
Association for Clinical Biochemistry
Association of Breastfeeding Mothers
Association of Clinical Biochemists, The
Association of the British Pharmaceuticals Industry (ABPI)
Birmingham Womens NHS Trust
BLISS - the premature baby charity
Bolton Council
Breastfeeding Network, The
Brighton and Sussex University Hospitals Trust
Brighton and Sussex University Hospitals Trust
British Dietetic Association
British National Formulary (BNF)
British Nuclear Medicine Society
British Nuclear Medicine Society
British Nuclear Medicine Society
British Nuclear Medicine Society
British Society for Haematology
British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN)
Brook London
Calderdale PCT
Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)
Care Quality Commission (CQC)
Central Medical Supplies Ltd
Children's Liver Disease Foundation
Cochrane Pregnancy & Childbirth Group
Commission for Social Care Inspection
Connecting for Health
Countess of Chester Hospital NHS Foundation Trust
Cytyc UK Limited
Department for Communities and Local Government
Department of Health
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Derbyshire Mental Health Services NHS Trust
Det Norske Veritas - NHSLA Schemes
Diabetes UK
Draeger Medical
EGAOH
Epsom & St Helier University Hospitals NHS Trust
Evidence based Midwifery Network
Gloucestershire PCT

Harrogate and District NHS Foundation Trust
Heart of England NHS Foundation Trust
Imperial College Healthcare NHS Trust
Independent Midwives UK
Insitute of Biomedical Science
Inspiration Healthcare Ltd
Institute of biomedical Science
King's College Hospital NHS Foundation Trust
Kingston Hospital NHS Trust
La Leche League GB
Leeds PCT
Liverool Women's NHS Foundation Trust
Liverpool Womens NHS Foundation Trust
Luton & Dunstable Hospital NHS Foundation Trust
Maternity Health Links
Medicines and Healthcare Products Regulatory Agency (MHRA)
Mid and West Regional Maternity Service Liasion Committe
MIDIRS (Midwives Information & Resource Service)
Ministry of Defence (MoD)
National Childbirth Trust
National Forum of LSA Midwifery Officers (UK)
National Patient Safety Agency (NPSA)
National Screening Committee
Natus Medical Incorporated
NCC - Cancer
NCC - Mental Health
NCC - National Clinical Guidance Centre (NCGC)
NCC - Women & Children
Neonatal & Paediatric Pharmacists Group (NPPG)
Neonatal & Paediatric Pharmacists Group (NPPG)
NETSCC, Health Technology Assessment
Newham University Hospital NHS Trust
NHS Bedfordshire
NHS Bournemouth and Poole
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Direct
NHS Isle of Wight
NHS Islington
NHS Kirklees
NHS Plus
NHS Quality Improvement Scotland
NHS Sheffield
NICE - CPHE
NICE - Guidelines Coordinator - for info
NICE - Guidelines HE for info
NICE - IMPLEMENTATION CONSULTANT Region - East
NICE - IMPLEMENTATION CONSULTANT - Region London/SE
NICE - IMPLEMENTATION CONSULTANT Region NW & NE
NICE - IMPLEMENTATION CONSULTANT Region West Midlands
NICE - IMPLEMENTATION CO-ORDINATION for info
NICE - Technical Appraisals (Interventional Procedures) FOR INFO
North Tees and Hartlepool Acute Trust
North Tees and Hartlepool Acute Trust
North Tees and Hartlepool Acute Trust
North Tees PCT
North Trent Neonatal Network
North West London Perinatal Network
North Yorkshire and York PCT

Northwick Park and St Mark's Hospitals NHS Trust
Nottingham University Hospitals NHS Trust
Oxford John Radcliffe NHS Trust
Patients Council
Pennine Acute Hospitals NHS Trust
PERIGON Healthcare Ltd
Philips Healthcare
Public Health North East
Public Wales NHS Trust
Queen Mary's Hospital NHS Trust (Sidcup)
RCM Consultant Midwives Group
Royal Brompton & Harefield NHS Trust
Royal College of General Practitioners
Royal College of Midwives
Royal College of Midwives
Royal College of Nursing
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians London
Royal College of Radiologists
Royal Devon and Exeter NHS Foundation Trust
Royal Society of Medicine
Salford Royal Hospitals Foundation NHS Trust
Sandwell & West Birmingham Hospital NHS Trust
Sandwell PCT
Sandwell PCT
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield Children's NHS Foundation Trust
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Southampton University Hospitals NHS Trust
St Richards Hospital
UK National Screening Committee
UNICEF Baby Friendly Initiative
United Lincolnshire Hospitals NHS Trust
University Hospitals Bristol NHS Foundation Trust
University of York
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
West Hertfordshire PCT & East and North Hertfordshire PCT
West Midlands SHA
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Wirral Hospital Acute Trust
York NHS Foundation Trust
Yorkshire and the Humber LSA

Appendix G

Clinical questions

I. Recognition

Q1. 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)?

Q2. What is the best method of recognising hyperbilirubinaemia?

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

II. Diagnosis

Q3. 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?

Q4. How useful are the following tests in predicting neonatal hyperbilirubinaemia?

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

i) Umbilical cord blood bilirubin levels
ii) Timed serum bilirubin levels
iii) Transcutaneous bilirubin levels
iv) End tidal CO levels Nomograms
v) Risk assessment
vi) Coombs' test

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

III. Management

Q5. Phototherapy

i) How effective is phototherapy?
ii) What is the best modality of giving phototherapy (clinical and cost-effectiveness)?
   a) Conventional phototherapy (single, double or multiple phototherapy)
   b) Sunlight
   c) Fibreoptic phototherapy (biliblankets, bilibeds and other products)

iii) What are the criteria/indications for starting and stopping phototherapy in babies with neonatal hyperbilirubinaemia?
iv) What is the correct procedure of giving phototherapy?

Focus on the method of feeding/types of feed, incubator/bassinet care, effect of intermittent versus constant method on maternal–infant bonding, parental anxiety

Q6. 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?

a) Oral – top milk feeds by bottle/cup/spoon or other liquids (water/juice)
b) Parenteral – IVF

Q7. Exchange transfusion

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

Q8. 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?

a) Metalloporphyrins
b) Gammaglobulins
c) Drugs (phenobarbitol, clofibrate, cholestyramine)
d) Agar, charcoal
e) Suppositories, other rectal modes of treatment
f) Complementary/alternative medicines (Chinese herbal remedies such as Yin-chen)

IV. Monitoring and follow-up

Q9. 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?

Q10. 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?

V. Information

Q11. 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

Appendix H

Evidence tables

Table of Contents

Which factors affect the relationship between neonatal hyperbilirubinaemia and kernicterus or other adverse outcomes (neurodevelopmental, auditory)?

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
Newman TB; Year: 2000 Country: USA [9]	Study Type: Nested case-control study Evidence Level: II	Cohort of all infants with BW = 2000 g and GA = 36 weeks born alive at 11 hospitals of a health maintenance organisation during a two year period (*n* = 51 387) <u>Cases:</u> Babies with maximum TSB levels ≥ 427 micromol/litre within the first 30 days after birth *n* = 73 Mean BW: Not reported Mean GA: Not reported Gender: Males = 67.1% Ethnicity: Not reported (only maternal race specified) <u>Controls:</u> Random sample of babies from the cohort with maximum TSB levels < 427 micromol/litre *n* = 423 Mean BW: Not reported Mean GA: Not reported Gender: Males = 54.4% Ethnicity: Not reported (only maternal race specified) For analyses examining the use of phototherapy only, additional random sample of 30 babies with maximum TSB levels of 342 to 426 micromol/litre added to the control group Exclusion criteria: Not defined	1) Relationship of clinical and demographic factors associated with hyperbilirubinaemia evaluated by bivariate analysis and OR 2) Risk factors significant in the univariate model entered into multiple regression analysis to find independent predictors of hyperbilirubinaemia – both by including and excluding early jaundice cases <u>Early jaundice cases</u> (*n* = 14) defined as babies with TSB exceeding recommended phototherapy threshold for age during birth hospitalisation, those given phototherapy during birth hospitalisation, when jaundice noted at less than 20 hours of age and TSB not measured within 6 hours of that time. 3) Risk index developed by assigning points equal to the OR for risk factors that were significant in the logistic regression model with the exclusion of early jaundice cases, and predictive accuracy compared by the c-statistic (equal to area under ROC curve) <u>Reference standard:</u> Significant hyperbilirubinaemia defined as maximum TSB levels = 428 micromol/litre within the first 30 days after birth.	<u>Maternal and prenatal factors associated with significant hyperbilirubinaemia (those with *P* < 0.05 in bivariate analysis)</u> *Maternal factors* ☐ Race, ☐ maternal age, ☐ family history of jaundice in a newborn, ☐ vacuum delivery *Neonatal factors* ☐ Male sex, ☐ lower GA, ☐ early jaundice, ☐ cephalohaematoma, ☐ bruising, ☐ breastfeeding at time of discharge <u>Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95% CI)</u> *All cases (n = 73)* Early jaundice: OR 7.3 (2.8–19) GA (per wk): OR 0.6 (0.4–0.7) Breastfeed only at discharge: OR 6.9 (2.7–17.5) Asian race: OR 3.1 (1.5–6.3) Bruising: OR 3.5 (1.7–7.4) Cephalohaematoma: OR 3.2 (1.1–9.2) Maternal age ≥ 25 years: OR 2.6 (1.1–9.2) *Cases excluding early jaundice (n = 59)* GA (per wk): OR 0.6 (0.4–0.7) Breastfeed only at discharge: 5.7 (2.1–15.5) Asian race: OR 3.5 (1.7–7.4)	Unselected population but exclusion criteria not defined Confounding variables controlled for during multivariate analysis Test & Reference test described adequately Reference test a standard test Blinding – Not reported

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
				Bruising: OR 4.0 (1.8–8.8) Cephalohaematoma: OR 3.3 (1.1–10) Maternal age ≥ 25 years: OR 3.1 (1.2–8.1) Family history of jaundice: 6.0 (1.0–36.0); *P* = 0.05 Risk Index scoring 6 points each for exclusive breastfeeding and family HISTORY OF jaundice in a newborn, 4 points each for bruising and Asian race, 3 points each for cephalhematoma and maternal age ≥ 25 years, 1 point for male sex, -2 points for black race, and 2(40-GA) Accuracy of Risk Index score in predicting significant hyperbilirubinaemia Overall c-statistic 0.85 *Risk index score < 10* +LR: 0.2 *Risk index score > 10* +LR: 2.2 *Risk index score > 20* +LR: 18.2	
Newman TB *et al.*; Year: 2002 Country: USA [10]	Study Type: Nested case-control study Evidence Level: II	Cohort of all infants with BW = 2000 g and GA = 36 weeks born alive at 12 hospitals of a health maintenance organisation during a four year period (*n* = 105 384) Cases: Babies with maximum TSB levels = 428 micromol/litre within the first 30 days after birth (*n* = 140) Controls: Random sample of babies from the cohort with maximum TSB levels = 428 micromol/litre (*n* = 631)	1) Frequency of jaundice noted in the medical record in term and near-term newborns less than 24 hours old 2) Association of jaundice noted in the first 24 hours after birth with the use of phototherapy and risk of developing hyperbilirubinaemia after controlling for confounding variables -	1) Frequency of jaundice noted in newborns within 24 hours of age (Kaplan Meier survival estimates + no. with TSB measured) *Less than 18 hours of age* 3.8% *Less than 24 hours of age* 6.7% 2) Association of jaundice noted within 24 hours of age with risk factors (results of bivariate analysis) No statistically significant difference	Nested case–control study Some cases were included in 42290 – should we excluded 42290 Cases and controls taken from comparable populations but exclusion criteria not well defined Confounding variables controlled Methodology described adequately but exact number of babies with jaundice noted in first 24 hours calculated with Kaplan Meier analysis

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
		Exclusion criteria: Babies with conjugated hyperbilirubinaemia		between the cases and the controls for risk factors ethnicity, sex, gestational age, breastfeeding, cephalhematoma or the birth cohorts Relationship between jaundice noted within 24 hours of birth and phototherapy/ hyperbilirubinaemia (Mantel–Haenszel OR with 95% CI) *Phototherapy* Cases: 18.9% Controls: 1.7% M-H OR 10.1 (4.2–24.4) *Hyperbilirubinaemia* Cases: 14.3% Controls: 5.9% M-H OR 2.9 (1.6–5.2)	
Kuzniewicz MW *et al.*; Year: 2008 Country: USA [11]	Study Type: Nested case-control study Evidence Level: II	Cohort of all babies with BW = 2000 g and GA = 34 weeks born alive at hospitals of a health maintenance organisation during a 10 year period (n = 285 295). From this cohort 13 843 babies with qualifying TSB level of 291 to 392 micromol/litre measured at = 48 hours of age taken as reference population Cases: Babies with maximum TSB levels = 427 micromol/litre after the qualifying TSB (n = 62) Mean BW: 3374 ± 527 g Mean GA: 38.3 + 1.7 weeks Mean age at entry: 71.5 ± 19.4 hours Gender: Males = 58.9% Ethnicity: asian = 27.4% black = 8.1%	Cases and controls matched on risk group status (low, medium and high risk based on the hour-specific bilirubin centiles, gestational age and DAT results) and difference between their TSB levels and the TSB threshold levels for phototherapy as defined by the AAP 1) Relationship of clinical and demographic factors associated with hyperbilirubinaemia evaluated by bivariate analysis 2) Risk factors significant in the bivariate model (at $P < 0.1$) entered into multiple regression analysis to find independent predictors of hyperbilirubinaemia 3) Predictive accuracy of the final risk factor model evaluated by the c-statistic (equal to area under ROC curve)	1) Variables associated with severe hyperbilirubinaemia (those with $P < 0.1$ in bivariate analysis) *Demographic factors* When compared to 40+ weeks GA 38–39 weeks ($P = 0.01$) GA 34–37 weeks ($P = 0.06$) birth hospitalisation < 48 hours ($P = 0.07$) *History & physical examination factors* Bruising ($P = 0.007$) *Laboratory values* Qualifying TSB occurring during birth hospitalisation ($P = 0.04$) TSB increase ≥ 102 micromol/litre ($P = 0.002$) *Interventions* Inpatient phototherapy ($p < 0.001$) Intravenous fluids after qualifying TSB ($P = 0.002$) exclusive breastfeeding after qualifying TSB ($P = 0.005$)	Nested case–control study Cases and controls taken from comparable populations with well defined exclusion criteria Confounding variables controlled Methodology described adequately

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
		Controls: Randomly selected sample of babies with maximum TSB levels < 427 micromol/litre after the qualifying TSB (4 controls per case, *n* = 248) Mean BW: 3414 ± 576 g Mean GA: 37.9 + 1.4 weeks Mean age at entry: 73.1 ± 17.5 hours Gender: Males = 61.3% Ethnicity: asian = 29.8% black = 6.8% Exclusion criteria: infants with resolving jaundice, those where TSB levels not documented after a maximum TSB recording or decline in TSB not recorded, and those with conjugated bilirubin level = 2 MG/DL		2) Factors independently associated with severe hyperbilirubinaemia from multivariate regression analysis (adj OR with 95% CI) GA (compared to 40 weeks as reference) For 38–39 weeks: 3.1 (1.2–8.0); *P* = 0.02 For 34–37 weeks: 3.7 (0.6–22.7); *P* = 0.15 Family history of jaundice: 3.8 (0.9–15.7): *P* = 0.06 Bruising on examination: 2.4 (1.2–4.8); *P* = 0.02 Exclusive breastfeeding after qualifying TSB: 2.0 (1.03–4.0); *P* = 0.04 TSB increase of = 102 micromol/litre per day: 2.5 (1.2–5.5); *P* = 0.02 Accuracy of risk factor model in predicting severe hyperbilirubinaemia c-statistic 0.82 (0.76 to 0.88)	
Keren R *et al.*; Year: 2005 Country: USA 12	Study Type: Retrospective cohort Evidence Level: II	Infants with BW = 2000 g if GA = 36 weeks and BW = 2500 g if GA = 35 weeks participating in the hospital's early discharge programme, and who had both pre and post-discharge TSB levels measured at the phase when ≥ 75% babies had both the samples (*n* = 899) Group 1: infants with post-discharge TSB > 95th centile on nomogram *n* = 98 mean BW: 3.4 ± 0.5 kg mean GA: Not reported Gender: males = 54.1% Ethnicity: White = 45.9% Black = 31.6% Asian = 10.2%	1) Association of risk factors with significant hyperbilirubinaemia derived from univariate analysis (at *P* < 0.2) 2) Multivariate regression analysis used to find factors independently associated with significant hyperbilirubinaemia To calculate risk, birthweight (kg) was transformed by subtracting 2 kg and dividing by 0.5 kg for every 0.5 kg above 2.5 kg 3) Comparison of diagnostic accuracy of the risk factor score (derived from regression modeling) with that of pre-discharge TSB levels in predicting significant	Prevalence of significant hyperbilirubinaemia 98/899 (10.9%) 1) Factors associated with significant hyperbilirubinaemia *Increased risk* GA < 38 weeks (*P* = 0.02) GA ≥ 40 weeks (*P* = 0.12) large for gestational age babies (*P* = 0.13) higher pre-discharge TSB risk zone > 76th centile (*P* < 0.001) breastfeeding (*P* < 0.001) combined breast and bottle feeding (*P* = 0.02) maternal diabetes (*P* = 0.17) vacuum extraction (*P* < 0.001) prolonged rupture (*P* = 0.08) oxytocin use (*P* = 0.002)	Retrospective cohort study Unselected population with well defined exclusion criteria Confounding variables controlled Methodology described adequately Blinding – not specified

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
		Hispanic = 3.1% Other = 8.2% Group 2: infants with post-discharge TSB < 95th centile on nomogram *n* = 801 mean BW 3.3 ± 0.5 kg mean GA: Not reported Gender: males = 52.2% Ethnicity: White = 43.1% Black = 39.9% Asian = 7.7% Hispanic = 4.5% Other = 4.7% Exclusion: admission and treatment in intensive care nursery for neonatal illness and babies requiring phototherapy during birth hospitalisation.	hyperbilirubinaemia Pre-discharge TSB levels expressed as risk zone on an hour-specific bilirubin nomogram (High risk > 95th centile, High intermediate risk 76th – 95th centile, Low intermediate risk 40th – 75th centile, Low risk 0 – 40th centile) Significant Hyperbilirubinaemia defined as TSB level > 95th centile on hour-specific nomogram.	*Decreased risk* Small for gestational age (*P* = 0.04) Parity (*P* = 0.03) Caesarean section (*P* = 0.18) 2) Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95% CI) Birthweight: 1.5 (1.2–1.9); *P* = 0.001 GA < 38 weeks: 2.6 (1.5–4.5); *P* = 0.001 Oxytocin: 2.0 (1.2–3.4); *P* = 0.005 Vacuum delivery: 2.2 (1.5–3.6); *P* = 0.003 Exclusive breastfeeding: 2.6 (1.5–4.5); *P* < 0.001 Breast and bottle feeding: 2.3 (1.1–4.9); *P* = 0.03 Clinical risk index scoring Birthweight: 3 points for 2501–3000 g 6 for 3001–3500 g 9 for 3501–4000 g 12 for 4001–4500 g 15 for 4501–5000 g GA < 38 weeks: 5 points Oxytocin: 4 points Vacuum delivery: 4 points Exclusive breastfeeding: 5 points Breast and bottle feeding: 4 points 3) Predictive accuracy for predicting significant hyperbilirubinaemia RISK FACTOR SCORE c-statistic 0.71 (0.66–0.76) *Risk index score 0–7* +LR: 0.1 *Risk index score 8–11* +LR: 0.4 *Risk index score 12–15* +LR: 0.9	

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
				Risk index score 16–19 +LR: 2.0 *Risk index score 20–23* +LR: 2.6 *Risk index score > 24* +LR: 3.2 PRE-DISCHARGE TSB c-statistic 0.83 (0.80–0.86) *TSB centile 0–40th* +LR: 0.05 *TSB centile 41–75th* +LR: 0.2 *TSB centile 76–95th* +LR: 2.2 *TSB centile > 95th* +LR: 9.4	
Seidman DS *et al.*; Year: 1999 Country: Israel [13]	Study Type: Prospective cohort study Evidence Level: II	Healthy full term infants with GA = 37 weeks born at two hospitals *n* = 1177 mean BW 3247 ± 453 g mean GA 39.8 ± 1.3 weeks Gender: Males = 47.3% Ethnicity: Not reported Exclusion: ABO or Rh incompatibility and a positive direct Coombs' test G6PD deficiency.	1) Association of various factors with jaundice derived from multiple regression analysis 2) Comparison of diagnostic accuracy of various tests for predicting hyperbilirubinaemia <u>Test:</u> TSB measured within first 8 to 24 hours of life and repeated daily for the next 4 days <u>Reference standard:</u> Hyperbilirubinaemia defined as TSB > 171 micromol/litre at day 2 > 239 micromol/litre at day 3 > 291 micromol/litre at day 4–5 <u>Analysis:</u> Association between various factors and jaundice calculated from multiple regression analysis	<u>1) Factors associated with jaundice after comparing Group 1 vs Group 2 (*n* = 1,177)</u> *Day 1 TSB (per 17 micromol/litre)* OR: 3.1 (95% CI 2.4 to 4.1) *Change in TSB from day 1 to day 2 (per 17 micromol/litre)* OR: 2.4 (95% CI 1.9 to 3.0) *Maternal age (per year)* OR: 1.1 (95% CI 1.0 to 1.2) *Mat education (per year)* OR: 0.8 (95% CI 0.7 to 0.9) *Maternal blood type O* OR: 2.9 (95% CI 1.5 to 5.8) *Full breastfeeding* OR: 0.4 (95% CI 0.2 to 0.9) *Day 1 TSB > 85 micromol/litre* OR: 36.5 (95% CI 15.9 to 83.6)	Unselected population No differences at baseline between the two groups Test & Reference test described in detail Reference test a standard one Blinding – Not reported Confounding factors adjusted for during modelling Data not available to calculate PPV or NPV. Raw figures not available

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
			using Odds ratios with 95% CI, and these factors used for modelling in predicting hyperbilirubinaemia	2) Prediction of hyperbilirubinaemia *Prediction by Day 1 TSB only (threshold value > 85 micromol/litre)* Sensitivity: 63.1% Specificity: 94.2% *Prediction by all model variables without Day 1 TSB* Sensitivity: 57.9% Specificity: 90.4% *Prediction by all model variables* Sensitivity: 81.8% Specificity: 82.9%	
Keren R *et al.*; Year: 2008 Country: USA [14]	Study Type: Prospective cohort study Evidence Level: II	Infants managed exclusively in the well infants nursery of an urban tertiary care hospital with GA = 36 weeks and BW = 2000 g or GA = 35 weeks and BW = 2500 g *n* = 812 mean BW 3.3 ± 0.5 kg GA < 38 weeks: 13.4% Gender: males = 49.4% Ethnicity: White = 33.5% Black = 53.2% Asian = 9.8% Other = 3.4% Since the population in the area was predominantly black, stratified sampling scheme used to get a representative sample. Group 1: Infants with significant hyperbilirubinaemia (*n* = 48) Group 2: Infants without significant hyperbilirubinaemia (*n* = 703) Exclusion: babies transferred to the intensive	1) Factors associated with significant hyperbilirubinaemia in univariate analysis entered into regression modeling for clinical risk factor model 2) Comparison of diagnostic accuracy of three tests in predicting significant hyperbilirubinaemia by the c-statistic (mathematically equal to area under ROC curve) Test 1: Pre-discharge bilirubin measured either by TcB or TSB at < 52 hours of age, and expressed as risk-zone on hour specific nomogram. Daily TcB levels recorded using BiliChek, and TSB performed if TcB above 75th centile on hour-specific nomogram or TcB reading = 205 micromol/litre TSB value taken for analysis when both TcB and TSB done. Test 2: Clinical risk factors assessed by review of hospital charts for	Prevalence of significant hyperbilirubinaemia 48/751 (6.4%) – 61 had an incomplete follow-up 1) Association of factors with significant hyperbilirubinaemia (Univariate analysis) (*n* = 812) *Factors increasing risk* Pre-discharge bilirubin – high risk zone OR: 147 (95% CI 34–639) high-intermediate risk zone OR: 21 (95% CI 4.9–93.0) GA < 38 weeks OR: 9.2 (95% CI 4.4–19.0) intended breastfeeding OR: 2.2 (95% CI 1.0–4.5) intended breast + bottle feeds OR: 3.7 (95% CI 1.6–8.6) Grade 4 or higher degree of clinical jaundice OR 6.0 (95% CI 2.1 to 17) *Factors decreasing risk* Black race OR 0.43)95% CI 0.23–0.80) Maternal history of smoking OR: Not reported	Unselected population (stratified sampling) with well defined exclusion criteria Baseline characteristics of two groups not compared Confounding variables controlled Methodology described adequately Blinding – not specified

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
		care nursery for any reason Babies who received intravenous antibiotics for concern for sepsis.	maternal race, intended method of feeding, GA, history of previous infant with jaundice, clinical assessment of jaundice, G6PD deficiency. Test 3: Combination of pre-discharge bilirubin risk zone and clinical risk factors. Reference standard: Bilirubin levels (TcB or TSB) measured on day 3–5 on both hospitalised and discharged babies (at home) using similar method as in Test 1, and Significant Hyperbilirubinaemia defined as bilirubin levels exceeding or within 17 micromol/litre of the hour-specific phototherapy treatment thresholds.	Factors significant in multivariate analysis model ($P < 0.05$) GA< 38 weeks OR 19 (95% CI 6.3- 56) Mother's plan of exclusive breastfeeding: OR 3.7 (95% CI 1.1- 13) Black race: OR 0.22 (95% CI 0.08- 0.61) Grade 4 or higher jaundice observed clinically: OR 1.7 (95% CI 1.2–2.6) Female sex: OR 3.2 (95% CI 1.2–8.4) 2) Predictive ability of the three tests in predicting significant hyperbilirubinaemia (multivariate regression) *Test 1: Pre-discharge bilirubin risk zone* c-statistic 0.88 (95% 0.85 to 0.91) *Test 2: Clinical risk factors (final model had 5 factors – GA, intended method of feeding, black race, extent of jaundice and gender)* c-statistic 0.91 (95% 0.86 to 0.97) *Test 3: Combination model (pre-discharge risk zone + clinical factors of GA and % weight loss)* c-statistic 0.96 (95% 0.93 to 0.98) *Test 3 vs Test 1* p-value for difference< 0.01 *Test 3 vs Test 2* p-value for difference = 0.15 *Test 2 vs Test 1* p-value for difference = 0.35	
Gale R; Year: 1990 Country: Israel [15]	Study Type: Nested case–control study Evidence Level: II	Term babies > 37 weeks delivered during a 5 year period in a university hospital (n = 10 122) Test group: Term babies who developed serum bilirubin levels = 221 micromol/litre n = 1154	1) Association of various factors with high serum bilirubin levels by comparing test group with comparison group (univariate analysis) 2) Step-wise regression analysis done to control for confounding variables	1) Factors associated high bilirubin levels (at $P < 0.01$ during univariate analysis) Male sex (p =0.001) maternal diabetes ($P = 0.01$) maternal PIH ($P = 0.005$) previous sibling with hyperbilirubinaemia ($P < 0.001$) delivery by caesarean section ($P < 0.001$) vacuum or forceps delivery ($P < 0.001$)	Cases and controls taken from comparable populations with exclusion criteria not well defined Confounding variables controlled Methodology not described adequately Blinding – not specified

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
		mean BW 3192 ± 508 g mean GA 39.3 ± 1.5 weeks Gender: Not reported Ethnicity: Not reported <u>Comparison group:</u> every tenth admission randomly selected from the group of with serum bilirubin levels < 221 micromol/litre *n* = 1154 mean BW 3257 ± 444 g mean GA 39.9 ± 1.35 weeks Gender: Not reported Ethnicity: Not reported Exclusion: Not defined		epidural anaesthesia (*P* = 0.001) mother with blood type O (*P* < 0.001) first delivery (*P* < 0.001) cephalohaematoma (*P* = 0.003) short gestation (*P* = 0.01) lower birthweight (*P* = 0.01) lower birth order (*P* = 0.01) <u>2) Factors independently associated with high TSB levels (adj OR with 95% CI)</u> Maternal age > 35 years: Adj OR 1.7 (95% CI 1.3–2.3) Male sex: Adj OR 1.4 (95% CI 1.2–1.7) Primipara: Adj OR2.7 (95% CI 2.1–3.5) Previous sibling with jaundice: Adj OR 2.3 (95% CI 1.9–2.8) Early gestation (with 40 weeks as reference): For 37 weeks Adj OR 4.5 (95% CI 3.2–6.3) For 38 weeks Adj OR 2.1 (95% CI 1.6–2.8) Vacuum extraction: Adj OR 3.0 (95% CI 2.1–4.4)	
Khoury MJ *et al.*; Year: 1988 Country: USA [16]	Study type: Retrospective study Evidence level: II	Offspring of 1669 male US Army veterans who entered the Army between 1965 and 1971 and who participated in a nationwide study of veterans' health (*n* = 3,301, 580 sib-ships with one sibling, 1089 sib-ships with two or more siblings) Exclusion: babies who had a different mother's name from the rest of the sibling relationship (paternal half sibs), stillbirths, babies with records showing evidence of haemolytic disease of newborn.	1) Univariate analysis to find association of maternal and infant variables with hyperbilirubinaemia (peak TSB levels = 205 micromol/litre) 2) Multiple logistic regression analysis to find factors independently associated with hyperbilirubinaemia 3) Recurrence risk of hyperbilirubinaemia by sibling order and degree of hyperbilirubinaemia in the first child before and after controlling for confounding variables *TSB levels for degree of jaundice* Mild: = 205 micromol/litre Moderate: 205 to	<u>Rate of hyperbilirubinaemia in first child of a sibling relationship</u> 83/1669 (5.0%) <u>1) Association of factors with hyperbilirubinaemia</u> Preterm birth (GA< 37 weeks) (OR 2.2) black race (OR 0.37) breastfeeding (OR 2.1) neonatal asphyxia (OR 1.8) <u>2) Factors independently associated with hyperbilirubinaemia</u> Year of birth (after 1975 vs before 1975): Adj OR1.49 (95% CI 1.03–2.15) Preterm birth (GA< 37weeks): Adj OR 2.4 (95% CI 1.4–3.9)	Retrospective study Selected population with well defined exclusion criteria Confounding variables controlled Methodology not described adequately

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
			257 micromol/litre Severe: = 257 micromol/litre	Breastfeeding: Adj OR 1.9 (95% CI 1.3–2.7) 1-minute Apgar score: Adj OR1.7 (95% CI 1.0–2.9) 3) Risk of recurrence of hyperbilirubinaemia *Unadjusted OR with 95% CI* 3.1 (1.4–6.8) *Adjusted OR with 95% CI* For Mild jaundice 2.7 (1.8–4.1) For Moderate jaundice 4.1 (1.5–10.8) For Severe jaundice 12.5 (2.3–65.3)	
Beal AC *et al.*; Year: 2005 Country: USA [18]	Study type: Cross-sectional survey Evidence level: III	Mothers of babies with GA = 35 weeks discharged from well-baby nursery of a health system organisation during 22 month period (*n* = 866) Exclusion: BW< 2000 g, GA< 35 weeks, babies who stayed = 3 days in an intensive care nursery, babies with TSB = 171 micromol/litre in the first 24 hours.	Maternal and neonatal data extracted from the organisation's database and maternal race categorised into 7 categories – American Indian, Asian, African American or black, Hispanic, Middle Eastern or Arabic, Caucasian or white, and Others Computerised telephonic survey conducted to collect further information from 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)	Response rate Total eligible = 3021 Contacted = 1248 Completed survey = 866 Agreement between Medical record documented maternal race vs Mother self-reported race White: 64.1% Black: 69.6% Hispanic: 97% Middle Eastern: 50% Asian: 35% American Indian: 0% Others: 4.3% Relationship between newborn's, mother's and father's first-named race for newborns reported to be = 2 races First-named race same for all = 40.9% Newborn and mother's race same = 22.6% Newborn and father's race same = 24.7%	Population not representative Poor response rate

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
				All 3 races different = 10.8%	
Murki S *et al.*; Year: 2001 Country: India [22]	Study type: Prospective study Evidence level: II	Term (37 completed weeks) neonates with severe non-haemolytic jaundice. The inclusion criteria were TSB > 308 micromol/litre, absence of hemolysis absence of major malformations. <u>Kernicterus group:</u> babies with stage II bilirubin encephalopathy characterised by presence of opisthotonus, rigidity and sun-setting of eyeballs *n* = 14 mean BW 2402 ± 525 g mean GA 37.8 ± 0.8 weeks Gender: males = 71.4% Ethnicity: Not reported <u>Non-kernicterus group:</u> babies without features of bilirubin encephalopathy *n* = 50 mean BW 2654 ± 446 g mean GA 38.1 ± 1.02 weeks Gender: males = 54% Ethnicity: Not reported	Diagnosis of haemolysis was based on positive direct Coomb's test, peripheral blood smear, reticulocyte count, plasma hemoglobin and packed cell volumes. Exchange transfusion was done whenever total serum bilirubin level reached 342 micromol/litre.	<u>Baseline comparison of two groups (kernicterus vs non-kernicterus group)</u> Higher number of kernicterus infants delivered vaginally (93% vs 74%, *P* < 0.05) oxytocin use was higher in non-kernicterus group (26% vs 42%, *P* < 0.05) *Neonatal risk factors* No statistically significant difference (at *P* < 0.05) between the two groups for sex distribution mean gestational age mean birthweight % of small for date (SFD) history of birth asphyxia pH at admission weight loss *Laboratory parameters* Mean max TSB levels: Kernicterus: 542 ± 171 micromol/litre Non-kernicterus: 438 ± 79 micromol/litre *P* = 0.002 Free bilirubin levels: Kernicterus: 25.5 ± 10.1 nmol/litre Non-kernicterus: 19.9 ± 6.9 nmol/litre *P* = 0.006 Bilirubin/albumin ratio: Kernicterus: 0.14 ± 0.05 Non-kernicterus: 0.11 ± 0.03 *P* = 0.05 <u>Results from multiple logistic regression analysis</u> History of birth asphyxia:	Selected population with small sample size Comparison of baseline characteristics done Methodology not clearly explained Confounding variables controlled (partially)

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
				OR 8.3 (95% CI 1.2–111.8); *P* = 0.03 Maximum TSB levels: OR 1.15 (195% CI .04–1.3); *P* = 0.005 Free bilirubin levels: OR 1.1 (95% CI 1.04–2.2); *P* = 0.009	
Turkel BS *et al.*; Year: 1980 Country: USA [21]	Study type: Retrospective matched-control study Evidence level: II	All infants with kernicterus found at autopsy. 32 infants identified with kernicterus matched to 32 control infants without kernicterus at autopsy born during the same year, of like gestational age, weight and length of survival. A second group of 13 pairs from the large group of 32 pairs were matched for sex as well.	Multiple historical, clinical, and laboratory factors were compared, including therapy sepsis hypothermia asphyxia (Apgar score) haematocrit acidosis hypercarbia hypoxia hypoglycaemia hyperbilirubinaemia	There were no statistically significant differences between the kernicteric and non-kernicteric infants for any of the factors, including peak total serum bilirubin levels. The multivariate analysis failed to determine a group of factors associated with increased risk for kernicterus.	It was difficult to separate infants with and without kernicterus at autopsy on the basis of the clinical factors evaluated. Some cases of kernicterus may have been missed due to the variables of relying on identification in fixed or fresh brains.
Bhutani VK *et al.*; Year:2006 Country: USA [20]	Study Type: Retrospective study Evidence Level: III	125 of 142 cases of the Pilot Kernicterus Registry met the inclusion criteria. These babies were discharged as healthy and were included for analysis if they exhibited clinical signs of acute bilirubin encephalopathy regardless of total serum bilirubin levels.	Main outcome measures were the comparison of etiology, severity and duration of extreme hyperbilirubinaemia (total serum bilirubin levels > 343 micromol/litre), response to interventions of intensive phototherapy and exchange transfusion, healthcare delivery experiences in preterm as compared with term infants.	The total serum bilirubin levels, age at re-hospitalisation, and birthweight distribution were similar for late preterm and term infants. Large for gestational age and late preterm infants disproportionately developed kernicterus as compared with those who were appropriate for gestational age and term. Clinical management of extreme of hyperbilirubinaemia, by the attending clinical providers, was not impacted or influenced by the gestational age, clinical signs, or risk assessment. This resulted in severe posticteric sequelae which was more severe and frequent in late preterm infants.	Late preterm birth ($34^{0/7}$ to $36^{6/7}$ $week_s$) of healthy babies was not recognised as a risk factor for hazardous hyperbilirubinaemia by clinical practitioners.
Newman T Year: 1993	Study Type: prospective cohort study	The study population included first born white and black babies with birthweight = 2500 g who survived for at least 1 year and had at least	Babies had TSB measured between 36 and 60 hours of age (as close to 48 hours as possible) and subsequent sampling was	About 1% of the white babies (*n* = 21 375) had peak TSB level = 342 micromol/litre while the proportion among the black babies (*n* = 19 949) was 0.6%.	Selected population Comparison of baseline characteristics done Confounding variables controlled

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
Country: USA [23]	Evidence Level: II	one bilirubin level recorded *n* = 41 324 Mean BW: 3285 g Mean GA: 39.3 ± 2.8 weeks Gender: males = 51.3% Ethnicity: White = 51.7% Black = 48.3% Exclusion criteria: Non-singleton babies Birthweight < 2500 or birthweight unknown	done depending on the initial levels Outcomes intelligence quotient (IQ) assessment by psychologists (using Wechsler Intelligence Scale for Children) at the age of 7 years, neurological examination by paediatric neurologists or specially trained paediatricians at the age of 7 years hearing evaluation performed at 8 years of age using pure-tone audiometry Multiple logistic regression analysis was performed to control for the effect of 11 potential confounding variables	No statistically significant association was seen between high TSB levels and IQ scores or sensorineural hearing loss. Abnormal neurological examination was reported more commonly in children with high TSB levels (= 342 micromol/litre) compared to those with lower TSB levels, but the difference was statistically not significant (4.5% vs 3.8%; RR 1.2, 95% CI 0.7–2.1). However it was observed that there was a significant linear increase in the risk of 'suspicious' abnormal neurological examination with an increase in the TSB levels (OR 1.12, 95% CI 1.06- 1.2).	Partially blinded (some tests)
Boo NY *et al.*; Year:1994 Country: Malaysia [25]	Study Type: Cohort study Evidence Level: II	136 jaundiced term neonates. *n* = 128 Mean BW: 3022 + 474 g Mean GA: 39.8 + 0.7 weeks Gender: males = 62.5% Ethnicity: Malays = 50.8% Chinese = 35.9% Indian = 10.9% Others = 2.3% 8 babies were excluded due to aminoglycoside treatment and congenital anomalies	Hearing loss was based on brain stem-evoked response. Hyperbilirubinaemia defined as TSB > 340 micromol/litre	Hearing loss: 28/128 (21.8%) Hearing loss: TSB < 340 micromol/l 13/83 (15.7%) TSB > 339 micromol/l 15/45 (33.3%) *P* = 0.11 <u>Risk factors for hearing loss</u> Severe jaundice which required exchange transfusion (*P* = 0.038) Earlier age of onset of hyperbilirubinaemia (*P* = 0.012)	
Oh W *et al.*; Year:2003 Country: USA [24]	Study Type: Retrospective cohort study Evidence Level: II	Extremely low birthweight infants (401–1000 g) who survived to 14 days of age *n* = 5630 mean BW: 789 ± 136 g mean GA: 26.2 ± 2.1 weeks	Demographic and clinical risk factors and serum bilirubin levels during the first 14 days were analysed with reference to death or adverse neurodevelopmental outcomes at 18 to 22 months' postmenstrual age.	3,246 infants survived at discharge, 79 died after discharge, and 592 were lost to follow-up. 2575 of 3167 infants were seen in the follow-up clinics with a compliance rate of 81%. Logistic regression analysis	PSB concentrations during the first 2weeks of life are directly correlated with death or NDI, hearing impairment, and PDI < 70 in extremely low birthweight infants.

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
		Gender: Not reported Ethnicity: Not reported Peak bilirubin levels that were recorded beyond the first 14 days of life were excluded.	Neurodevelopmental variables were Psychomotor Developmental Index (PDI) < 70 Mental Developmental Index (MDI) < 70 moderate or severe cerebral palsy hearing impairment (hearing aids), composite category designated as neuro-developmental impairment (NDI). The NDI is defined as infants with any 1 or more of the following: PDI < 70, MDI < 70, moderate to severe cerebral palsy bilateral blindness, bilateral hearing impairment requiring amplification.	showed that various demographic and clinical variables were associated with poor neurodevelopmental outcomes. After adjustment for these risk factor, significant association were found between peak TSB and death or NDI - OR 1.068 (95% CI 1.03–1.11) PDI < 70 - OR1.057 (95% CI 1.00–1.12) hearing impairment requiring hearing aids OR 1138 (95% CI 1.00–1.30) There was no significant association between peak TSB and other variables	
Maisels MJ *et al.*; Year:2009 Country: USA [17]	Study Type: Retrospective nested- case–control study Evidence Level: II	From a cohort of 11 456 infants, 75 infants who following discharge, had been readmitted with hyperbilirubinaemia (TSB > 291 micromol/litre) were compared with 75 matched controls. Hyperbilirubinaemia group *n* = 75 mean BW: Not reported mean GA: Not reported Gender: Males 59% Ethnicity: White: 77% Asian: 12% Black: 1% Other: 10% Control group *n* = 75 mean BW: Not reported mean GA: Not reported Gender: Males 52%	Demographic and clinical risk factors and serum bilirubin levels were analysed in terms of readmittance for hyperbilirubinaemia Factors include Maternal age Gestational age Ethnicity Mode of delivery Gender Feeding TCB percentile Bruising/cephalohaematoma Jaundice in 1st 24 hours Length of stay after birth .	11.456 infants survived at discharge, 75 were readmitted with TSB > 291 micromol/litre. The step-wise logistic regression analysis showed that various demographic and clinical variables were associated with readmission for hyperbilirubinaemia After adjustment for these risk factor, significant association were found between TSB > 291 micromol/litre and Gestation age 35 to 36 6/7 weeks Adj OR 20.79 2.34, 184.74) 37 to 37 6/7 weeks Adj OR 14.86 (1.91, 115.38) Feeding Breast only adj OR 10.75 (2.37, 48.82) TCB > 95%centile Adj OR 149.89 (20.41, > 999.99)	

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
		Ethnicity: White: 81% Asian: 7% Black: 7% Other: 5% Babies who received phototherapy prior to discharge were excluded .		There was no significant association between peak TSB and other variables	

How useful are the following tests in predicting neonatal hyperbilirubinaemia?

Prediction of hyperbilirubinaemia (diagnostic accuracy)

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Knupfer M; Year: 2005 Country: Germany [30]	Study Type: Diagnostic study Evidence Level: II	Healthy babies with GA > 34 weeks cared for in a maternity ward of a University hospital. The study population divided into 3 groups: **Group 1: Term appropriate for gestational age** *n* = 1100 mean GA 39.6 ± 1.1 weeks mean BW 3562 ± 418 g Gender: Not reported Ethnicity: Not reported **Group 2: Term small for gestational age** *n* = 163 mean GA 39.4 ± 1.2 weeks mean BW 2683 ± 274 g Gender: Not reported Ethnicity: Not reported **Group 3: Preterm** *n* = 78 mean GA 35.3 ± 0.8 weeks mean BW 2578 ± 437 g Gender: Not reported Ethnicity: Not reported Exclusion: discharge before 4th postnatal day, significant illness followed by special therapy such as antibiotics, CPAP or artificial ventilation	Test: Umbilical cord blood bilirubin (UCB) measured within 2 hours of storage in amber Threshold values < 20 micromol/litre 20–30 micromol/litre 30–40 micromol/litre > 40 micromol/litre Reference standard: TcB from forehead every morning for 4 days and laboratory TSB performed if TcB index > 16. Diagnostic accuracy also calculated for predicting TSB levels requiring phototherapy	Mean UCB (micromol/litre) Group 1: 32.4 ± 9.2 Group 2: 31.7 ± 9.1 Group 3: 30.9 ± 6.7 Comparison of prevalence of hyperbilirubinaemia in Group 1, 2 and 3 (in %) *With TSB > 250 micromol/litre* 10.6 vs 9.8 vs 25.6 *With TSB > 300 micromol/litre* 3.0 vs 3.1 vs 6.4 *Treated with phototherapy* 3.4 vs 10.4 vs 47.7 Diagnostic accuracy of UCB (threshold > 30 micromol/litre) in predicting TSB > 300 micromol/litre **Group 1:** Prevalence: 33/1100 (3.0%) Sensitivity: 32/33 (97%) Specificity: 442/1067 (41.4%) PPV: 32/657 (4.9%) NPV: 442/443 (99.8%) **Group 2:** Prevalence: 5/163 (3.1%) Sensitivity: 5/5 (100%) Specificity: 70/158 (44.3%) PPV: 5/93 (5.4%) NPV: 70/70 (100%) **Group 3:** Prevalence: 5/78 (6.4%) Sensitivity: 5/5 (100%) Specificity: 32/73 (43.8%)	Unselected population Test and Reference described adequately Reference test a standard one Blinding – Not reported

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				PPV: 5/46 (10.9%) NPV: 32/32 (100%) Diagnostic accuracy of UCB (threshold > 30 micromol/litre) in predicting need for phototherapy **Group 1:** Prevalence: 40/1100 (3.6%) Sensitivity: 36/40 (90%) Specificity: 439/1060 (41.4%) PPV: 36/657 (5.5%) NPV: 439/443 (99.1%) **Group 2:** Prevalence: 17/163 (10.4%) Sensitivity: 16/17 (94.1%) Specificity: 69/146 (47.3%) PPV: 16/93 (17.2%) NPV: 69/70 (98.6%) **Group 3:** Prevalence: 37/78 (47.4%) Sensitivity: 26/37 (70.3%) Specificity: 21/41 (51.2%) PPV: 26/46 (56.5%) NPV: 21/32 (65.6%)	
Taksande A; Year: 2005 Country: India [31]	Study Type: Diagnostic study Evidence Level: II	Healthy full term babies born in the hospital with GA > 37 weeks and absence of significant illness requiring NICU admission and any congenital malformation. *n* = 200 mean GA 38.9 ± 2.07 weeks mean BW 2555 ± 442 g Gender: Males = 41% Ethnicity: Not reported Exclusion: babies with ABO or Rh incompatibility, G6PD deficiency, those who later developed significant illness requiring NICU admission.	Test: Umbilical cord blood bilirubin (UCB) measured at birth Threshold value > 34 micromol/litre Reference standard: Laboratory TSB measured after 72 hours TSB > 290 micromol/litre taken as hyperbilirubinaemia	Diagnostic accuracy of UCB (threshold value > 2 mg% or 34 micromol/litre) for predicting TSB > 17 mg% or 290 micromol/litre Prevalence: 19/200 (9.5%) Sensitivity: 17/19 (89.5%) Specificity: 154/181 (85.1%) PPV: 17/44 (38.6%) NPV: 154/156 (98.7%)	Unselected population Test & Reference test not described in detail Reference test is a standard one Blinding – yes
Knudsen A;	Study Type:	Healthy term babies admitted to the	Test:	Diagnostic accuracy of UCB (threshold	Unselected population

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Year: 1992 Country: Denmark [29]	Diagnostic study Evidence Level: II	newborn nursery. *n* = 138 median GA 40 weeks - range 38 to 43 median BW 3495 g - range 2571 to 4456 Gender: Males = 52.2% Ethnicity: Not reported Exclusion: preterm babies, sick babies Rhesus sensitisation.	Umbilical cord blood bilirubin (UCB) measured at birth Threshold values: ≥ 20 micromol/litre ≥ 25 micromol/litre ≥ 30 micromol/litre ≥ 35 micromol/litre 40 micromol/litre Reference standard: Laboratory TSB measured on Day 3 TSB ≥ 200 micromol/litre taken as value for hyperbilirubinaemia ROC curve used to find the best cut-off value of UCB.	value > 35 micromol/litre) for predicting TSB > 200 micromol/litre Prevalence: 28/138 (20.3%) Sensitivity: 20/28 (71.4%) Specificity: 75/110 (68.2%) PPV: 20/55 (36.4%) NPV: 75/83 (90.4%)	Test & Reference test described in detail Reference test is a standard one Blinding – Not reported. Reported using Minolta JM to estimate TcB but no details given
Carbonell X; Year: 2001 Country: Spain [26]	Study Type: Diagnostic study Evidence Level: II	Healthy term babies *n* = 2004 – 610 in phase one + 1394 in phase 2, mean BW 3230 ± 491 g mean GA 39 weeks Gender: Males = 50.7% Ethnicity Not reported In first phase (*n* = 610), cord blood bilirubin (UCB) at birth and TcB with Minolta JM-102 measured at 24hrs, 48 hours & 60–96 hours of life. Additionally TSB done for all at 60–96 hours. On 169 babies TSB also measured at 24 & 48hrs In second phase (*n* = 1394), TcB and lab TSB values obtained to find accuracy of TSB and TcB at 24hrs and 48 hours to predict hyperbilirubinaemia. Prevalence of TSB > 290 micromol/litre = 2.9% in phase 1 (18/610) and 3.25% in phase 2 (46/1324)	Test: 1. Umbilical cord blood bilirubin (UCB) measured at birth (threshold value: ≥ 37 micromol/litre) ROC curve used to find the best cut-off value of UCB. 2. TSB (in phase 1 & 2) and TcB (phase 1 only) measured at 24 hours (threshold value for TSB = 102 micromol/litre and for TcB > 11) 3. TSB and TcB (in phase 1 & 2) measured at 48 hours (threshold value for TSB = 154 micromol/litre and for TcB > 13) TcB reading using Minolta JM-102 at the forehead and the sternum (mean of 3 measurements recorded at each site used for analysis) Reference standard: Laboratory TSB measured on Day 3–4 TSB = 290 micromol/litre taken as indicative of	Correlation of TcB levels with lab TSB levels for Sternal vs Forehead site (Pearson correlation coefficient) At < 24 hours (*n* = 120) *Sternum Forehead* 0.81 0.77 At 24–48 hours (*n* = 126) *Sternum Forehead* 0.89 0.83 At > 48 hours (*n* = 412) *Sternum Forehead* 0.94 0.83 Diagnostic accuracy of TcB for detecting TSB > 222 micromol/litre Sensitivity: 98% Specificity: 72% Diagnostic accuracy for predicting TSB = 290 micromol/litre *Prevalence of TSB = 290 micromol/litre* 2.9% in phase 1 (18/610) and 3.25% in	Unselected population but no exclusion criterion Test & Reference test described in detail Reference test a standard one Test and reference test carried out within one hour Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Exclusion: not defined	hyperbilirubinaemia	phase 2 (46/1324) **1. For UCB** **(threshold = 37 micromol/litre)** Sensitivity: 4/18 (22.2%) Specificity: 537/567 (94.7%) **2. At 24 hours** *For TcB in phase 1 (threshold > 11 Reflectance Units)* Sensitivity: 15/18 (83.3%) Specificity: 368/556 (66.2%) PPV: 15/203 (7.4%) NPV: 368/371 (99.2%) *For TSB in phase 1 (threshold = 102 micromol/litre)* Sensitivity: 7/7 (100%) Specificity: 74/162 (45.7%) PPV: 7/95 (7.4%) NPV:74/74 (100%) *For TSB in phase 2 (threshold = 102 micromol/litre)* Sensitivity: 25/25 (100%) Specificity: 239/398 (60%) PPV: 25/95 (26.3%) NPV: 239/239 (100%) **2. At 48 hours** *For TcB in phase 1 (threshold > 13 reflectance units)* Sensitivity: 17/18 (94.4%) Specificity: 288/556 (51.7%) PPV: 17/285 (5.9%) NPV: 288/289 (99.6%) *For TcB in phase 2 (threshold > 13 reflectance units)* Sensitivity: 45/46 (97.8%) Specificity: 262/819 (32.0%) PPV: 45/602 (7.5%) NPV: 262/263 (99.6%) *For TSB in phase 1 (threshold = 154 micromol/litre)* Sensitivity: 11/11 (100%) Specificity: 102/158 (64.6%)	

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				PPV: 11/67 (16.4%) NPV: 101/102 (100%) *For TSB in phase 2* *(threshold = 154 micromol/litre)* Sensitivity: 45/46 (97.8%) Specificity: 348/774 (45%) PPV: 45/471 (9.5%) NPV: 348/349 (99.7%)	
Agarwal R; Year: 2002 Country: India [27]	Study Type: Diagnostic study Evidence Level: 1b	All infants with GA > 35 weeks with no significant illness requiring NICU admission for > 12 hours, absence of any major congenital malformations and residing near hospital whose parents agreed to come for follow-up. *n* = 220 mean GA 38 ± 1.4 weeks mean BW 2827 ± 459 g Gender: Males = 53.3% Ethnicity: Not reported Exclusion: babies requiring NICU admission, Rh hemolysis.	Test: TSB at 24 ± 6 hours after birth – three samples taken and mean of two closest values taken for analysis Threshold value: > 102 micromol/litre Reference standard: Laboratory TSB measured on Day 5 when clinical jaundice > 171 micromol/litre TSB ≥ 290 micromol/litre taken as indicative of hyperbilirubinaemia	Diagnostic accuracy of TSB (threshold value > 102 micromol/litre) for predicting TSB = 290 micromol/litre (*n* = 213) Prevalence: 22/213 (10.3%) Sensitivity: 21/22 (95.4%) Specificity: 135/191 (70.7%) PPV: 21/77 (27,3%) NPV: 135/136 (99.3%)	Unselected population Test & Reference test described in detail Reference test a standard one Blinding – yes
Alpay F; Year: 2000 Country: Turkey [28]	Study Type: Diagnostic study Evidence Level: II	All healthy full term newborn babies with GA = 38 weeks. *n* = 498 mean GA Not reported mean BW Not reported Gender: Not reported Ethnicity: Not reported Exclusion: babies with blood groups A, AB, B and O/Rhesus blood factor incompatibility and a positive direct antiglobulin test result G6PD deficiency	Test: TSB within first 24 hours (mean 17.1 hours) ROC curve used for threshold value with highest sensitivity for predicting hyperbilirubinaemia (threshold value: = 102 micromol/litre) Results also given for threshold values = 120 micromol/litre and = 137 micromol/litre Reference standard: Laboratory TSB measured at 24 hours interval for next 4 days	Diagnostic accuracy of TSB for predicting TSB = 290 micromol/litre (*n* = 498) *Threshold value = 102 micromol/litre* Prevalence: 60/498 (12.0%) Sensitivity: 54/60 (90%) Specificity: 286/438 (65.3%) PPV: 54/206 (26.2%) NPV: 286/292 (97.9%) *Threshold value = 120 micromol/litre* Sensitivity: 36/60 (60%) Specificity: 363/438 (82.9%) PPV: 36/111 (32.4%) NPV: 363/387 (97.8%) *Threshold value = 137 micromol/litre* Sensitivity: 21/60 (35%)	Unselected population Test & Reference test described in detail Reference test a standard one Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
			TSB = 290 micromol/litre till Day 5 taken as indicative of hyperbilirubinaemia	Specificity: 413/438 (94.3%) PPV: 21/46 (45.6%) NPV: 413/452 (91.4%)	
Seidman DS; Year: 1999 Country: Israel [13]	Study Type: Diagnostic study Evidence Level: II	Healthy full term infants with GA = 37 weeks born at two hospitals *n* = 1177 mean BW 3247 ± 453 g mean GA 39.8 ± 1.3 weeks Gender: Males = 47.3% Ethnicity: Not reported Exclusion: ABO or Rh incompatibility and a positive direct Coombs' test G6PD deficiency.	1) Association of various factors with jaundice derived from multiple regression analysis 2) Comparison of diagnostic accuracy of various tests for predicting hyperbilirubinaemia Test: TSB measured within first 8 to 24 hours of life and repeated daily for the next 4 days Reference standard: Hyperbilirubinaemia defined as TSB > 171 micromol/litre at day 2 > 239 micromol/litre at day 3 > 291 micromol/litre at day 4–5 Analysis: Association between various factors and jaundice calculated from multiple regression analysis using Odds ratios with 95% CI, and these factors used for modelling in predicting hyperbilirubinaemia	Factors associated with jaundice after comparing Group 1 vs Group 2 (*n* = 1177) *Day 1 TSB (per 17 micromol/litre)* OR: 3.1 (95% CI 2.4 to 4.1) *Change in TSB from day 1 to day 2 (per 17 micromol/litre)* OR: 2.4 (95% CI 1.9 to 3.0) *Maternal age (per year)* OR: 1.1 (95% CI 1.0 to 1.2) *Mat education (per year)* OR: 0.8 (95% CI 0.7 to 0.9) *Maternal blood type O* OR: 2.9 (95% CI 1.5 to 5.8) *Full breastfeeding* OR: 0.4 (95% CI 0.2 to 0.9) *Day 1 TSB > 85 micromol/litre* OR: 36.5 (95% CI 15.9 to 83.6) Prediction of hyperbilirubinaemia *Prediction by Day 1 TSB only (threshold value > 85 micro*mol/litre*)* Sensitivity: 63.1% Specificity: 94.2% *Prediction by all model variables without Day 1 TSB* Sensitivity: 57.9% Specificity: 90.4% *Prediction by all model variables* Sensitivity: 81.8% Specificity: 82.9%	Unselected population No differences at baseline between the two groups Test & Reference test described in detail Reference test a standard one Blinding – Not reported Confounding factors adjusted for during modelling Data not available to calculate PPV or NPV. Raw figures not available
Stevenson DK;	Study Type:	Newborns with GA = 35 weeks as	Test:	Prevalence of hyperbilirubinaemia at 30 +	Unselected population

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Year: 2001 Country: USA [32]	Diagnostic study/cohort Evidence Level: II	determined by best obstetric estimate and enrolled serially from 9 clinical sites (4 domestic and 5 international) within the first 36 hours of life. *n* = 1895 Mean BW: Not reported Mean GA: Not reported Gender: Males = 49% Ethnicity: Asian/Pacific Islander = 38.9% White = 33.1% Black = 16.4% Hispanic = 3.9% Other = 7.7% Exclusion: babies requiring admission to NICU, severe congenital anomalies, babies in incubators, pulmonary disease requiring oxygen or any form of ventilatory support, with BW < 850 g, and respiratory rates = 10 or = 100 breaths/min. Babies with age-specific TSB = 95th centile either at < 24 hours, at 30 ± 6 hours, at 24–84 hours or at 96 ± 12 hours exited the study after giving test samples. Also babies with TSB < 40th centile at 96 ± 12 hours exited.	1. End-tidal CO measurement corrected for inhaled CO (ETCOc) at 30 ± 6 hours (threshold value: value > population mean) 2. TSB at 30 ± 6 hours (threshold value: TSB = 75th centile) Timing of various TSB measurements: a) at 30 ± 6 hours for all babies (Test) b) between 24 - 84 hours only on clinical grounds c) at 96 ± 12 hours for all babies d) till 168 hours as per study protocol Reference standard: Lab TSB confirmed hyperbilirubinaemia Hyperbilirubinaemia was defined as Age-specific lab TSB = 95th centile Analysis: Logistic regression analysis models performed for prediction of hyperbilirubinaemia with ETCOc and TSB at 30 ± 6 hours using multiple variables (bruising, type of feeding, BW, race, maternal diabetes, type of labor, gender, infection, PIH, parity, maternal blood type and Rh status)	6 hours and 96 + 12 hours 120/1370 (8.8%) Comparison of ETCOc levels between Group 1 vs Group 2 (mean ± SD) 1.45 ± 0.47 ppm vs 1.81 ± 0.59 ppm (*P* < 0.001) Diagnostic accuracy of ETCOc, TSB and combined test in predicting hyperbilirubinaemia - derived from ROC curves - (at 30 ± 6 hours) *ETCOc (threshold > population mean)* Sensitivity: 92/120 (76.7%) Specificity: 635/1250 (50.8%) PPV: 92/707 (13.0%) NPV: 635/663 (95.8%) *TSB (threshold > 75th centile) after excluding babies with TSB > 95th centile at < 36 hours* PPV: 16.7% NPV: 98.1% *Combined test* PPV: 6.4% NPV: 99.0%	Baseline data presented for total group (1370 (72.3%) completed the study) Test & Reference test described in detail Reference test a standard one Blinding – Not reported Data not given for calculating TP, FP, FN, and TN. Confounding factors adjusted for during modelling
Okuyama H; Year: 2001 Country: Japan	Study Type: Diagnostic study Evidence Level: II	Full-term infants with GA = 37 weeks and BW = 2500 g. *n* = 51 mean BW 3108 ± 327 g, mean GA	Test: End-tidal CO measurement corrected for inhaled CO (ETCOc) every 6 hours during the first 72 hours. (different threshold values at different age)	Group 1 vs Group 2 No statistical differences between the two groups for sex, GA, mode of delivery, Apgar score at 1 min, age at peak TcB, and feeding type.	Unselected population but small sample size Test & Reference test described adequately Reference test a standard test

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
[33]		39.3 ± 1.4 weeks Gender: Males = 51% Ethnicity: Not reported Exclusion: subjects with maternal smoking, infants of diabetic mother, haemolytic disease such as blood group incompatibilities, closed space haemorrhage, respiratory distress, polycythemia.	Reference standard: TcB measured every 12 hours during the first 5 days using JM-102, and serum TSB measured when TcB index = 22 reflectance units Hyperbilirubinaemia defined as TSB = 257 micromol/litre ROC curve used for predicting hyperbilirubinaemia	*ETOCc levels* At 6–36 hours – No statistical difference At 42, 48, 54 and 66 hours – levels significantly higher in Group 1 Diagnostic accuracy of ETCOc in predicting hyperbilirubinaemia *Threshold 1.6 ppm at 36hrs* Sensitivity: 5/7 (71.4%) Specificity: 27/44 (61.4%) PPV: 5/22 (22.7%) NPV: 27/29 (93.1%) *Threshold 1.8 ppm at 42hrs* Sensitivity: 6/7 (85.7%) Specificity: 35/44 (79.5%) PPV: 6/15 (40%) NPV: 35/36 (97.2%) *Threshold 1.8 ppm at 48hrs* Sensitivity: 6/7 (85.7%) Specificity: 32/44 (72.7%) PPV: 6/18 (33.3%) NPV: 32/33 (96.9%) *Threshold 1.8 ppm at 60hrs* Sensitivity: 6/7 (85.7%) Specificity: 29/44 (65.9%) PPV: 6/21 (28.6%) NPV: 29/33 (87.9%)	but not done in all babies Blinding – Not reported
Bhutani VK; Year: 1999 Country: USA [34]	Study Type: Diagnostic study Evidence Level: II	Birth cohort Term (BW = 2000 g for = 36 weeks) and near-term appropriate for gestational age (BW = 2500 g for GA = 35 weeks) newborn babies in a tertiary hospital (*n* = 13 003) For nomogram *n* = 2840 mean BW 3318 ± 457 g mean GA 38.7 ± 1.3 weeks mean age for pre-discharge sampling 33.7 ± 14.6 hours Gender: Males = 50.1%	Test: Pre-discharge TSB characterised by postnatal age in hours and measured between 18–72 hours Reference standard: Hour-specific nomogram or TSB centiles developed from pre and post-discharge TSB values. Post-discharge values obtained on clinical grounds from day 1–6. Data recorded in epochs of: 4 hours for first 48 hours, 12 hours for 48–96 hours, 24 hours for age 5–7 days.	Prevalence of significant hyperbilirubinaemia *Including both pre and post-discharge TSB* 230/2840 (8.1%) *Post-discharge TSB only* 126/2840 (4.4%) Predictive ability of pre-discharge TSB percentile tracks as risk demarcators for subsequent hyperbilirubinaemia (*n* = 2840)	Unselected population Test & Reference test described adequately Reference test a standard test as nomogram developed from lab TSB values Blinding – Not reported

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		Ethnicity: White = 43.4% Black = 41.2% Hispanic = 3.6% Asian = 4.1% Other = 7.7% Exclusion: admission and treatment in intensive care nursery for neonatal illness, positive Coombs' test, TSB measured after initiation of phototherapy, babies requiring phototherapy before 60 hours to control unexplained rapidly rising TSB levels.	Predictive ability of pre-discharge TSB levels (given as percentile tracks and risk zones) evaluated for subsequent Significant Hyperbilirubinaemia (defined as TSB level reaching into the high-risk zone or = 95th centile) <u>Threshold zones:</u> High risk zone above 95th percentile, High intermediate risk zone between 75th and 95th centile, Low intermediate risk zone between 75th and 40th centile Low risk zone below 40th centile	*Pre-discharge TSB above 95th percentile (n = 172)* Sensitivity: 68/126 (54.0%) Specificity: 2610/2714 (96.2%) PPV: 68/172 (39.5%) NPV: 2610/2668 (97.8%) *Pre-discharge TSB above 75th percentile (n = 528)* Sensitivity: 114/126 (90.5%) Specificity: 2300/2714 (84.7%) PPV: 114/528 (21.6%) NPV: 2300/2312 (99.5%) *Pre-discharge TSB above 40th percentile (n = 1084)* Sensitivity: 126/126 (100%) Specificity: 1756/2714 (64.7%) PPV: 126/1084 (11.6%) NPV: 1756/1756 (100%) <u>Likelihood ratio (LR) based on risk zones</u> *High risk zone* +LR: 14.1 *Upper-intermediate risk zone* +LR: 3.2 *Lower-intermediate risk zone* +LR: 0.5 *Low risk zone* +LR: 0	
Romagnoli C; Year: 2005 Country: Italy [37]	Study Type: Diagnostic study Evidence Level: II	<u>Phase 1: Development of nomogram</u> Full term appropriate for gestational age babies delivered by vaginal or caesarean section after uneventful pregnancy, without asphyxia and with no Rh or major ABO incompatibility. *n* = 438 mean BW 3389 ± 668 g	<u>Test:</u> Laboratory TSB measured between 30–72 hours on clinical suspicion (single measurement in all babies, two consecutive TSB determinations 12 hours apart in 514/1244 babies in Hospital A and 175/498 babies in Hospital B) <u>Reference standard:</u>	<u>Phase 1: Time of reaching highest TSB values in Phase 1</u> At 24–48 hours: 20.3% At 49–72 hours: 48.4% At 73–96 hours: 26.0% At 97–120 hours: 5.3% <u>Phase 2: Predictive ability of Trend 12 and</u>	Unselected population Test & Reference test described adequately Reference test a standard test as nomogram developed from lab TSB values Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		mean GA 40 ± 1.8 weeks Gender: Males = 51.6% Ethnicity: Not reported Exclusion: congenital anomalies, any illness requiring admission to neonatal intensive care unit, infants with delayed meconium passage, hypothermia, hypoglycaemia, cephalohematoma, local bleeding, hemorrhagic disease of newborn, UTI or suspected clinical sepsis. <u>Phase 2: Application of the nomogram</u> Healthy term babies in two hospitals who had TSB estimation between 30–72 hours due to clinical jaundice Hospital A: *n* = 1244, mean BW 3299 ± 447 g, mean GA 39.2 ± 1.4 weeks Gender: Males = 56.4% ethnicity: Not reported Hospital B: *n* = 498, mean BW 3312 ± 394 g, mean GA 39.5 ± 1.3 weeks Gender: Males = 51.8% ethnicity: Not reported	Hour-specific nomogram. TSB curves developed from TSB values measured at 6 hours of age and then every 4–6 hours during day and 6–12 hours during night. Curves of babies with TSB > 205 micromol/litre and those with TSB > 205 micromol/litre taken separately, their 1st percentile TSB values determined for each hour of life and connected to form percentile tracks. Predictive ability of TSB levels measured in Phase 2 evaluated for subsequent hyperbilirubinaemia at 24–36 hours, 37–48 hours, 49–60 hours, 61–72 hours and all together (threshold value – Trend 12 defined as TSB value exceeding the 1st percentile track of babies with TSB > 205 micromol/litre, and Trend 15 defined as TSB value exceeding the 1st percentile track of babies with TSB > 256 micromol/litre	<u>15 as risk demarcators for subsequent hyperbilirubinaemia</u> **HOSPITAL A** *Prevalence of TSB > 205 micro*mol/litre 230/1244 (18.5%) *Prevalence of TSB > 205 micromol/litre* 100/1244 (8.0%) *Single TSB measurement with Trend 12 as threshold* Sensitivity: 228/230 (99.1%) Specificity: 496/1014 (48.9%) PPV: 228/746 (30.6%) NPV: 496/498 (99.6%) + LR: 1.9 *Single TSB measurement with Trend 15 as threshold* Sensitivity: 100/100 (100%) Specificity: 859/1144 (75.1%) PPV: 100/385 (26.0%) NPV: 859/859 (100%) +LR: 4.0 *Two TSB measurements with Trend 12 as threshold* Sensitivity: 85/85 (100%) Specificity: 217/429 (50.6%) PPV: 85/302 (28.6%) NPV: 217/217 (100%) +LR: 2.0 *Two TSB measurements with Trend 15 as threshold* Sensitivity: 92/92 (100%) Specificity: 355/422 (84.1%) PPV: 92/159 (57.9%) NPV: 355/355 (100%) +LR: 6.3 **HOSPITAL B** *Prevalence of TSB > 12 MG/DL* 129/498 (25.9%)	

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				Prevalence of TSB > 15 MG/DL 59/498 (11.8%) *Single TSB measurement with Trend 12 as threshold* Sensitivity: 127/129 (98.4%) Specificity: 131/369 (35.5%) PPV: 127/365 (34.8%) NPV: 131/133 (98.5%) + LR: 1.5 *Single TSB measurement with Trend 15 as threshold* Sensitivity: 52/59 (88.1%) Specificity: 344/439 (78.4%) PPV: 52/147 (35.4%) NPV: 344/351 (98.0%) +LR: 4.1 *Two TSB measurements with Trend 12 as threshold* Sensitivity: 54/54 (100%) Specificity: 84/121 (69.4%) PPV: 54/91 (59.3%) NPV: 84/84 (100%) +LR: 3.3 *Two TSB measurements with Trend 15 as threshold* Sensitivity: 23/24 (95.8%) Specificity: 117/151 (77.5%) PPV: 23/58 (40.4%) NPV: 117/118 (99.2%) +LR: 4.3	
Bhutani VK; Year: 2000 Country: USA [36]	Study Type: Diagnostic study Evidence Level: 1b	All term and near-term babies (either = 36 weeks GA and BW = 2000 g or = 35 weeks and BW = 2500 g) discharged as healthy from the well-baby nursery in a tertiary hospital *n* = 490, observations=1788, mean BW 3404 ± 518 g, mean GA 38. 9 ± 1.5 weeks	Test: Pre-discharge TcB reading from the forehead using BiliChek measured between 24 and 72 hours of age. Reference standard: Laboratory TSB measured at same time as TcB, and also sent for HPLC assays. Paired TcB and HPLC TSB values plotted on the hour-specific	Prevalence of significant hyperbilirubinaemia 30/490 (6.1%) Correlation of TcB levels with TSB levels using HPLC (Pearson correlation coefficient, *n* = 1788 samples) r = 0.91, *P* < 0.01 Bland Altman analysis for difference between TSB and TcB MD = -8 micromol/litre (95% CI -38.9 to	Unselected population but only 1.1% of study population had TSB values > 256 micromol/litre Test & Reference test described adequately Reference test a standard test as nomogram developed from lab TSB values Blinding – specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Gender: Not reported Ethnicity: White = 59.1% Black = 29.5% Hispanic = 3.5% Asian = 4.5% Others = 3.5% Exclusion: clinical manifestation of sepsis, heart or circulatory disease, respiratory distress, clinical evidence of haemoglobinopathy, initiation of phototherapy.	nomogram. Predictive ability of pre-discharge TcB levels (threshold = 75th centile) evaluated for subsequent significant hyperbilirubinaemia (defined as TSB = 95th centile or in the high-risk zone on the hour-specific nomogram)	54.9) Predictive ability of pre-discharge TcB (threshold = 75th centile) for significant hyperbilirubinaemia (*n* = 419) Sensitivity: 23/23 (100%) Specificity: 349/396 (88.1%) PPV: 23/70 (32.9%) NPV: 349/349 (100%) +LR: 8.4	
Newman TB; Year: 2000 Country: USA [9]	Study Type: Nested case- control study Evidence Level: II	Cohort of all infants with BW = 2000 g and GA = 36 weeks born alive at 11 hospitals of a health maintenance organisation during a two year period (*n* = 51 387) Cases: Babies with maximum TSB levels = 428 micromol/litre within the first 30 days after birth *n* = 73 Mean BW: Not reported Mean GA: Not reported Gender: Males = 67.1% Ethnicity: Not reported (only maternal race specified) Controls: Random sample of babies from the cohort with maximum TSB levels = 428 micromol/litre *n* = 423 Mean BW: Not reported Mean GA: Not reported Gender: Males = 54.4% Ethnicity: Not reported (only maternal race specified) For analyses examining the use of	1) Relationship of clinical and demographic factors associated with hyperbilirubinaemia evaluated by bivariate analysis and OR 2) Risk factors significant in the univariate model entered into multiple regression analysis to find independent predictors of hyperbilirubinaemia – both by including and excluding early jaundice cases Early jaundice cases (*n* = 14) defined as babies with TSB exceeding recommended phototherapy threshold for age during birth hospitalisation, those given phototherapy during birth hospitalisation, when jaundice noted at less than 20 hours of age and TSB not measured within 6 hours of that time. 3) Risk index developed by assigning points equal to the OR for risk factors that were significant in the logistic regression model with the exclusion of early jaundice	Maternal and prenatal factors associated with significant hyperbilirubinaemia (those with *P* < 0.05 in bivariate analysis) *Maternal factors* ☐ Race, ☐ maternal age, ☐ family HISTORY OF jaundice in a newborn, ☐ vacuum delivery *Neonatal factors* ☐ Male sex, ☐ lower GA, ☐ early jaundice, ☐ cephalohaematoma, ☐ bruising, ☐ breastfeeding at time of discharge Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95% CI) *All cases (n = 73)* Early jaundice: OR 7.3 (2.8–19) GA (per wk): OR 0.6 (0.4–0.7)	Unselected population but exclusion criteria not defined Confounding variables controlled for during multivariate analysis Test & Reference test described adequately Reference test a standard test Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		phototherapy only, additional random sample of 30 babies with maximum TSB levels of 342 to 426 micromol/litre added to the control group Exclusion criteria: Not defined	cases, and predictive accuracy compared by the c-statistic (equal to area under ROC curve) Reference standard: Significant hyperbilirubinaemia defined as maximum TSB levels = 428 micromol/litre within the first 30 days after birth.	Breastfeed only at discharge: OR 6.9 (2.7–17.5) Asian race: OR 3.1 (1.5–6.3) Bruising: OR 3.5 (1.7–7.4) Cephalohaematoma: OR 3.2 (1.1–9.2) Maternal age ≥ 25 years: OR 2.6 (1.1–9.2) *Cases excluding early jaundice (n = 59)* GA (per wk): OR 0.6 (0.4–0.7) Breastfeed only at discharge: 5.7 (2.1–15.5) Asian race: OR 3.5 (1.7–7.4) Bruising: OR 4.0 (1.8–8.8) Cephalohaematoma: OR 3.3 (1.1–10) Maternal age ≥ 25 years: OR 3.1 (1.2–8.1) Risk Index scoring 6 points each for exclusive breastfeeding and family HISTORY OF jaundice in a newborn, 4 points each for bruising and Asian race, 3 points each for cephalhematoma and maternal age ≥ 25 years, 1 point for male sex, -2 points for black race, and 2(40-GA) Accuracy of Risk Index score in predicting significant hyperbilirubinaemia Overall c-statistic 0.85 *Risk index score < 10* +LR: 0.2 *Risk index score > 10* +LR: 2.2 *Risk index score > 20* +LR: 18.2	
Newman TB; Year: 2005 Country: USA [35]	Study Type: 1) Nested case- control study 2) Retrospective cohort Evidence Level: II	**Study 1:** Cohort of all infants with BW = 2000 g and GA = 36 weeks born alive at 11 hospitals of a health maintenance organisation during a two year period (*n* = 53 997)	**Study 1:** Risk index score developed by assigning points equal to the OR for risk factors significant in the logistic regression model (not including family history of jaundice) with the exclusion of	**Study 1:** Comparison of 1995–96 cohort (*n* = 51 387) with 1997–98 cohort (*n* = 53 997) No difference regarding % of babies with TSB level ≥ 342 micromol/litre, TSB ≥ 428 micromol/litre,	Retrospective cohort study Unselected population but exclusion criteria not defined Confounding variables controlled for during multivariate analysis Test & Reference test described

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Cases: Babies with maximum TSB levels = 428 micromol/litre within the first 30 days after birth (*n* = 67) Controls: Random sample of babies from the cohort with maximum TSB levels = 428 micromol/litre (*n* = 208) Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity: Not reported **Study 2:** All infants with BW = 2000 g and GA = 36 weeks born alive at 11 hospitals of a health maintenance organisation during a four year period, and who had TSB measured at < 48 hours of age (*n* = 5706) Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity: Not reported Exclusion criteria: Babies developing TSB levels > 342 micromol/litre at < 48 hours	early jaundice cases. Predictive accuracy compared by the c-statistic (equal to area under ROC curve) **Study 2:** Test 1 Partial clinical risk index derived from Risk index in Study 1 by deleting factors family history of jaundice, breastfeeding, bruising and by substituting scalp injury in medical records with cephalohaematoma. Test 2 TSB levels measured at < 48 hours and classified into 4 age-specific percentile groups < 40th centile, 40th to < 75th centile, 75th to < 95th centile, > 95th centile). The data was then transformed into hour-specific z scores Reference standard Significant Hyperbilirubinaemia defined as maximum TSB levels = 342 micromol/litre	age more than 7 days at the time of highest TSB levels, average number of TSB tests per patient, length of hospitalisation stay and treatment with phototherapy Accuracy of Modified risk index score (with exclusion of family HISTORY OF jaundice) in predicting significant hyperbilirubinaemia (with 95% CI) *1997–1998 cohort* c-statistic 0.83 (95% CI 0.77 to 0.89) *1995–96 cohort* c-statistic 0.84 (95% CI 0.79 to 0.89) **Study 2:** Prevalence of hyperbilirubinaemia 230/5,706 (4.7%) Risk of developing TSB levels > 342 micromol/litre based on TSB percentile group < 40th centile = 0.5 40th to < 75th centile = 0.7 75th to < 95th centile = 3.3 ≥ 95th centile = 13.8 Accuracy of tests in predicting hyperbilirubinaemia (TSB levels = 342 micromol/litre *Partial risk index score* c-statistic 0.69 *TSB centile group* c-statistic 0.79 *TSB z score* c-statistic 0.83 *TSB z score + Partial risk index score* c-statistic 0.86	adequately Reference test a standard test Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Keren R; Year: 2005 Country: USA [12]	Study Type: Retrospective cohort/ diagnostic study Evidence Level: II	Infants with BW = 2000 g if GA = 36 weeks and BW = 2500 g if GA = 35 weeks participating in the hospital's early discharge programme, and who had both pre and post-discharge TSB levels measured at the phase when ≥ 75% babies had both the samples (*n* = 899) Group 1: infants with post-discharge TSB > 95th centile on nomogram (*n* = 98, 54% males, mean BW 3.4 ± 0.5 kg) Group 2: infants with post-discharge TSB < 95th centile on nomogram (*n* = 801, 52% males, mean BW 3.3 ± 0.5 kg) Exclusion: admission and treatment in intensive care nursery for neonatal illness and babies requiring phototherapy during birth hospitalisation.	Test 1: Clinical risk factor score derived from regression modelling using the factors found independently associated with significant hyperbilirubinaemia. Test 2: Pre-discharge TSB levels expressed as risk zone on an hour-specific bilirubin nomogram (High risk > 95th centile, High intermediate risk 76th – 95th centile, Low intermediate risk 40th – 75th centile, Low risk 0 – 40th centile) Reference standard: Significant Hyperbilirubinaemia defined as TSB level > 95th centile on hour-specific nomogram. Accuracy of Clinical risk score and pre-discharge TSB risk zone evaluated for predicting significant hyperbilirubinaemia	Prevalence of significant hyperbilirubinaemia 98/899 (11%) Factors associated with significant hyperbilirubinaemia (those with *P* < 0.2 in univariate analysis) *Increased risk* GA < 38 weeks and ≥ 40 weeks, large for gestational age babies, higher pre-discharge TSB risk zone, combined breast and bottle feeding, maternal diabetes, vacuum extraction, prolonged rupture, oxytocin use *Decreased risk* Small for gestational age, parity, caesarean section Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95% CI) Birthweight: 1.5 (1.2–1.9) GA < 38 weeks: 2.6 (1.5–4.5) Oxytocin: 2.0 (1.2–3.4) Vacuum delivery: 2.2 (1.5–3.6) Exclusive breastfeeding: 2.6 (1.5–4.5) Breast and bottle feeding: 2.3 (1.1–4.9) Clinical risk index scoring Birthweight: 3 points for 2501–3000 g, 6 for 3001–3500 g, 9 for 3501–4000 g, 12 for 4001–4500 g, 15 for 4501–5000 g GA < 38 weeks: 5 points Oxytocin: 4 points Vacuum delivery: 4 points Exclusive breastfeeding: points Breast and bottle feeding: 4 points Predictive accuracy for predicting significant hyperbilirubinaemia	Retrospective cohort study Unselected population Test & Reference test described adequately Reference test a standard test Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				RISK FACTOR SCORE c-statistic 0.71 (0.66–0.76) *Risk index score 0–7* +LR: 0.1 *Risk index score 8–11* +LR: 0.4 *Risk index score 12–15* +LR: 0.9 *Risk index score 16–19* +LR: 2.0 *Risk index score 20–23* +LR: 2.6 *Risk index score > 24* +LR: 3.2 PRE-DISCHARGE TSB c-statistic 0.83 (0.80–0.86) *TSB centile 0–40th* +LR: 0.05 *TSB centile 41–75th* +LR: 0.2 *TSB centile 76–95th* +LR: 2.2 *TSB centile > 95th* +LR: 9.4	
Keren R *et al.*; Year: 2008 Country: USA [14]	Study Type: Prospective cohort study Evidence Level: II	Infants managed exclusively in the well infants nursery of an urban tertiary care hospital with GA = 36 weeks and BW = 2000 g or GA = 35 weeks and BW = 2500 g *n* = 812	1) Factors associated with significant hyperbilirubinaemia in univariate analysis entered into regression modeling for clinical risk factor model 2) Comparison of diagnostic	<u>Prevalence of significant hyperbilirubinaemia</u> 48/751 (6.4%) – 61 had an incomplete follow-up <u>1) Association of factors with significant</u>	Unselected population (stratified sampling) with well defined exclusion criteria Baseline characteristics of two groups not compared Confounding variables controlled

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		mean BW 3.3 ± 0.5 kg GA < 38 weeks: 13.4% Gender: males = 49.4% Ethnicity: White = 33.5% Black = 53.2% Asian = 9.8% Other = 3.4% Since the population in the area was predominantly black, stratified sampling scheme used to get a representative sample. Group 1: Infants with significant hyperbilirubinaemia (*n* = 48) Group 2: Infants without significant hyperbilirubinaemia (*n* = 703) Exclusion: babies transferred to the intensive care nursery for any reason Babies who received intravenous antibiotics for concern for sepsis.	accuracy of three tests in predicting significant hyperbilirubinaemia by the c-statistic (mathematically equal to area under ROC curve) Test 1: Pre-discharge bilirubin measured either by TcB or TSB at < 52 hours of age, and expressed as risk-zone on hour specific nomogram. Daily TcB levels recorded using BiliChek, and TSB performed if TcB above 75th centile on hour-specific nomogram or TcB reading = 205 micromol/litre. TSB value taken for analysis when both TcB and TSB done. Test 2: Clinical risk factors assessed by review of hospital charts for maternal race, intended method of feeding, GA, history of previous infant with jaundice, clinical assessment of jaundice, G6PD deficiency. Test 3: Combination of pre-discharge bilirubin risk zone and clinical risk factors. Reference standard: Bilirubin levels (TcB or TSB) measured on day 3–5 on both hospitalised and discharged babies (at home) using similar method as in Test 1, and Significant Hyperbilirubinaemia defined as bilirubin levels exceeding or within 17 micromol/litre of the hour-specific phototherapy treatment thresholds.	hyperbilirubinaemia (Univariate analysis) (*n* = 812) *Factors increasing risk* Pre-discharge bilirubin – high risk zone OR: 147 (95% CI 34–639) high-intermediate risk zone OR: 21 (95% CI 4.9–93.0) GA < 38 weeks OR: 9.2 (95% CI 4.4–19.0) intended breastfeeding OR: 2.2 (95% CI 1.0–4.5) intended breast + bottle feeds OR: 3.7 (95% CI 1.6–8.6) Grade 4 or higher degree of clinical jaundice OR 6.0 (95% CI 2.1 to 17) *Factors decreasing risk* Black race OR 0.43)95% CI 0.23–0.80) Maternal history of smoking OR: Not reported Factors significant in multivariate analysis model (*P* < 0.05) GA< 38 weeks OR 19 (95% CI 6.3- 56) Mother's plan of exclusive breastfeeding: OR 3.7 (95% CI 1.1- 13) Black race: OR 0.22 (95% CI 0.08- 0.61) Grade 4 or higher jaundice observed clinically: OR 1.7 (95% CI 1.2–2.6) Female sex: OR 3.2 (95% CI 1.2–8.4) 2) Predictive ability of the three tests in predicting significant hyperbilirubinaemia (multivariate regression) *Test 1: Pre-discharge bilirubin risk zone* c-statistic 0.88 (95% 0.85 to 0.91) *Test 2: Clinical risk factors (final model had 5 factors – GA, intended method of feeding, black race, extent of jaundice and gender)* c-statistic 0.91 (95% 0.86 to 0.97) *Test 3: Combination model (pre-discharge risk zone + clinical factors of GA and %*	Methodology described adequately Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				weight loss) c-statistic 0.96 (95% 0.93 to 0.98) *Test 3 vs Test 1* p-value for difference< 0.01 *Test 3 vs Test 2* p-value for difference = 0.15 *Test 2 vs Test 1* p-value for difference = 0.35	
Herschel M; Year: 2002 Country: USA [41]	Study Type: Prospective diagnostic study Evidence Level: II	All consecutive babies admitted to the General Care Nursery of a tertiary care city hospital. Mean GA: 38.9 ± 1.4 weeks Mean BW: 3267 ± 480 g Gender: Males = 47.6%, Ethnicity: black - 82.9% white = 9.8% Hispanic = 3.3% Asian = 2% Other = 2% Results given separately for babies with smoking mothers and non-smoking mothers. Exclusion: not defined	**Objective 1:** Diagnostic accuracy of DAT Test: Direct Antiglobulin Test (DAT) done on cord blood of all newborn babies. Reference standard: Haemolysis identified by measuring ETCOc levels in all babies at 12 ± 6 hours and 24 ± 6 hours. Significant haemolysis defined as ETCOc levels = 95th centile in babies of non-smoking mothers at 12 hours (= 3.2 microlitre/litre), and among all babies at 24 hours (= 2.5 microlitre/litre). **Objective 2:** Accuracy of DAT and ETCOc in predicting hyperbilirubinaemia defined as bilirubin reading = 75th centile on the nomogram (TcB readings with BiliChek at the time of discharge or earlier as clinically indicated, and subsequent TSB as deemed necessary)	**Objective 1:** Prevalence of DAT positive results 23/659 (3.5%) Accuracy of DAT in detecting haemolysis (ETCOc = 3.2 microlitre/litre) in babies of non-smoking mothers (*n* = 499) Sensitivity: 10/26 (38.5%) Specificity: 466/473 (98.5%) PPV: 10/17 (58.8%) NPV: 466/482 (96.7%) Accuracy of DAT in detecting haemolysis (ETCOc = 2.5 microlitre/litre) in babies of all mothers (*n* = 563) Sensitivity: 4/47 (8.5%) Specificity: 504/516 (97.6%) PPV: 4/16 (25.0%) NPV: 504/547 (92.1%) **Objective 2:** Prevalence of hyperbilirubinaemia. In babies of non-smoking mothers 61/499 (12.2%) Accuracy of positive DAT test in predicting hyperbilirubinaemia in babies of non-smoking mothers (*n* = 499) Sensitivity: 9/61 (14.7%) Specificity: 430/438 (98.2%) PPV: 9/17 (52.9%) NPV: 430/482 (89.2%) Accuracy of ETCOc (threshold = 2.5 microlitre/litre) in	Unselected population but exclusion criteria not defined Test and Reference described adequately Reference test a standard one Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				predicting hyperbilirubinaemia in babies of non-smoking mothers (*n* = 499) Sensitivity: 17/61 (27.9%) Specificity: 429/438 (97.9%) PPV: 17/26 (65.4%) NPV: 429/473 (90.7%)	
Risemberg HM; Year: 1977 Country: USA [42]	Study Type: Prospective diagnostic study Evidence Level: III	All consecutive newborns of hetero-specific pregnancies (blood group O mothers with babies having blood group A or B) born in two hospitals (*n* = 91) Mean GA: Not reported Mean BW: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: Rh incompatible babies	Test 1: Coombs' test done on cord blood of all newborn babies. Test 2: UCB levels measured (threshold value > 68 micromol/litre) Reference standard: Severe hyperbilirubinaemia defined as TSB > 274 micromol/litre at 12–36 hours of age	Prevalence of severe hyperbilirubinaemia 13/91 (14.3%) Prevalence of DAT positive 31/91 (34.1%) Accuracy of positive DAT test in predicting severe hyperbilirubinaemia (*n* = 91) Sensitivity: 12/13 (92.3%) Specificity: 59/78 (75.6%) PPV: 12/31 (38.7%) NPV: 58/60 (98.3%) Accuracy of UCB levels (threshold > 68 micromol/litre) in predicting severe hyperbilirubinaemia (*n* = 91) Sensitivity: 12/13 (92.3%) Specificity: 78/78 (100%) PPV: 12/12 (100%) NPV: 78/79 (98.7%)	Small sample Test and Reference standard not described in details Reference test a standard one Blinding – Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Chen JY; Year: 1994 Country: Taiwan [40]	Study Type: Diagnostic accuracy study Evidence Level: III	Healthy term babies born to blood group O, Rh positive mothers and weighing = 2.5 kg with no evidence of perinatal asphyxia, polycythemia, huge cephalhematoma or infection. (*n* = 88) Mean GA: Not reported Mean BW: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: not defined	Test 1: Direct Coombs' test from cord blood. Test 2: UCB levels measured threshold value > 68 micromol/litre Reference standard: Hyperbilirubinaemia defined as TSB levels = 256 micromol/litre) within first 4 days of life and/or early jaundice with TSB levels = 171 micromol/litre within 24 hours of birth	Prevalence of DAT positive 14/53 (26.4%) Prevalence of hyperbilirubinaemia 29/53 (54.7%) Diagnostic accuracy of Coombs' test for predicting hyperbilirubinaemia (*n* = 53) Sensitivity: 13/29 (44.8%) Specificity: 23/24 (95.8%) PPV: 13/14 (92.8%) NPV: 23/39 (59.0%) Diagnostic accuracy of UCB (> 68 micromol/litre for predicting hyperbilirubinaemia (*n* = 53) Sensitivity: 12/29 (41.4%) Specificity: 24/24 (100%) PPV: 12/12 (100%) NPV: 24/41 (58.5%)	Small sample and data derived from results of two groups of babies with blood group A & B only Test & Reference test not described in detail Reference test is a standard one Blinding: none
Sarici SU Year: 2002 Country: Turkey [39]	Study type: Prospective diagnostic study Evidence level: III	All full-term babies (GA > 38 weeks) with blood groups A or B born to mothers with blood group O without simultaneous Rhesus blood factor incompatibility. (*n* = 150) Mean GA: 39.4 ± 1.2 weeks Mean BW: 3212 ± 415 g Gender: Males = 50.7% Ethnicity: Not reported	Test: Direct Antiglobulin Test (DAT) on cord blood Reference standard: Total serum bilirubin level (TSB) at 6, 30, 54, 78 and 102 hours Hyperbilirubinaemia was defined as: TSB ≥ 85 micromol/litre and increase of 8.5 micromol/litre per hour in first 24 hours Day 2 TSB > 205 micromol/litre Day 3 TSB > 256 micromol/litre Day 4/5 TSB > 290 micromol/litre	Prevalence of DAT positive 4.4% (6/136) Prevalence of Hyperbilirubinaemia 29/136 (21.3%) Accuracy of DAT in predicting hyperbilirubinaemia (*n* = 136) Sensitivity: 6/23 (20.1%) Specificity: 107/107 (100%) PPV: 6/6 (100%) NPV: 107/130 (82.3%)	Aim of study was to see if 6hr TSB levels predicted hyperbilirubinaemia No data on 14 babies for clinical or consent reasons Selected sample and test not described. Reference is a standard test and was adequately described Blinding: None
Meberg A Year: 1998 Country: Norway	Study Type: Diagnostic Accuracy study Evidence level: III	All babies born in a general hospital. (*n* = 2463) Mean GA: Not reported (94.8% were term babies ≥ 27 weeks)	Test: Direct Antiglobulin Test (DAT) on cord blood Reference: TSB levels requiring	Prevalence of DAT positive 4.1% (100/2,463) Prevalence of Hyperbilirubinaemia	Universal sample Test: not adequately described Reference test is a standard one

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
[38]		Mean BW: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: Stillbirth, death, high-risk deliveries. severe neonatal conditions	phototherapy according to the Hillingdon Hospital bilirubin chart. Phototherapy indicated at TSB > 350 micromol/litre at ≥ 72 hours for term babies TSB > 250 micromol/litre at ≥ 120 hours for preterm babies TSB at lower levels for younger babies	139/2,463 (5.6%) Accuracy of DAT in predicting need for phototherapy for hyperbilirubinaemia (*n* = 2463) Sensitivity: 20/139 (14.4%) Specificity: 2244/2324 (96.6%) PPV: 20/100 (20.0%) NPV: 2244/2463 (91.1%)	but not described adequately Blinding: None

Evidence table – Prediction of hyperbilirubinaemia (effectiveness)

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Petersen JR; Year: 2005 Country: USA [43]	Study Type: Retrospective cohort study Evidence Level: II	Babies with a diagnosis-related group designation indicating 'normal newborn' and admitted in the newborn unit of a tertiary hospital from August 2002 to December 2003. (*n* = 6603, males 52.9%) Group 1: babies born before TcB introduced – August 2002 to March 2003 (*n* = 3237, 51.3% males) Group 2: babies born after TcB introduced – May 2003 to December 2003 (*n* = 3366, 53.2% males) Exclusion: babies who did not fit the criterion of 'normal newborns', and those born in the transitional time – April 2003	Comparison of the number of births, number of vaginal and caesarean deliveries, ethnicity and gender distribution, newborn readmission rates, and number of serum bilirubin measurements between Group 1 vs Group 2	<u>Comparison of bilirubin testing (values in mean (SD)</u> *Number of monthly admissions* 404.6 (33.2) vs 420.7 (36.8), p=0.42 *Number of newborns tested monthly* 128.0 (26.1) vs 152.1 (26.2), p=0.10 *% of newborns tested by TSB levels* 6.4% vs 8.7% p=0.21 *Serum bilirubin measurement per newborn* 1.51 vs 1.56 p=0.33 *Total bilirubin measurement (TcB +TSB)* 0.37 vs 0.61 p=0.007 *% of newborns treated with phototherapy* 5.9% vs 7.7% p=0.014 *Newborn readmissions for hyperbil. within 7 days of initial discharge (per 1000 births)* 4.5 vs 1.8 p=0.044	Retrospective cohort study Some of the baseline characteristics compared between the two groups, but information not given for all variables. Confounding variables not adjusted
Ebbesen F; Year: 2002 Country: Denmark [45]	Study Type: Diagnostic study Evidence Level: III	All newborns more than 24 hours old who for clinical reasons had their plasma bilirubin determination during the day, except at weekends. <u>Group 1:</u> Both preterm infants < 35 weeks and sick term and near-term infants in the NICU *n* = 261 mean BW 2521 g - range 680 to 4645 g, mean GA 34.6 weeks - range 25 to 43 weeks postnatal age at 1st TcB: 98.4 - range 48 – 840	TcB measurement using BiliChek from forehead, sternum, knee and the foot – mean of 5 measurements from each site taken for data analysis. <u>Reference standard:</u> Laboratory TSB levels taken concurrently with TcB measurement Diagnostic accuracy of TcB from forehead (threshold ≥ 0.70 of phototherapy limit) estimated for predicting TSB levels ≥	<u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 210)</u> **Group 1:** *Forehead* r = 0.88, p > 0.05 *Sternum* r = 0.82, *P* < 0.001 *Knee* r = 0.77, *P* < 0.001 *Foot* r = 0.51, *P* < 0.001	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified Data not given for the mean difference and SD from Bland Altman analysis for TSB - TcB

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Gender: Males = 60.1% Ethnicity: Non-northern European descent = 9% <u>Group 2:</u> Healthy term and near-term infants with GA ≥ 35 weeks in the maternity ward *n* = 227 mean BW 3362 g - ange 2170 to 5000 g mean GA 38.6 weeks - range 35 to 43 weeks postnatal age at 1st TcB: 74.4 - range 48 – 360 Gender: Males = 55.5% Ethnicity: Non-northern European descent = 7% Exclusion: babies already receiving phototherapy or who received phototherapy 6 hours before TSB measurement, with skin infection, purpura, bruising	phototherapy limits as suggested by the Danish Pediatric Society	On comparing correlation coefficient of forehead with that for sternum, knee and foot, $P < 0.001$ for each of the comparison **Group 2:** *Forehead* r = 0.87, p > 0.05 *Sternum* r = 0.90, $P < 0.05$ *Knee* r = 0.83, $P < 0.05$ *Foot* r = 0.63, $P < 0.001$ On comparing correlation coefficient of forehead with that for sternum, knee and foot, $P < 0.05$ for comparison with knee and foot only <u>Diagnostic accuracy of TcB (threshold value > 0.70 times the phototherapy limit) from forehead in detecting TSB > phototherapy limit</u> **Group 1 (*n* = 504 observations):** Sensitivity: 108/109 (99.1%) Specificity: 177/395 (44.8%) PPV: 108/326 (33.1%) NPV: 177/178 (99.4%) **Group 2 (*n* = 317 observations):** Sensitivity: 3/3 (100%) Specificity: 254/314 (80.9%) PPV: 3/63 (4.8%) NPV: 254/254 (100%)	
Samanta S; Year: 2004 Country: UK [44]	Study Type: Diagnostic study Evidence Level: II	All babies > 33 weeks in the postnatal ward of a regional teaching hospital who were due to have blood taken for TSB estimation *n* = 300 median BW 3295 g – range 1972 to 4720 median GA 39 weeks – range 33 to 42 median postnatal age: 72 hours – range 24 to 264	TcB using BiliChek (site not specified) – single measurement taken. <u>Reference standard:</u> Laboratory TSB levels taken concurrently with TcB measurement Diagnostic accuracy of TcB (various thresholds) estimated by plotting ROC curve.	<u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 300)</u> r = 0.77, $P < 0.0001$ <u>Bland Altman analysis for difference between TcB and lab TSB</u> MD = -10.6 micromol/litre (95% CI -80.0 to +60.0)	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Gender: Males = 50% Prevalence of TSB > 250 micromol/litre = 55/300 (18.3%) Exclusion: babies who had previously received phototherapy		SD = Not reported Diagnostic accuracy of TcB (threshold value > 195 micromol/litre) for detecting TSB > 250 micromol/litre Sensitivity: 50/55 (90.9%) Specificity: 162/245 (66.1%) PPV: 50/133 (37.6%) NPV: 162/167 (97%)	
Briscoe L; Year: 2002 Country: UK [46]	Study Type: Diagnostic study Evidence Level: II	Babies > 34 weeks who were having blood taken for any reason, mostly done for clinical jaundice. *n* = 303 median BW 3267 g - range 1800–5008 median GA 39 weeks - range 34–42 median age at presentation: 3 – range 0 to 13 days Gender: Not reported Ethnicity White: 94.7% Prevalence of TSB > 300 micromol/litre = 3.3% (10/303) Exclusion: babies who had previously received phototherapy	TcB reading using Minolta JM-102 at the forehead (mean of 3 readings used for analysis) Reference standard: Laboratory TSB levels measured concurrently For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 249 micromol/litre	Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, *n* = 303) r = 0.76, *P* < 0.0001 Diagnostic accuracy of JM-102 for detecting TSB > 249 micromol/litre (*n* = 303) Area under ROC = 0.89 *Predictive accuracy of JM-102 value 19.9 (highest accuracy from ROC curve)* Sensitivity: 86% (81–89%) Specificity: 78% (73–83%) PPV: Not reported NPV: Not reported In this study a reading of > 18 reflectance units was taken as an indicator for serum bilirubin, resulting in a reduction of 34% in the number of blood samples taken.	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN
Bhutani VK; Year: 2006 Country: USA [47]	Study Type: Observational study Evidence Level: III	All babies born from 01 January 1990 to 31 December 2000 who were discharged from the well-baby nursery of a tertiary hospital as term and near-term healthy babies. *n* = 31 059 mean BW: 3318 ± 457 g mean GA: 38.7 ± 1.3 weeks Gender: Males = Not reported Ethnicity: White = 43.5%	Incremental hospital systems approach in the management of neonatal hyperbilirubinaemia studied with different clinical approaches at different phases: Phase 1: selective pre-discharge TSB measurements (1990–1992) Phase 2: universal TSB measurement at the time of metabolic screening with an authority given to nurses (after in-service workshops and training) to obtain bilirubin estimation at their	Incidence of adverse outcomes for term and near-term infants in the well-baby nursery *Hospital-based intensive phototherapy* Phase 1: 3.6% Phase 2: 4.5% Phase 3: 5.4% Phase 4: 2.5% Phase 5: 1.3% *Exchange transfusion (in risk)* Phase 1: 1:2137 Phase 2: 1:1322 Phase 3: 1:1637	Non-comparative observational study Time periods of different clinical approaches overlapping. Confounding variables not adjusted

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Black = 39.1% Asian = 6.9% Hispanic = 4.5% Exclusion: low BW preterm babies admitted to the well-baby nursery babies admitted to and treated in the intensive care nursery for any neonatal illness	own discretion (1993–95) <u>Phase 3:</u> universal TSB screening along with post-discharge follow-up based on the hour-specific nomogram (1996–98) <u>Phase 4:</u> organised institutional systems-based management of newborn jaundice (1999–2000) <u>Phase 5:</u> impact of the complete approach assessed in 2001–2003. Under the systems-based approach all babies had pre-discharge bilirubin estimation (TSB or TcB) and follow-up care for jaundice was given 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 services, counselling and information to parents on the clinical course and rare risk of neurotoxicity, and close follow-up of jaundiced babies based on their hour-specific bilirubin levels. A clinical evaluation for jaundice severity was mandatory for all babies at about the age of 4 days, along with subsequent follow-up of at-risk infants at age 7 days and 2 weeks.	Phase 4: 1:3198 Phase 5: 1:11995 *Number of readmissions* 14 per 1000 well-baby infants discharged in 1994 to 5.5 per 1000 in 2001–2003. <u>Results in babies (6 – 72 hours of age) with ABO incompatibility (*n* = 553)</u> *High risk zone or TSB > 95th centile (n = 55 or 9.9%)* Phototherapy: 54.5% Exchange Transfusion: 5.4% Length of stay: 3.3 days *Intermediate risk zone or TSB 40th-74th centile (n = 233 or 42.1%)* Phototherapy: 22.7%, Exchange Transfusion: 0% Length of stay 2.6 days *Low risk zone or TSB < 40th centile (n = 265 or 48.0%)* Phototherapy: 2.6% Exchange Transfusion: 0% length of stay: 2.36 days	
Eggert LD; Year: 2006 Country: USA [48]	Study Type: Retrospective cohort study Evidence Level: II	Retrospective cohort study to determine the effectiveness of a pre-discharge bilirubin screening programme instituted in December 2002. All babies delivered at = 35 weeks of gestation within a private healthcare organisation involving 18 hospitals during two time periods:	Pre-discharge bilirubin screening programme started in December 2002 to measure bilirubin levels in every baby either at the recognition of jaundice or before discharge from hospital. Two hospitals used TcB (BiliChek) levels while others used TSB. Bilirubin levels plotted on the hour-specific nomogram and levels = 40th centile notified to the relevant healthcare provider and	<u>Incidence of severe hyperbilirubinaemia</u> *TSB levels ≥ 342 micromol/litre* Group 1 - 1:77 Group 2 - 1:142 *P* < 0.0001 *TSB levels ≥ 428 micromol/litre* Group 1 - 1:1522 Group 2 - 1:4037 *P* < 0.005	Retrospective cohort study with exclusion criteria not defined Baseline characteristics of the two groups not compared Confounding variables not adjusted

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Group 1: before the programme started from 01 March 2001 to 31 December 2002, **Group 2:** after the programme started from 01 January 2003 to 31 December 2004. Exclusion: Not defined	baby managed according to his/her discretion. After first 3 months percentile tracks of the nomogram modified since a large number of babies had bilirubin levels in the high or intermediate-high zones	*TSB levels ≥ 513 micromol/litre* Group 1 - 1:9742 Group 2 - 1:17494 p=0.24 Incidence of hospital readmissions for hyperbilirubinaemia Group 1 - 0.55% Group 2 - 0.43% *P* < 0.005	
Madan A Year: 2004 Country: USA [49]	Study type: Retrospective observational study Evidence level: III	All babies (*n* = 4450) of which those born to blood type O or Rh negative mothers (*n* = 2443) Mean GA: Not reported Mean BW: Not reported Gender: Not reported Ethnicity: Asian = 45.9% White = 36.8% Exclusion criteria: None	Test: Direct Antiglobulin Test (DAT) on cord blood. Reference standard: phototherapy/readmission for phototherapy	Prevalence of DAT positive 7.9% (193/2,443) Rate of phototherapy: among DAT positive cases was 18.6% (36/193). Rates for readmission for phototherapy: among tested babies: 1.1% (26/2,443) among untested babies : 0.9% (19/2,097) Odds Ratio (OR): 1.18 (95% CI 0.65 – 2.13)	Data not reliable: authors reported not determining the number of DAT negative who were treated for jaundice before readmission Sample: Selective Blinding: None
Leistikow EA Year: 1995 Country: USA [51]	Study type: Health economics study Evidence level: III	All patients in Neonatal Intensive Care Unit; babies with clinical jaundice; babies with Rh negative mothers and/or positive maternal antibody screenings; no available maternal blood Mean GA: Not reported Mean BW: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: Not reported	Test: Direct Antiglobulin Test (DAT) on cord blood. Reference standard: Readmission for jaundice	Prevalence of DAT positive: Not reported Percentage of babies tested Among universal testing (2,253/4,003) 56.3% among selective testing (1,048/4,498) 23.3% Rate of readmission for hyperbilirubinaemia among universally tested babies 0.4 (15/4,003) among selectively tested babies 0.3 (15/4,498) Odds Ratio (OR) 1.12 (95% CI 0.56 – 2.30)	Small study No definition on readmission for hyperbilirubinaemia given Sample: Non-selective Blinding: None
Madlon-Kay DJ Year: 1992	Study type Retrospective cohort study:	All babies in normal nursery cared for by family practice service were included (*n* = 301)	Test: Direct Antiglobulin Test (DAT) on cord blood. Reference standard:	Overall Prevalence of DAT positive 9.0% (27/301)	Small sample Test and reference standard not described in details

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Country: USA [50]	Evidence Level: III	Sample was split between those tested automatically (*n* = 113) and those tested selectively (*n* = 188) Mean GA: 39.4 weeks Mean BW: 3344 g Gender: Males = 50.5% Ethnicity: White = 44.5% Black = 16.3% Asian = 17.9% Other = 21.3% Exclusion criteria: babies in intensive care	Need for phototherapy (no clear definition)	Overall rate of phototherapy 12/301 (3.9%) Rates of phototherapy among universally tested babies 4/113 (3.5%) among selectively tested babies 8/188 (4.3%) Odds Ratio (OR) 0.83 (95% CI: 0.24 – 2.81) Rates of readmission for phototherapy among universally tested babies 2/113 (1.8%) among selectively tested babies 1/188 (0.5%) Odds Ratio (OR) 3.36 (0.32 – 37.58)	Blinding: None

What is the best method of recognising hyperbilirubinaemia?

Evidence table – Recognition

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Riskin A; Year: 2008 Country: Israel [61]	Study Type: Diagnostic study Evidence Level: Ib	Healthy full term and late preterm babies (≥ 35 weeks) examined for clinical jaundice before discharge (days 2 to 5 of life) in a hospital *n* = 1129, total observations = 3532, mean BW 3298 ± 462 g, mean GA 39.5 ± 1.4 weeks, mean time of assessment 62 ± 24 hours (median 55 hours; range 9 to 252 hours) Gender: Males = 52.3% Ethnicity Majority reported as Ashkenazi or Sephardic Jews (73%) or Arabs (26%) Exclusion: babies with < 50 observations, visual assessment done after starting phototherapy	Test: Visual assessment of jaundice (BiliEye) by experienced observers (total 23 observers – 5 neonatologists and 17 nurses, mean experience 11.4 ± 10.2 years). No. of observations per observer were record in 1195 encounters with a mean of 3.0 ± 1.8 observers. The observers were identified by code numbers and unaware of laboratory TSB values and BiliEye values made by other observers. Reference standard: Laboratory TSB levels within 1 hr Analysis: After determining correlation between BiliEye and lab TSB, the values were grouped into risk zones according to Bhutani nomogram. Accuracy of BiliEye in determining TSB levels (or degree of hyperbilirubinaemia) evaluated. Ability of BiliEye to detect significant hyperbilirubinaemia (defined as zones C+D on nomogram) analysed by ROC curve – after correcting for postpartum age and GA	Correlation of visual assessment of TSB levels with lab TSB (Pearson correlation coefficient, *n* = 3532 observations) *All observers* Weighted r = 0.75, $P < 0.001$ κ (weighted) = 0.363 *Each observer separately (range)* r = 0.51 to 0.88 κ = 0.11 to 0.52 Accuracy of BiliEye for determining TSB values (after grouping Zones B, C & D together versus Zone A) Sensitivity: 337/567 (59.4%) Specificity: 2627/2965 (88.6%) PPV: 337/675 (49.9%) NPV: 2627/2857 (91.9%) *False negative rate of BiliEye* Zone A: 230/2857 (8.1%) Zone C + D: 67/109 (61.5%) Zone D only: 13/15 (86.7%) Difference between BiliEye and laboratory TSB values *All observers* MD = 0.11 ± 2.17	Unselected population with defined exclusion criterion Test & Reference test described in detail Test and reference test carried out within one hour Blinding – yes Funding: None specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				Each observer separately $P < 0.001$ for both the mean values and absolute values Diagnostic accuracy of BiliEye in detecting hyperbilirubinaemia Area ROC = 0.82 *Best AROC* 0.93 for observations at > 60 hours in babies ≥ 37 weeks GA *Worst AROC* 0.64 for observations at < 36 hours 0.61 for babies < 37 weeks	
Moyer VA; Year: 2000 Country: USA [60]	Study Type: Diagnostic study Evidence Level: II	Full-term healthy babies (BW > 2000 g and GA> 36 weeks) in well-newborn nursery of an urban public hospital, in whom TSB was measured because of clinical jaundice, Rh-negative mother or positive maternal Coomb's test. *n* = 122, GA: > 36 weeks BW > 2,000 g mean age = 2 days (range 8 to 168 hours) Gender: Males = 54.1% Ethnicity Not reported Exclusion: babies having previous TSB determination and under phototherapy	Visual observation by two experienced staff (paediatric residents, paediatric nurse practitioners, paediatric physicians) regarding a) Subjective assessment of presence/absence of icterus at different sites b) Estimated TSB levels Reference standard: Laboratory TSB levels within 1 hr	Agreement between observers on presence/absence of icterus at different sites (Weighted κ with 95% CI) Face & neck: 0.16 (-0.02 to 0.34) Neck to nipple line: 0.15 (0.01 to 0.29) Nipple line to umbilicus: 0.23 (0.09 to 0.38) Umbilicus to groin: 0.19 (0.05 to 0.34) Upper legs: 0.20 (0.06 to 0.35) Weighted K not statistically significant for other sites – Lower legs, Soles, Arms, Palms, Tip of nose and palate Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient) Observer 1: r = 0.43 Observer 2: r = 0.54 Accuracy of clinical icterus in lower chest (nipple line to umbilicus) in detecting TSB > 205 micromol/litre (*n* = 243 observations)	Unselected population Reference test not described adequately Test and reference test carried out within one hour Blinding – yes Funding: Not reported

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				Sensitivity: 97.1% (67/69) Specificity: 19.0% (33/174) PPV: 32.2% (67/208) NPV: 94.3% (33/35)	
Madlon-Kay DJ; Year: 2001 Country: USA [59]	Study Type: Diagnostic study Evidence Level: II	Newborn babies delivered in a hospital with follow-up visit at home by Home Health Nurses. (*n* = 164, mean GA: Not reported mean BW: Not reported mean age at assessment 6.4 ± 2.5 days) Gender: Not reported Ethnicity (nurse determination) white = 60% black = 18% Asian = 6% Hispanic = 7% Other = 9% Exclusion: babies who were in intensive care nursery or received phototherapy, Also babies whose mothers lived more than 10 miles from hospital or were not proficient in English Babies examined by 12 home health nurses.	1) Clinical assessment by nurses with their usual method (e.g blanching skin, judging degree of yellowness with caudal progression, looking for jaundice at sclera, gums, nose) 2) Caudal progression of jaundice alone as assessed by nurses 3) Ingram Icterometer reading from nose Threshold for diagnostic accuracy – reading > 2.5 Reference standard: Laboratory TSB levels within 1 hr	TSB levels (micromol/litre) *All babies (n = 164)* Mean (sd) 125 (80) Range: 12 to 345 *Babies assessed to be jaundiced by nurses (n = 82)* Mean (sd): 180 (68.4) *Babies assessed not to be jaundiced by nurses (n = 82)* Mean (sd): 72 (46) Comparison 1: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, n = 82 where sampling done)* r = 0.61, *P* < 0.01 Comparison 2: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, n = 82 where sampling done)* r = 0.47, *P* < 0.01 *Accuracy of test (caudal progression to nipple line) in detecting TSB > 205 micromol/litre (N = Not reported)* Sensitivity: 76% Specificity: 60% Comparison 3: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, n = 82 where sampling done)* r = 0.48, *P* < 0.01 *Accuracy of test in detecting TSB*	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating exact values of TP, FP, TN & FN Funding: Ramsey Foundation

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				> 205 micromol/litre (N = Not reported) Sensitivity: 75% Specificity: 72%	
Riskin A; Year: 2003 Country: Israel [58]	Study Type: Diagnostic study Evidence Level: II	Full term babies (37–42 weeks) with clinical jaundice in the nursery of a tertiary care hospital. Includes babies with ABO incompatibility and G6PD deficiency. *n* = 283 mean age at assessment 63.8 ± 21.6 hours mean GA: 39.5 ± 1.5 weeks mean BW: 3223 ± 484 g Gender: Males = 51.2% Ethnicity Majority reported as Jews (76%) or Arabs (24%) Exclusion: not defined	Visual observation by one of four attending neonatologists before discharge of baby from the nursery regarding a) Assessment of clinical jaundice severe enough to draw blood sample b) Estimated TSB levels <u>Reference standard:</u> Laboratory TSB levels within 30 mins	<u>Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient)</u> All physicians (*n* = 283): r = 0.68, *P* < 0.001 Physician 1 (*n* = 74) r = 0.79, *P* < 0.001 Physician 2 (*n* = 62) r = 0.64, *P* < 0.001 Physician 3 (*n* = 69) r = 0.70, *P* < 0.001 Physician 4 (*n* = 78) r = 0.62, *P* < 0.001	Selected population with no exclusion criterion Test & Reference test described in detail Test and reference test carried out within one hour Blinding – yes Data not extractable for calculating TP, FP, TN & FN values

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Madlon-Kay DJ; Year: 1997 Country: USA [57]	Study Type: Diagnostic study Evidence Level: II	Babies with age > 2 days in a normal newborn nursery.in a teaching hospital (*n* = 171 mean GA 39 weeks) mean BW: Not reported Gender: Not reported Maternal ethnicity white = 50% black = 24% Asian = 13% Hispanic = 9% Other = 4% Exclusion: babies who received phototherapy, and whose parents were unable to read and understand the instruction form	1) Clinical estimation of degree of jaundice and cephalo-caudal progression by nurses and physicians by blanching the skin. (36 nurses, 20 family physicians and 4 paediatricians) 2) Clinical assessment of jaundice by the parents after receiving written and verbal instructions about the process (147 parents with 81% having English as the primary language and 46% having completed high school) 3) Ingram Icterometer readings from nose (*n* = 132 readings) Reference standard: Laboratory TSB levels within 1 hr Correlation between the estimated and the observed TSB values determined before and after adjusting for various factors	Prevalence of hyperbilirubinaemia (TSB = 205 micromol/litre 11/89 (12.3%) Correlation of estimated TSB levels with lab TSB values after adjusting for various confounding factors like level of training, race, etc (Pearson correlation coefficient) *Nurse estimate of TSB* r = 0.52, *P* < 0.001 *Nurse assessment of cephalo-caudal progress* r = 0.48. *P* < 0.05 *Physician estimate of TSB* r = 0.55, *P* < 0.05 *Physician assessment of cephalo-caudal progress* r = 0.35. p > 0.05 *Parent assessment of cephalo-caudal progress* r = 0.71, *P* < 0.01 *Icterometer* r = 0.57, *P* = 0.002	Study population selected by convenience sampling Test & Reference test described in detail Test and reference test carried out within one hour, but reference test (laboratory TSB) not conducted in all babies (89/171) Blinding – yes Data not extractable for calculating exact values of TP, FP, TN & FN
Szabo P; Year: 2004 Country: Switzerland [55]	Study Type: Diagnostic study Evidence Level: II	Healthy preterm babies 34–37 weeks with BW > 2000 g and no older than 6 days in maternity ward and intermediate care neonatal unit. *n* = 69, median GA: 35.7 weeks – range 34 to 36.9 weeks median BW 2530 g – range 2050 to 3630 g Gender: Not reported Ethnicity white = 87%	1) Clinical assessment by nurses and primary investigator using Kramer criterion 2) TcB using Minolta JM-102 at the sternum (mean of two readings used for analysis) 3) TcB using BiliChek at the forehead and sternum (mean of 5 readings used for analysis)	Comparison 1: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, n = 107 observations)* By nurses R^2 = 0.22, *P* < 0.01 By primary investigator R^2 = 0.20, *P* < 0.01 *Diagnostic accuracy for detecting TSB > 190 micromol/litre (Area under ROC curve, N = Not reported)*	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values for TP, FP, TN & FN

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		black = 4% Asian = 7% Other = 2% Exclusion: jaundice above zone 3 of Kramer scale within 48 hours, positive DCT, BW < 10th centile for GA, any sign or symptom of illness, phototherapy already started	Reference standard: Laboratory TSB levels within 30 min. Mean of two samples used for analysis. For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 190	By nurses Area = 0.73 By primary investigator Area = 0.70 κ = 0.48 Comparison 2: *Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, n = 107 observations)* R^2 = 0.76, *P* < 0.01 Difference to TSB: 56 ± 28 micromol/litre *Diagnostic accuracy for detecting TSB > 190 micromol/litre (Area underROC curve, N = Not reported)* Area = 0.96 Comparison 3: **At forehead** *Correlation of BiliChek with lab TSB levels (Pearson correlation coefficient, n = 107 observations)* R^2 = 0.45, *P* < 0.01 Difference to TSB: -8 ± 33 micromol/litre *Diagnostic accuracy for detecting TSB > 190 micromol/litre (Area underROC curve, N = Not reported)* Area = 0.88 **At sternum** *Correlation of BiliChek with lab TSB levels (Pearson correlation coefficient, n = 107 observations)* R^2 = 0.59, *P* < 0.01 Difference to TSB: 10 ± 31 micromol/litre *Diagnostic accuracy for detecting TSB > 190 micromol/litre (Area underROC*	

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				curve, N = Not reported) Area = 0.89	
Szabo P; Year: 2004 Country: Switzerland [56]	Study Type: Diagnostic study Evidence Level: II	Healthy full-term babies (37–41 weeks) with BW > 2000 g and no older than 6 days. (*n* = 140, 92 white and 48 non-white babies, median BW 3320 g) range 2050 to 4400 g median GA: 39 weeks – range 37 to 41.9 weeks Gender: Not reported Ethnicity white = 66% Asian = 13% Other = 21% Exclusion: Haemolysis jaundice within first 36 hours phototherapy	1) Clinical assessment by nurses and primary investigator using Kramer criterion 2) TcB using Minolta JM-102 at the sternum (higher of two readings used for analysis) 3) TcB using BiliChek at the forehead and sternum (mean of 5 readings used for analysis) Reference standard: Laboratory TSB levels within 30 min For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 250 micromol/litre	Comparison 1: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, N = not reported)* For white babies R^2 = 0.74 (by nurse) R^2 = 0.70 (by investigator) For non-white babies R^2 = 0.71 (by nurse) R^2 = 0.65 (by investigator) *Diagnostic accuracy for detecting TSB > 250 micromol/litre (Area underROC curve, N = Not reported)* Area = 0.84 Comparison 2: *Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = Not reported)* R^2 = 0.82, $P < 0.01$ *Diagnostic accuracy for detecting TSB > 250 micromol/litre (Area under ROC curve, N = Not reported)* Area = 0.98 Comparison 3 (at forehead): *Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = Not reported)* R^2 = 0.79, $P < 0.01$ *Diagnostic accuracy for detecting TSB > 250 micromol/litre (Area under ROC curve, N = Not reported)*	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				Area = 0.92	
Crofts DJ; Year: 1999 Country: UK [62]	Study Type: Non-diagnostic study (Project report) Evidence Level: III	Mothers and their newborn babies born and resident of Sheffield and who were routinely visited by the health visitor at 28 days of age. Phase 1: (*n* = 109 parent-baby pairs, total stool observations = 5053) Mean BW: Not reported Mean GA: Not reported Gender: Males = 56.9% Ethnicity: Not reported Phase 3: (*n* = 3629 mother-baby pairs)	Phase 1: Inspection of stools, by parents, from healthy babies and babies with cholestatic liver disease during the first 28 days of age to devise a stool colour chart using 20 colours Phase 2: development of stool chart – six most commonly selected stool colours from each of main colour groups together with three pale colours used to develop a stool chart. Phase 3: Assess specificity of colour chart – charts given to all mothers at first health visitor visit (at 10–14 days), and information collected at second visit of health visitor (at 28 days). Babies with suspicion of jaundice or history of passing pale stools referred for further investigation	Incidence of jaundice *Related to breastfeeding* 3.4% (95% CI 2.9%, 4.1%) *At 28 days in breastfed babies* 9.2% (95% CI 7.8%, 11.0%) % with abnormal LFT (*n* = 60) *Abnormal GGT and ALT* 38.3% (23/60) *Abnormal Alk. phosphate* 70% (42/60) Reasons for non-referral of babies with prolonged jaundice (*n* = 14) 9 = babies well and thriving 2 = confusion between midwife and health visitor 2 = family moving out 1 = refusal	Report of a community programme (non-diagnostic study) Unselected population No demographic details reported
Bilgen H; Year: 1998 Country: Turkey [66]	Study Type: Diagnostic study Evidence Level: II	Healthy term babies with jaundice aged more than 1 day but less than 5 days in a hospital. *n* = 96 mean BW 3380 ± 419 g mean GA: 39.6 ± 1.4 weeks age at presentation: range 1 to 5 days Gender: Males = 58% Ethnicity: Not reported Exclusion: not received phototherapy	1) Ingram Icterometer on the nose Threshold: reading ≥ 33 for best accuracy results 2) TcB using Minolta JM-102 on the forehead Threshold: reading > 13 for best accuracy results Reference standard: Laboratory TSB levels within 30 min	Prevalence of TSB > 220 micromol/litre = 18% (17/96) Comparison 1: *Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, n = 96)* r = 0.83, *P* < 0.01 *Diagnostic accuracy for detecting TSB > 220 micromol/litre* Sensitivity: 100% (17/17) Specificity: 55.7% (35/79) PPV: 32.7% (17/52) NPV: 100% (44/44) Comparison 2: *Correlation of Icterometer with lab TSB levels (Pearson correlation coefficient,*	Selected population Test & Reference test not described in detail Test and reference test carried out within one hour Blinding – yes

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				n = 96) r = 0.78, *P* < 0.01 *Diagnostic accuracy for detecting TSB > 220 micromol/litre* Sensitivity: 100% (17/17) Specificity: 48.1% (38/79) PPV: 29.3% (17/58) NPV: 100% (38/38)	
Merritt KA; Year: 1994 Country: USA [65]	Study Type: Diagnostic study Evidence Level: II	Preterm babies with jaundice in a hospital. *n* = 90 mean BW 1676 g, mean GA 31.7 weeks age at presentation: Not reported Gender: Not reported Ethnicity White = 95% Other = 5% Exclusion: not defined	1) Gosset Icterometer on the nose by two experienced and one inexperienced observer Reference standard: Laboratory TSB levels within 30 min	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = number of observations) All infants (*n* = 296) r = 0.72, *P* < 0.01 Experienced observer 1 (*n* = 239) r = 0.71, *P* < 0.01 Experienced observer 2 (*n* = 166) r = 0.75, *P* < 0.01 Inexperienced observer r = 0.63, *P* < 0.01	Selected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – yes Data not extractable for calculating values of TP, FP, TN & FN
Hamel BCJ; Year: 1982 Country: Tanzania [64]	Study Type: Diagnostic study Evidence Level: III	Newborn babies with clinical jaundice admitted for various reasons to neonatal unit of a medical centre *n* = 70 Mean BW: Not reported GA: Range 30 to 42 weeks Postnatal age: Range 2 to 14 days Gender: Not reported Ethnicity: Black = 100% Exclusion: not defined	Gosset Icterometer reading by blanching the gum Reference standard: Blood drawn for laboratory TSB levels at the same time	Correlation of Icterometer readings with lab TSB levels (Pearson correlation coefficient) r = 0.91, *P* < 0.01	Unselected population Test & Reference test not described in detail Test and reference test carried out simultaneously (exact timing not specified) Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN
Chaibva NT; Year: 1974 Country:	Study Type: Diagnostic study Evidence Level: III	Newborn babies with clinical jaundice *n* = 55 infants and 125 readings BW: Range 1050 to 3925 g	Gosset Icterometer reading (site not specified) Reference standard: Laboratory TSB levels (timing not specified)	Correlation of Icterometer readings with lab TSB levels (Pearson correlation coefficient) r = 0.96, *P* < 0.001	Unselected population Test & Reference test not described in detail Test and reference test carried out at same time (exact timing

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Rhodesia 63		GA: Not reported Postnatal age: Range 2 to 24 days Gender: Not reported Ethnicity: Black = 100% Exclusion: not defined			not specified) Blinding – yes Data not extractable for calculating values of TP, FP, TN & FN
Briscoe L; Year: 2002 Country: UK 46	Study Type: Diagnostic study Evidence Level: II	Babies > 34 weeks who were having blood taken for any reason, mostly done for clinical jaundice. *n* = 303 median BW 3267 g - range 1800–5008 median GA 39 weeks - range 34–42 median age at presentation: 3 – range 0 to 13 days Gender: Not reported Ethnicity White: 94.7% Prevalence of TSB > 300 micromol/litre = 3.3% (10/303) Exclusion: babies who had previously received phototherapy	TcB reading using Minolta JM-102 at the forehead (mean of 3 readings used for analysis) Reference standard: Laboratory TSB levels measured concurrently For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 249 micromol/litre	Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, *n* = 303) r = 0.76, *P* < 0.0001 Diagnostic accuracy of JM-102 for detecting TSB > 249 micromol/litre (*n* = 303) Area under ROC = 0.89 *Predictive accuracy of JM-102 value 19.9 (highest accuracy from ROC curve)* Sensitivity: 86% (81–89%) Specificity: 78% (73–83%) PPV: Not reported NPV: Not reported	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN
Carbonell X; Year: 2001 Country: Spain 26	Study Type: Diagnostic study Evidence Level: II	Healthy term babies *n* = 2004 – 610 in phase one ± 1394 in phase 2 mean BW 3230 ± 491 g mean GA 39 weeks Gender: Males = 50.7% Ethnicity Not reported In first phase (*n* = 610), cord blood bilirubin (UCB) at birth and TcB with Minolta JM-102 measured at 24 hours, 48 hours & 60–96 hours of life. Additionally TSB was done for all at 60–96 hours. On 169 babies TSB also measured at 24 & 48hours	Test: 1. Umbilical cord blood bilirubin (UCB) measured at birth (threshold value: ≥ 37 micromol/litre) ROC curve used to find the best cut-off value of UCB. 2. TSB (in phase 1 & 2) and TcB (phase 1 only) measured at 24 hours (threshold value for TSB = 102 micromol/litre and for TcB > 11) 3. TSB and TcB (in phase 1 & 2) measured at 48 hours (threshold value for TSB = 154 micromol/litre and for TcB > 13) TcB reading using Minolta JM-102	Correlation of TcB levels with lab TSB levels for Sternal vs Forehead site (Pearson correlation coefficient) At < 24 hours (*n* = 120) *Sternum Forehead* 0.81 0.77 At 24–48 hours (*n* = 126) *Sternum Forehead* 0.89 0.83 At > 48 hours (*n* = 412) *Sternum Forehead* 0.94 0.83 Diagnostic accuracy of TcB for detecting TSB > 222 micromol/litre	Unselected population but no exclusion criterion Test & Reference test described in detail Reference test a standard one Test and reference test carried out within one hour Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		In second phase (*n* = 1394), TcB and lab TSB values obtained to find accuracy of TSB and TcB at 24hours and 48 hours to predict hyperbilirubinaemia. Prevalence of TSB > 290 micromol/litre = 2.9% in phase 1 (18/610) and 3.25% in phase 2 (46/1324) Exclusion: not defined	at the forehead and the sternum (mean of 3 measurements recorded at each site used for analysis) Reference standard: Laboratory TSB measured on Day 3 - 4 TSB = 290 micromol/litre taken as indicative of hyperbilirubinaemia	Sensitivity: 98% Specificity: 72% Diagnostic accuracy for predicting TSB = 290 micromol/litre *Prevalence of TSB = 290 micromol/litre* 2.9% in phase 1 (18/610) and 3.25% in phase 2 (46/1324) **1. For UCB** **(threshold = 37 micromol/litre)** Sensitivity: 4/18 (22.2%) Specificity: 537/567 (94.7%) PPV: 4/34 (11.7%) NPV: 537/551 (97.4%) **2. At 24 hours** *For TcB in phase 1 (threshold > 11 Reflectance Units)* Sensitivity: 15/18 (83.3%) Specificity: 368/556 (66.2%) PPV: 15/203 (7.4%) NPV: 368/371 (99.2%) *For TSB in phase 1 (threshold = 102 micromol/litre)* Sensitivity: 7/7 (100%) Specificity: 74/162 (45.7%) PPV: 7/95 (7.4%) NPV:74/74 (100%) *For TSB in phase 2 (threshold = 102 micromol/litre)* Sensitivity: 25/25 (100%) Specificity: 239/398 (60%) PPV: 25/95 (26.3%) NPV: 239/239 (100%) **2. At 48 hours** *For TcB in phase 1 (threshold > 13 reflectance units)* Sensitivity: 17/18 (94.4%) Specificity: 288/556 (51.7%) PPV: NPV: *For TcB in phase 2 (threshold > 13*	

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				reflectance units) Sensitivity: 45/46 (97.8%) Specificity: 262/819 (32.0%) PPV: 45/602 (7.5%) NPV: 262/263 (99.6%) *For TSB in phase 1* *(threshold = 154 micromol/litre)* Sensitivity: 11/11 (100%) Specificity: 102/158 (64.6%) PPV: 11/67 (16.4%) NPV: 101/102 (100%) *For TSB in phase 2* *(threshold = 154 micromol/litre)* Sensitivity: 45/46 (97.8%) Specificity: 348/774 (45%) PPV: 45/471 (9.5%) NPV: 348/349 (99.7%)	
Knudsen A; Year: 1989 Country: Denmark [70]	Study Type: Diagnostic study Evidence Level:III	Babies in a newborn nursery were eligible if a visible jaundice was noted in first 5 days of life *n* = 76, Mean BW: Not reported Median GA: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: None	Test: TcB reading from the forehead using JM-102 Reference standard: Laboratory TSB method measured on blood collected at the same time as TcB.	Correlation of TcB levels with TSB levels (Pearson correlation coefficient, *n* = 76) *Forehead* r = 0.83; *P* < 0.0001	Unselected population Test & Reference test not described in detail Test and reference test carried out within one hour Blinding – not specified No demographic details reported
Karrar Z; Year: 1989 Country: Saudi Arabia [69]	Study Type: Diagnostic study Evidence Level: III	Healthy term babies with visible jaundice aged between 4 and 10 days. *n* = 155 Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity Saudi 100% Prevalence of TSB >	TcB using Minolta JM-101 on the forehead – single measurement made Reference standard: Laboratory TSB levels at the same time as TcB measured	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 155) r = 0.82, *P* < 0.01 Diagnostic accuracy of TcB (threshold value > 21 reflectance units) for detecting TSB > 214 micromol/litre Sensitivity: 36/49 (73.5%) Specificity: 95/106 (89.6%)	Unselected population Test & Reference test not described in detail Test and reference test carried out within one hour Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		214 micromol/litre = 31.6% (49/155) Exclusion: preterm infants, ill newborns, those requiring phototherapy or exchange transfusion		PPV: 36/47 (76.6%) NPV: 95/108 (88.0%)	
Maisels MJ; Year: 1982 Country: USA [68]	Study Type: Diagnostic study Evidence Level: II	Randomly selected full term White babies in a well-baby nursery *n* = 157 Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity Not reported Exclusion: not defined Prevalence of TSB > 221 micromol/litre = 7/157 (4.5%)	TcB using Minolta JM-102 from the forehead and the sternum Measurements routinely made on the 3rd day except in 11 infants where earlier sampling done Reference standard: Laboratory TSB levels at the same time as TcB measured	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient) *At forehead (157 observations)* r = 0.93, *P* < 0.0001 *At mid-sternum (135 observations)* r = 0.93, *P* < 0.0001 Diagnostic accuracy of TcB (Sternum threshold value > 23 reflectance units) for detecting TSB > 221 micromol/litre Sensitivity: 4/4 (100%) Specificity: 126/131 (96.2%) PPV: 4/9 (44.4%) NPV: 126/126 (100%) Diagnostic accuracy of TcB (Forehead threshold value > 24 reflectance units) for detecting TSB > 221 micromol/litre Sensitivity: 7/7 (100%) Specificity: 145/150 (96.7%) PPV: 7/12 (58.3%) NPV: 145/145 (100%)	No exclusion criterion Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified
Tsai LT; Year: 1988 Country: Taiwan [67]	Study Type: Diagnostic study Evidence Level: III	Term healthy babies > 37 weeks and less than 7 days old who had jaundice or TSB measurement *n* = 98 paired observations from each of the 8 sites = 178 mean BW: Not reported mean GA: Not reported Gender: Not reported	TcB using Minolta JM-102 Measurements made at the time of sampling from 8 sites – forehead, cheek, sternum, abdomen, upper back, lower back, palm and sole. Reference standard: Laboratory TSB levels at the same time as TcB measured	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 178) *Forehead* r = 0.87, *P* < 0.001 *Cheek* r = 0.76, *P* < 0.001 *Sternum*	No exclusion criterion Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Ethnicity Chinese (100%) Exclusion: not defined Prevalence of TSB > 222 micromol/litre = 19.6% (35/178 – site forehead)		r = 0.78, *P* < 0.001 *For all other sites* r from 0.47 to 0.76 Diagnostic accuracy of TcB (threshold value > 16 relectance units) for detecting TSB > 222 micromol/litre Sensitivity: 19/21 (90.5%) Specificity: 141/157 (89.8%) PPV: 19/35 (54.3%) NPV: 141/143 (98.6%)	
Maisels MJ; Year: 2004 Country: USA [71]	Study Type: Diagnostic study Evidence Level: II	Convenience sample of newborn babies ≥ 35 weeks in the well-baby nursery of 3 hospitals. *n* = 849 Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity white = 59.2% black = 29.8% other = 10.9% Prevalence of TSB > 257 micromol/litre = 3.3% (28/849) Exclusion: babies who had received phototherapy	TcB using Minolta JM-103 from the mid-sternum Triplicate measurements made in two hospitals while only single made in the third, but single TcB measurement taken for each baby for data analysis. Reference standard: Laboratory TSB levels within 1 hour of TcB measurement Area under ROC curve (AROC) calculated for detecting TSB > 170, 222 and 255 micromol/litre	Correlation of TcB levels with lab TSB levels and area under ROC curve (Pearson correlation coefficient, AROC for TSB > 222 micromol/litre) *All infants (n = 849)* r = 0.91, *P* < 0.001 AROC = 0.96 *White infants (n = 503)* r = 0.95, *P* < 0.001 AROC = 0.96 *Black infants (n = 253)* r = 0.82, *P* < 0.001 AROC = 0.97 *Other infants (n = 93)* r = 0.92, *P* < 0.001 AROC = 0.96 % of infants with difference between TSB & TcB levels of > 34 micromol/litre (overestimation by TcB) *Difference 34 to 50 micromol/litre* White – 4.0% Black – 24.1% Others – 5.4% *Difference 51 to 67 micromol/litre* White – 2.0% Black – 10.7% Others – 2.2%	No exclusion criterion Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN for different thresholds

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				Difference > 68 micromol/litre White – 0% Black – 6.7% Others – 1.1%	
Schmidt ET *et al.*; Year: 2009 Country: USA [73]	Study Type: Diagnostic study Evidence Level: II	Convenience sample of newborn babies ≤ 34 weeks in a NICU of 1 hospital. *n* = 90 Range of BW: 370 – 2989 g Range GA: 24 – 34 weeks Gender: Males = 56.7% Ethnicity white = 11.1% black = 18.9% hispanic = 70.0% Exclusion: Hydrops fetalis Severe haemolytic disease Non-viable Had receive or were receiving phototherapy or an exchange transfusion	TcB using Minolta JM-103 from the sternum, and included a single determination and a device – calculated mean of 5 determinations TCB was carried out within 45 minutes of TSB./ Reference standard: Laboratory TSB levels Sensitivity and specific of TCB > 68, 103, 137 micromol/litre	Correlation of TcB levels with lab TSB levels *All groups* *R = 0.88, P < 0.001* *Group 1 GA 24 – 28 weeks* r = 0.92 *Group 2 GA 29 – 31 weeks* r = 0.90 *Group 3 GA 32 –34 weeks* r = 0.79 Bland-Altman analysis for mean difference between TCB and TSB *Group 1 GA 24 – 28 weeks* -19 ± 32 micromol/l *Group 2 GA 29 – 31 weeks* -14 ± 22 micromol/litre *Group 3 GA 32 –34 weeks* -17 ± 27 micromol/litre	Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified
Engle WD; Year: 2005 Country: USA [72]	Study Type: Diagnostic study Evidence Level: II	Term and near term neonates who had been discharged from the hospital and evaluated during first week postnatally in a follow-up centre. *n* = 121 median BW: 3280 g – range 2265 to 4590 median GA: 40 weeks – range 35 to 41 median age at TSB: 91 hours – range 51 to 166 Gender: Males = 56.2%) Ethnicity	TcB using Minolta JM-103 from the sternum – single measurements taken. Reference standard: Laboratory TSB levels within 30 minutes of TcB measurement Diagnostic accuracy of TcB (various thresholds) calculated for detecting TSB > 255, > 272, > 290 and > 306 micromol/litre	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 121) r = 0.77, *P* < 0.001 Bland Altman analysis for difference between TSB and TcB MD = 27 micromol/litre Diagnostic accuracy of TcB (threshold value > 205 micromol/litre for detecting TSB > 255 micromol/litre	Exclusion criterion not defined Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Hispanic = 92% Black = 3% Asian = 3% White = 2% Prevalence of TSB > 255 micromol/litre = 47% (57/121) Exclusion: not defined		Sensitivity: 52/57 (91.2%) Specificity: 34/64 (53.1%) PPV: 52/82 (63.4%) NPV: 34/39 (87.2%)	
Sanpavat S; Year: 2004 Country: Thailand 74	Study Type: Diagnostic study Evidence Level: II	Term and near term clinically healthy neonates ≥ 36 weeks with visible jaundice which necessitated TSB determination. *n* = 388 mean BW 3117 ± 425 g mean GA: Not reported Postnatal age: range 11 to 216 hours Gender: Males = 57.5% Ethnicity Not reported Prevalence of TSB > 255 micromol/litre = 2.8% (13/460) Exclusion: babies receiving phototherapy or already received exchange transfusion	TcB using Minolta JM-103 from the forehead Mean of three measurements taken for data analysis. Reference standard: Laboratory TSB levels within 10–15 minutes of TcB measurement Diagnostic accuracy of TcB (various thresholds) calculated for detecting TSB > 170, > 204, > 222 and > 255 micromol/litre	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 460 observations) r = 0.80, *P* < 0.001 Bland Altman analysis for difference between TSB and TcB MD = 12 micromol/litre (95% CI 9.4 to 14.5) SD = 27.4micromol/litre Diagnostic accuracy of TcB (threshold value > 205 micromol/litre) for detecting TSB > 255 micromol/litre Sensitivity: 13/14 (92.9%) Specificity: 373/446 (83.6$) PPV: 13/86 (15.1%) NPV: 373/374 (99.7%)	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified
Sanpavat S; Year: 2007 Country: Thailand 75	Study Type: Diagnostic study Evidence Level: II	Clinically healthy preterm babies with BW > 1000 g and GA < 36 weeks with visible jaundice which necessitated TSB determination. *n* = 196 mean BW 1887 ± 344.4 g mean GA 33.2 ± 1.7 weeks, postnatal age: 108 ± 77 hours Gender: Males = 55% Ethnicity Not reported	TcB using Minolta JM-103 from the forehead Mean of three measurements taken for data analysis. Reference standard: Laboratory TSB levels within 1 hour of TcB measurement Percentage of TcB readings which overestimated (TcB > 10% of TSB) or underestimated (TcB < 10% of TSB)	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 249 observations) r = 0.79, *P* < 0.0001 Bland Altman analysis for difference between TSB and TcB MD = -5.0 micromol/litre (95% CI -1.7 to -8.5) SD = 25.5 micromol/litre Comparison of TcB readings with TSB levels at different postnatal ages (*n* = 249)	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Total paired (TcB-TSB) observations = 249 Exclusion: babies receiving phototherapy or already received exchange transfusion		*Day 1–2 (n = 67)* Overestimate = 47.8% Underestimate = 14.9% *Day 3–4 (n = 103)* Overestimate = 34.0% Underestimate = 13.6% *Day 5–7 (n = 45)* Overestimate = 20.0% Underestimate = 28.9% *> 7 day (n = 34)* Overestimate = 17.6% Underestimate = 35.3%	
Chang YH; Year: 2006 Country: Taiwan [76]	Study Type: Diagnostic study Evidence Level: II	Healthy term and near term babies born in a tertiary hospital. *n* = 447 mean BW 3185 ± 399.9 g mean GA 38.6 ± 1.3 weeks Postnatal age: Not reported Gender: Males = 51.2% Prevalence of TSB > 255 micromol/litre = 15% (67/447) Exclusion: not defined	TcB using Minolta JM-103 Three measurements made from the forehead, right and left side of the anterior chest wall, and their mean taken for data analysis. Reference standard: Laboratory TSB levels within 1 hour of TcB measurement Diagnostic accuracy calculated for detecting TSB > 255 micromol/litre	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 447) r = 0.83, *P* < 0.0001 Bland Altman analysis for difference between TSB and TcB MD = -17 micromol/litre (95% CI 15.3 to 20.4) SD = 27.2micromol/litre Diagnostic accuracy of TcB (threshold value > 200 micromol/litre) for detecting TSB > 255 micromol/litre Sensitivity: 53/67 (79.1%) Specificity: 301/380 (79.2%) PPV: 53/132 (40.1%) NPV: 301/315 (95.6%)	No exclusion criterion Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified
Rubaltelli FF; Year: 2001 Country: Europe (multicentre study in UK, Germany,	Study Type: Diagnostic study Evidence Level: Ib	Term and preterm neonates who underwent TSB tests as part of normal care at 6 European Hospitals. *n* = 210 with 35 babies from each hospital BW: < 2500 g = 16.3%	TcB using BiliChek from the forehead and sternum – single measurement taken from each site. Reference standard: Laboratory TSB levels within 30 minutes of TcB measurement	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 210) *Forehead* r = 0.87, *P* < 0.001	Unselected population but exclusion criterion not defined Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
France, Italy, Switzerland) [77]		GA: > 36 week = 80.2% Postnatal age: < 48 hours = 16.3% Gender: Not reported Ethnicity White = 66.7% Asian = 14.8% Hispanic = 6.7% Other = 11.9% Exclusion: not defined	Blood sample also collected for TSB estimation using HPLC-B technique at the same time Diagnostic accuracy of TcB (various thresholds) estimated at various thresholds and plotted on ROC curve.	*Sternum* r = 0.85, *P* < 0.001 Correlation of lab TSB levels with TSB levels using HPLC-B (Pearson correlation coefficient, *n* = 210) r = 0.93, *P* < 0.001 Bland Altman analysis for difference between lab TSB and TcB *Forehead* MD = +2.4 micromol/litre (95% CI -2.4 to +7.1) SD = 35.4 micromol/litre *Sternum* MD = -14.8 micromol/litre (95% CI -19.9 to +9.5) SD = 38.4 micromol/litre Diagnostic accuracy of TcB on forehead (threshold 187 micromol/litre) for detecting TSB > 222 micromol/litre by HLPC-B Sensitivity: 93% Specificity: 73% Diagnostic accuracy of TcB (threshold 238 micromol/litre) for detecting TSB > 290 micromol/litre by HLPC-B Sensitivity: 90% Specificity: 87%	
Boo NY; Year: 2007 Country: Malaysia [78]	Study Type: Diagnostic study Evidence Level: Ib	Healthy term Malaysian babies with hyperbilirubinaemia *n* = 345 mean BW: 3056 ± 487 g, median GA 38 weeks postnatal age: range 9 – 388 Gender: Males = 60% Ethnicity Malays = 63.8%	TcB using BiliChek from the forehead and midpoint of sternum – number of measurements from each site not specified Reference standard: Laboratory TSB levels within 30 minutes of TcB measurement Diagnostic accuracy of TcB (various thresholds) calculated for	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 345) *Forehead* All babies r = 0.80, *P* < 0.0001 Malays: r = 0.79, *P* < 0.0001 Chinese: r = 0.84, *P* < 0.0001 Indians: r = 0.83, *P* < 0.0001	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes Data not given for the mean difference and SD from Bland Altman analysis for TSB – TcB

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		Chinese = 30.7% Indians = 5.5%, Prevalence of TSB > 300 micromol/litre = 27.5% (95/345) Exclusion: infants who had received phototherapy or exchange transfusion, congenital anomalies, severely ill, foreigners, those with conjugated hyperbilirubinaemia.	detecting TSB > 250, > 280, and > 300 micromol/litre	*Sternum* All babies r = 0.86, $P < 0.0001$ Malays: r = 0.86, $P < 0.0001$ Chinese: r = 0.86, $P < 0.0001$ Indians: r = 0.94, $P < 0.0001$ Correlation of TcB levels with lab TSB levels depending on the time of measurement (Pearson correlation coefficient, 79% of infants with TSB > 300 had measurement at > 80 hours) *At ≤ 80 hours* r = 0.85, $P < 0.001$ *At > 80 hours* r = 0.71, $P < 0.001$ Diagnostic accuracy of TcB for detecting TSB > 300 micromol/litre *Forehead (threshold 250 micromol/litre)* Sensitivity: 100% Specificity: 39.2% *Forehead (threshold 260 micromol/litre)* Sensitivity: 75.8% Specificity: 84.8% *Sternum (threshold 200 micromol/litre)* Sensitivity: 100% Specificity: 33.6% *Sternum (threshold 280 micromol/litre)* Sensitivity: 92.6% Specificity: 84%	
Ebbesen F; Year: 2002 Country: Denmark [45]	Study Type: Diagnostic study Evidence Level: III	All newborns more than 24 hours old who for clinical reasons had their plasma bilirubin determination during the day, except at weekends. Group 1: Both preterm infants < 35 weeks and sick term and near-term infants in the NICU	TcB measurement using BiliChek from forehead, sternum, knee and the foot – mean of 5 measurements from each site taken for data analysis. Reference standard: Laboratory TSB levels taken concurrently with	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, $n = 210$) **Group 1:** *Forehead* r = 0.88, p > 0.05 *Sternum*	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified Data not given for the mean difference and SD from Bland

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
		n = 261 mean BW 2521 g - range 680 to 4645 g, mean GA 34.6 weeks - range 25 to 43 weeks postnatal age at 1st TcB: 98.4 - range 48 – 840 Gender: Males = 60.1% Ethnicity: Non-northern European descent = 9% <u>Group 2:</u> Healthy term and near-term infants with GA ≥ 35 weeks in the maternity ward *n* = 227 mean BW 3362 g - ange 2170 to 5000 g mean GA 38.6 weeks - range 35 to 43 weeks postnatal age at 1st TcB: 74.4 - range 48 – 360 Gender: Males = 55.5% Ethnicity: Non-northern European descent = 7% Exclusion: babies already receiving phototherapy or who received phototherapy 6 hours before TSB measurement, with skin infection, purpura, bruising	TcB measurement Diagnostic accuracy of TcB from forehead (threshold ≥ 0.70 of phototherapy limit) estimated for predicting TSB levels ≥ phototherapy limits as suggested by the Danish Pediatric Society	r = 0.82, *P* < 0.001 *Knee* r = 0.77, *P* < 0.001 *Foot* r = 0.51, *P* < 0.001 On comparing correlation coefficient of forehead with that for sternum, knee and foot, *P* < 0.001 for each of the comparison **Group 2:** *Forehead* r = 0.87, p > 0.05 *Sternum* r = 0.90, *P* < 0.05 *Knee* r = 0.83, *P* < 0.05 *Foot* r = 0.67, *P* < 0.001 On comparing correlation coefficient of forehead with that for sternum, knee and foot, *P* < 0.05 for comparison with knee and foot only <u>Diagnostic accuracy of TcB (threshold value ≥ 0.70 times the phototherapy limit) from forehead in detecting TSB > phototherapy limit</u> **Group 1 (*n* = 504 observations):** Sensitivity: 108/109 (99.1%) Specificity: 177/395 (44.8%) PPV: 108/326 (33.1%) NPV: 177/178 (99.4%) **Group 2 (*n* = 317 observations):** Sensitivity: 3/3 (100%) Specificity: 254/314 (80.9%) PPV: 3/63 (4.8%) NPV: 254/254 (100%)	Altman analysis for TSB - TcB
Samanta S; Year: 2004 Country: UK	Study Type: Diagnostic study Evidence Level: II	All babies > 33 weeks in the postnatal ward of a regional teaching hospital who were due to have blood taken for TSB estimation *n* = 300	TcB using BiliChek (site not specified) – single measurement taken. <u>Reference standard:</u> Laboratory TSB levels taken concurrently with	<u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 300)</u> r = 0.77, *P* < 0.0001	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
[44]		median BW 3295 g – range 1972 to 4720 median GA 39 weeks – range 33 to 42 median postnatal age: 72 hours – range 24 to 264 Gender: Males = 50% Prevalence of TSB > 250 micromol/litre = 55/300 (18.3%) Exclusion: babies who had previously received phototherapy	TcB measurement Diagnostic accuracy of TcB (various thresholds) estimated by plotting ROC curve.	Bland Altman analysis for difference between lab TSB and TcB MD = -10.6 micromol/litre (95% CI -80.0 to +60.0) SD = Not reported Diagnostic accuracy of TcB (threshold value > 195 micromol/litre) for detecting TSB > 250 micromol/litre Sensitivity: 50/55 (90.9%) Specificity: 162/245 (66.1%) PPV: 50/133 (37.6%) NPV: 162/167 (97%)	
De Luca D; Year: 2007 Country: Italy [79]	Study Type: Diagnostic study Evidence Level: Ib	Preterm babies with GA between 30–36 weeks admitted in the neonatal sub-intensive unit of tertiary hospital. *n* = 340 mean BW 2145 ± 518 g mean GA 33.5 ± 1.9 weeks mean postnatal age: Not reported Gender: Males = 48.2% Exclusion: babies receiving phototherapy or exchange transfusion, asphyxia (Apgar score < 7 at 5 min), Rh or major ABO incompatibility, conjugated bilirubin > 17.1 micromol/litre, congenital malformation, liver disease.	TcB using BiliChek from the forehead – mean of 5 measurements taken for data analysis. Reference standard: Laboratory TSB levels within 10 minutes of TcB measurement Diagnostic accuracy of TcB estimated by plotting ROC curve and results given for best thresholds	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, *n* = 210) r = 0.79, *P* < 0.001 Bland Altman analysis for difference between mean lab TSB and mean TcB % with difference > 8.55 micromol/litre = 61.5% (209/340) MD = -18.8 micromol/litre SD = 34.2 micromol/litre Diagnostic accuracy of TcB (threshold value > 111 micromol/litre) for detecting TSB > 171 micromol/litre Sensitivity: 100% Specificity: 40% Diagnostic accuracy of TcB (threshold value > 171 micromol/litre) for detecting TSB > 205 micromol/litre Sensitivity: 100% Specificity: 72%	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes but only investigator Data not extractable for calculating values of TP, FP, TN & FN for detecting hyperbilirubinaemia
Karon B; Year: 2008 Country: USA	Study Type: Diagnostic study Evidence Level: III	Babies in a well-infant nursery were eligible if a serum bilirubin was ordered to assess risk of hyperbilirubinaemia. *n* = 177	Test: TcB reading from the forehead using BiliChek – mean of 5 measurements taken for data analysis	Correlation of TcB levels with TSB levels (Pearson correlation coefficient, *n* = 177) *Forehead* Diazo: $r^2 = 0.65$	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
[81]		Mean BW: Not reported Median GA: 39.9 weeks (32.7 to 41.4) Gender: Not reported Ethnicity: White = 82.5% Black = 1.7% Hispanic = 5.1% Asian = 10.7% Exclusion: None	Reference standard: 1.Laboratory TSB diazo method measured on blood collected within 30 minutes as TcB. 2. Laboratory TSB VITROS method measured on blood collected within 30 minutes as TcB.	VITROS: $r^2 = 0.66$ Diagnostic accuracy of TcB (threshold value >75 centile on Bhutani nomogram **Diazo:** Sensitivity: 56/57 (98.2%) Specificity: 48/120 (40%) PPV: 56/127 (43.7%) NPV: 48/49 (98%) **Vitros:** Sensitivity: 63/67 (94%) Specificity: 35/64 (54.7%) PPV: 63/92 (68.5%) NPV: 35/39 (89.7%)	Blinding – No
Slusher TM; Year: 2004 Country: Nigeria [80]	Study Type: Diagnostic study Evidence Level: II	Clinically jaundiced term and preterm babies with age < 14 days admitted in two hospitals *n* = 127 mean BW: 2.72 ± 0.62 kg mean GA: Not reported Gender: Males = 60%, Pigmentation – dark pigmentation 10% medium pigmentation = 36% light pigmentation = 54% Hospital A: 500-bed tertiary teaching hospital (*n* = 98) Hospital B: 168-bed hospital located in a rural village (*n* = 29) Exclusion: not defined	TcB using BiliChek from the forehead and before starting phototherapy Skin pigmentation determined through visual observation Reference standard: Laboratory TSB levels obtained simultaneously with TcB measurement	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient) *Both hospital together* r = 0.92 *Babies with TSB ≥ 205 micromol/litre* r = 0.84 *Babies with TSB < 205 micromol/litre* r = 0.67 *Based on pigmentation* Light: r = 0.91 Medium: r = 0.94 Dark: r = 0.87 Bland Altman analysis for difference between mean TcB and mean lab TSB values *Both hospitals together* MD = 8.5 micromol/litre (95% CI -3.4 to 21.4 micromol/litre SD = 129.2 micromol/litre *Babies with TSB ≥ 205 micromol/litre* MD = --21.4 micromol/litre (95% CI -40.8 to 0.0 micromol/litre) SD = 146.2 micromol/litre	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes but only investigator Data not extractable for calculating values of TP, FP, TN & FN for detecting hyperbil

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
				Babies with TSB < 205 micromol/litre MD = 35.7 micromol/litre (95% CI 25.5 to 45.9 micromol/litre) SD = 129.2 micromol/litre *Based on pigmentation* **Light:** MD = 18.4 micromol/litre, SD = 91.8 micromol/litre **Medium:** MD = 13.6 micromol/litre, SD = 132.6 micromol/litre **Dark:** MD = -3.4 micromol/litre, SD = 197.2 micromol/litre	

What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia?

Evidence Table – Assessment Tests
TSB < 255micromol/litre

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Werblinska B Year: 1981 Country: Nigeria Ref ID: [83]	Study type: Case–control study Evidence level: 2⁻	Diagnosis: Jaundice Criteria: TSB ≥ 171 micromol/litre Setting: Hospital Sample Size: 40 GA: Not reported Mean BW: Not reported. Gender M/F: 19/21 Ethnicity: Not reported Exclusion: None	Mean bilirubin levels TSB: 253 micromol/litre ABO incompatibility: 8/40 (20%) Rh incompatibility: 3/40 (7.5%) G6PD deficiency: 13/40 (32.5%) P value < 0.001 Infection: 34/40 (85%) P value < 0.001 Idiopathic: 3/40 (7.5)	Small study, Incomplete data from three subject so not included in analysis All 38controls (14 M & 24 F) were delivered by Caesarean Section due to maternal complication
Author: Azubuike J Year: 1979 Country: Nigeria Ref ID: [82]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 170 micromol/litre Setting: Hospital Sample Size: 424 GA: Not reported Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Days 0 – 10 Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 178/424 (41.2%) Rh incompatibility:2/424 (0.5%) G6PD deficiency: 229/424 (54%) Infection: 60/424 (14.1%) Idiopathic: 39/424 (9.2%)	
Author: Guaran R Year: 1992 Country: Australia Ref ID: [89]	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 154 micromol/litre Setting: Hospital Sample Size: 10944 GA: Not reported. Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None (4,815 Not investigated)	Mean bilirubin levels TSB: Not reported ABO incompatibility: 601/6129 (9.8%) Rh incompatibility:193/6129 (3.1%) G6PD deficiency: 51/6129 (0.8%) Infection: 198/6129 (3.2%) **Exchange Transfusion (*n* = 248)** ABO incompatibility: 58/248 (23.4%)	4815 cases had no investigations Preterm birth is reported to be the most common cause 2226/61290 (36.3%)

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
			Rh incompatibility: 108/248 (43.5%) G6PD deficiency: 2/248 (0.8%) Infection: 2/248 (0.8%)	
Author: Sodeinde O Year: 1995 Country: Nigeria Ref ID: [85]	Study type: Case control study Evidence level: 2⁻	Diagnosis: Jaundice Criteria: TSB ≥ 205 micromol/litre Setting: Hospital Sample Size: 327 Mean GA: Not reported. 87 (26.5%) were preterm < 37 weeks Mean BW: 2.73 ± 0.74 kg Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 40/150 (26.7%) Rh incompatibility: 3/150 (2.0%) G6PD deficiency: 109/327 (33.3%) (P value < 0.0087) Infection: 38/217 (17.5%) Idiopathic: Not reported	Not all subjects tested for ABO incompatibility or infection
Author: Yeung C Year: 1973 Country: China Ref ID: [90]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 171 micromol/litre Setting: Hospital Sample Size: 1811 Mean GA: Not reported Mean BW: Not reported. 65 (3.6%) were preterm < 38 weeks Gender M/F: 1054/755 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 10 Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 414/1811(22.8%) Rh incompatibility: Not reported G6PD deficiency: 241/1811 (13.3) Infection: Not reported Idiopathic: Not reported **Exchange transfusion (*n* = 581)** ABO incompatibility: 157/581 (27.0%) G6PD deficiency: 13/581 (22.4%) Infection: Not reported Idiopathic: Not reported **Kernicterus (*n* = 156)** ABO incompatibility: 51/156 (32.7%)	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
			G6PD deficiency: 58/156 (37.2%) Infection: Not reported Idiopathic: Not reported	
Author: Bhandari A Year: 1982 Country: India Ref ID: [86]	Study type: Case control study Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 171 micromol/litre Setting: Hospital Sample Size: 100 Mean GA: Not reported Mean BW: Not reported Gender M/F: 58/42 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 5 Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 10/100 (10.0%) Rh incompatibility: 20/100 (20.0%) G6PD deficiency: 4/100 (4.0%) Infection: Not reported Idiopathic: Not reported	
Author: Bajpai P Year: 1971 Country: India Ref ID: [87]	Study type: Case control study Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 205 micromol/litre Setting: Hospital Sample Size: 50 Mean GA: Not reported Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 8/50 (16.0%) Rh incompatibility: 1/50 (2.0%) G6PD deficiency: 2/50 (4.0%) Infection: 7/50 (14.0%) Idiopathic: 19/50 (38%)	
Author: Arif K Year: 1999 Country: Pakistan Ref ID: [88]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice *Criteria:* None Setting: Hospital Sample Size: 869 Mean GA: 37.2 ± 2.8 weeks Mean BW: 27574 ± 735 g Gender M/F: 484/385 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 221 ± 42 micromol/litre ABO incompatibility: 56/869 (6.4%) Rh incompatibility: 57/869 (6.6%) G6PD deficiency: 20/869 (2.3%) Infection: 165/869 (19.0%) **Exchange transfusion** ABO incompatibility: 4/27 (14.8%)	Retrospective study

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
			Rh incompatibility: 7/27 (25.9%) G6PD deficiency: 2/27 (7.4%) Infection: 6/27 (22.2%)	
Author: Singhal P Year: 1992 Country: India Ref ID: [84]	Study type: Case series Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: TsB > 205 micromol/litre Setting: Hospital Sample Size: 454 Mean GA: Not reported Mean BW: Not reported Gender M/F: 258/196 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 65/454 (14.3%) Rh incompatibility: 37/454 (8.1%) G6PD deficiency: 23/454 (5.1%) **Exchange transfusion** ABO incompatibility: 18/66 (27.4%) Rh incompatibility: 21/66 (31.8%) G6PD deficiency: 11/66 (16.7%)	From 7680 live births 454 (5.9%) has TsB > 205 micromol/litre

Evidence Table – Assessment Tests
TSB 255 – 399 micromol/litre

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Biddulph J Year: 1974 Country: Papua New Guinea Ref ID: [95]	Study type: Consecutive case-series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 256 micromol/litre Setting: *Hospital* Sample Size: 50 Mean GA: Not reported Mean BW: Not reported Gender M/F:29/21 Ethnicity: Not reported Breastfeeding: 50 (100%) Onset of Jaundice: Day 1 - 17 Duration of jaundice: 26 (52%) < 1 week Exclusion: None	Mean bilirubin levels TSB: Not reported Incidence of ABO incompatibility: 12/50 (24%) Rh incompatibility: Not reported Incidence of G6PD deficiency: 11/50 (22%) Incidence of sepsis: 8/50 (16%) Idiopathic: 19/50 (38%) **Exchange transfusion (*n* = 11)** Incidence of ABO incompatibility: 4/11 (36.4%) Incidence of G6PD deficiency: 3/11 (27.3%) Incidence of sepsis: 2/11 (18.2%) Idiopathic: 2/11 (18.2%)	Small study
Author: Seidman D Year: 1995 Country: Israel Ref ID: [93]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 308 micromol/litre Setting: Hospital Sample Size: 21 Mean GA: 39.3 ± 1.2 weeks Mean BW: 3206 ± 340 gms Gender M/F: 15/6 Ethnicity: 9 Jew Askenazi, 3 Kurdish, 2 Iraqi and others. Breastfeeding: 20/21 Onset of Jaundice: Day 0 - 10 Exclusion: None	Mean bilirubin levels TSB: 335 ± 43 micromol/litre ABO incompatibility: 0/21 (0%) Rh incompatibility: 0/21 (0%) G6PD deficiency: 2/21 (9.5%) Infection: 0/21 (0%) Idiopathic: Not reported	Small study Subjects had received phototherapy and were discharged with TSB > 171 micromol/litre so could qualify as persistent jaundice
Author: Effiong C Year: 1975 Country: Nigeria Ref ID: [94]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 256 micromol/litre Setting: Hospital Sample Size: 125 Mean GA: Not reported Mean BW: Not reported Gender M/F: 70/55	Mean bilirubin levels TSB: Not reported ABO incompatibility: 26/125 (20.6%) Rh incompatibility: 2/125 (1.6%) G6PD deficiency:	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
		Ethnicity: Not reported Breastfeeding: Onset of Jaundice: Days 0 – 7 Duration of jaundice: Exclusion: None	49/125 (39.2%) Infection: 1/125 (0.8%) Idiopathic: 35/125 (28%) **Exchange Transfusion (*n* = 53)** ABO incompatibility: 15/53 (20.6%) Rh incompatibility:1/53 (1.9%) G6PD deficiency: 21/53 (39.6%) Infection: 0/53 (0%) Idiopathic: 11/53 (20.7%)	
Author: Ho K Year: 1991 Country: Singapore Ref ID: [96]	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 256 micromol/litre Setting: Hospital Sample Size: 270 Mean GA: Not reported Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 73/270 (27.0%) Rh incompatibility:1/270 (0.4%) G6PD deficiency: 18/270 (6.7%) Infection: Not reported Idiopathic: Not reported **Exchange Transfusion (*n* = 46)** ABO incompatibility: 17/46 (37.0%) Rh incompatibility: 1/46 (2.2%) G6PD deficiency: 2/46 (4.3%) Infection: 8/46 (17.4%) Idiopathic: 6/46(13.0%)	Authors report a drop in number of G6PD cases requiring exchange transfusion on new guidelines that specified that G6PD be screened for at birth and deficient babies be kept in hospital for a minimum of 2 weeks
Author: Ahmed H Year: 1995 Country: Nigeria Ref ID: [92]	Study type: Case control study Evidence level: 2$^-$	Diagnosis: Jaundice Criteria: TSB ≥ 171 micromol/litre Setting: Hospital Sample Size: 102 Mean GA: Not reported Mean BW: Not reported	Mean bilirubin levels TSB: 312 micromol/litre ABO incompatibility: 24/102 (23.5%) Rh incompatibility: 0/102 (0%)	Incidence of infection higher in babies readmitted from home

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
		Gender M/F: 65/37 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	G6PD deficiency: 41/102 (41.2%) Infection: 57/102 (55.9%) Idiopathic: Not reported	
Author: Mamtani M Year: 2007 Country: India Ref ID: [91]	Study type: Cohort Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 256 micromol/litre if the age of the baby is ≤15 days Setting: Tertiary care Hospital Sample Size: 92 Mean GA: Not reported. 17 were Preterm Mean BW: Not reported: 35 were small for GA Gender M/F: 57/35 Ethnicity: Not reported Breastfeeding: 58 (63%) Onset of Jaundice: Day 0 - 15 Exclusion: None	Mean bilirubin levels TSB: 376 ± 85 micromol/litre ABO incompatibility: 14/92 (15.3%) Rh incompatibility:10/92 (10.9%) G6PD deficiency: 4/92 (4.3%) Infection: 18/92 (19.6%) Idiopathic: Not reported	
Author: Tay J Year: 1984 Country: Singapore Ref ID: [97]	Study type: Cohort Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 222 micromol/litre Setting: Hospital Sample Size: 181 Mean GA: Not reported. 15 were preterm Mean BW: Not reported. 25 were less than 2500gms Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 330 ± 51micromol/litre ABO incompatibility: 42/181 (23.2%) Rh incompatibility: 1/181 (0.6%) G6PD deficiency: 4/181 (2.2%) Infection: Not reported Idiopathic: Not reported **Kernicterus (*n* = 8)** ABO incompatibility: 4/8 (50.0%) Rh incompatibility: 1/8 (12,5) G6PD deficiency: 0/8 (0%) Infection: Not reported Idiopathic: Not reported	Those with G6PD deficiency kept in hospital for 21 days
Author: Chen W Year: 1981	Study type: Case series	Diagnosis: Jaundice Criteria: TSB ≥ 25 micromol/litre Setting: Hospital	Mean bilirubin levels TSB: 327 ± 72 micromol/litre	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Country: Taiwan Ref ID: [98]	Evidence level: 3	Sample Size: 196 Mean GA: Not reported. Mean BW: Not reported: 25 had low birthweight Gender M/F: Not reported Ethnicity: Chinese Breastfeeding: Not reported Onset of Jaundice: Day 0 - 15 Exclusion: None	ABO incompatibility: 61/196(31.1%) Rh incompatibility:1/196 (0.5%) G6PD deficiency: 43/196(21.9%) Infection: 10/196 (5.1%) Idiopathic: 53/196 (17.0%)	
Author: Atay E Year: 2006 Country: Turkey Ref ID: [99]	Study type: Case series Evidence level: 3	Diagnosis: Indirect hyperbilirubinaemia Criteria: None Setting: Hospital Sample Size: 624 Mean GA: Not reported. Mean BW: 3082 ± 530 g Gender M/F: 330/294 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: 6.57 ± 4.04 days Exclusion: None	Mean bilirubin levels TSB: 359 ± 70 micromol/litre ABO incompatibility: 171/624 (27.4%) Rh incompatibility:52/624 (8.3%) G6PD deficiency: 24/624 (3.8%) Infection: 36/624 (5.8%) Idiopathic: 312/624 (50.0%) **Kernicterus** ABO incompatibility: 2/6 (33.3%) Rh incompatibility: 1/6 (16.6%) G6PD deficiency: 1/6 (16.6%) Infection: 0/6 (0%) Idiopathic: 0/6 (0%)	
Author: Al-Omran A Year: 1999 Country: Saudi Arabia Ref ID: [102]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TsB > 256 micromol/litre Setting: Hospital Sample Size: 211 Mean GA: Not reported. Mean BW: Not reported Gender M/F: Not reported Ethnicity: Saudis (97%) Breastfeeding: Not reported Onset of Jaundice: Not reported	Mean bilirubin levels TSB: Not reported ABO incompatibility: 21/211 (9.9%) Rh incompatibility: 2/211 (0.9%) G6PD deficiency: 64/211 (30.3%) Infection: 4/211 (1.9%) Idiopathic: 108/211 (51.2%)	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
		Exclusion: None		
Author: Dawodu A Year: 1998 Country: UAE Ref ID: [101]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: Cockington Setting: Hospital Sample Size: 85 Mean GA: Not reported. Mean BW: Not reported Gender M/F: Not reported Ethnicity: 57 (67%) Arab 26 (30%) Asian Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 22/85 (25.9%) Rh incompatibility: 1/85 (1.2%) G6PD deficiency: 8/85 (9.4%)	
Author: Koosha A Year: 2007 Country: Iran Ref ID: [100]	Study type: Case series Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: ICD Setting: Hospital Sample Size: 376 Mean GA: Not reported. Mean BW: Not reported Gender M/F: 159/217 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 14/376 (3.7%) Rh incompatibility: 8/376 (2.1%) G6PD deficiency: 8/376 (2.1%) Infection: 59/376 (15.7%)	

Evidence Table – Assessment Tests
TSB >400 micromol/litre / or Exchange Transfusion

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Nkrumah F Year: 1973 Country: Ghana Ref ID: [104]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 342 micromol/litre Setting: Hospital/Paediatric outpatient Sample Size: 35 Mean GA: Not reported Mean BW: Not reported Gender M/F: 26/9 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 8 Duration of jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 551 ± 182 micromol/litre Incidence of ABO incompatibility: 14/35 (40%) Rh incompatibility: 1/35 (2.9%) Incidence of G6PD deficiency: 13/35 (37.1%) Incidence of sepsis: Not reported Idiopathic: 10/35 (28.6%) **Kernicterus** Incidence of ABO incompatibility: 6/17 (35.3%) Rh incompatibility: 1/17 (5.9%) Incidence of G6PD deficiency: 8/17 (47.0%) Incidence of sepsis: Not reported Idiopathic: 3/17 (17.6%)	Small study
Author: Manning D Year: 2007 Country: UK & Republic of Ireland Ref ID: [106]	Study type: Survey Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 513 micromol/litre Setting: Not reported Sample Size: 106 Mean GA: 38.2 ± 1.7 weeks Mean BW: 3170 ± 480 gms Gender M/F: 64/42 Ethnicity: White 52 (48.1%), Asian 18 (16.7%), Black 11 (10.1%), Mixed 11 (10.1%) Breastfeeding: 87 (80.5%) Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 581 micromol/litre (510–802) ABO incompatibility: 33/106 (31.1%) Rh incompatibility:6/106 (5.7%) G6PD deficiency: 5/106 (4.7%) Infection: 4/106 (3.8%) Idiopathic: 29/106 (27.3%) **Kernicterus Cases (*n* = 14)** ABO incompatibility: 3/14 (21.4%) Rh incompatibility: 1/14 (7.1%) G6PD deficiency: 3/14 (21.4%)	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
			Infection: 2/14 (14.3%) Idiopathic: 1/14 (7.1%)	
Author: Katar S Year: 2008 Country: Turkey Ref ID: [107]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB > 342 micromol/litre at 24–48 hours or ≥ 427 micromol/litre) at > 48 hours after birth Setting: Neonatal clinic Sample Size: 21 Mean GA: Not reported. All were term babies Mean BW: 2943 ± 533 gms Gender M/F: 15/6 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 598 ± 185 micromol/litre ABO incompatibility: 4/21 (19.5) Rh incompatibility: 4/21 (19.5%) G6PD deficiency: 4/21 (19.5%) Infection: Not reported Idiopathic: 10/21 (47.5%)	Small study
Author: Dawodu A Year: 1984 Country: Nigeria Ref ID: [105]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 205 micromol/litre Setting: Hospital Sample Size: 109 Mean GA: Not reported Mean BW: Not reported Gender M/F: 77/32 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 616 ± 197 micromol/litre : ABO incompatibility: 15/109 (13.8%) Rh incompatibility: Not reported G6PD deficiency: 67/109 (61.5%) Infection: 24/109 (22.0%) Idiopathic: 13/109 (11.9%)	Only subjects with indication for infection were tested
Author: Tiker F Year: 2006 Country: Turkey Ref ID: [108]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 428 micromol/litre Setting: Neonatal Intensive Care Unit Sample Size: 93 Mean GA: 38.57 weeks Mean BW: Not reported Gender M/F: 51/42 Ethnicity: Not reported Breastfeeding: 93/93 Onset of Jaundice: Day 0 - 30 Exclusion: None	Mean bilirubin levels TSB: 515 ± 97 micromol/litre ABO incompatibility: 7/93 (7.5%) Rh incompatibility: 7/93 (7.5%) G6PD deficiency: 2/39 (5.1%) Infection: 7/93 (7.5%) Idiopathic: 61/93 (615.6%) **Kernicterus (*n* = 6)** ABO incompatibility: 1/6 (16.7%)	Not all babies tested for G6PD levels

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
			Rh incompatibility: 0/6 (0%) G6PD deficiency: 1/6 (16.7%) Infection: 3/6 (50.0%) Idiopathic: 1/6 (16.7%)	
Author: Sgro M Year: 2006 Country: Canada Ref ID: [111]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 427 micromol/litre) Setting: Hospital Sample Size: 258 Mean GA: 38.5 ± 1.4 weeks Mean BW: 3360 ± 489 gms Gender M/F: 162/96 Ethnicity: White 55.4%, Asian 24.3%, Aboriginal 7.6%, black 5.2%, Middle Eastern 4.0%, Latin American 2.8% Breastfeeding: Not reported Onset of Jaundice: Day 0 - 60 Exclusion: None	Mean bilirubin levels TSB: 464 ± 75 micromol/litre ABO incompatibility: 49/258 (18.9%) Rh incompatibility: Not reported Incidence of G6PD deficiency: 20/258 (7.7%) Infection: 3/258 (1.2%) Idiopathic: Unclear	
Author: Bjerre J Year: 2008 Country: Denmark Ref ID: [110]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 445 micromol/litre Setting: Hospital Sample Size: 113 GA (range): 35 – 42 weeks BW (range): 2380 - 4870gms Gender M/F: 69/44 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 28 Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 52/113 (46.0%) Rh incompatibility: 2/113 (0.2%) Incidence of G6PD deficiency: 1/113 (0.9%) Infection: Not reported Idiopathic: Unclear	
Author: Necheles T Year: 1976 Countries: United States & Greece Ref ID: [109]	Study type: *Case series* Evidence level: 3	Diagnosis: Severe jaundice requiring exchange transfusions Criteria: Not reported Setting: Hospital Sample Size: 75 GA: Not reported BW: Not reported Gender M/F: 69/44 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported	Mean bilirubin levels TSB: Not reported ABO incompatibility: 29/75 (38.7%) Rh incompatibility: 6/75 (8.0%) Incidence of G6PD deficiency: 14/75 (18.7%) **Kernicterus** ABO incompatibility: 1/6 (16.7%)	66 babies were in Greece and 9 were in the USA

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
		Exclusion: None	Rh incompatibility: 0/6 (0%) Incidence of G6PD deficiency: 3/6 (50.0%)	
Author: Narang A Year: 1997 Country: India Ref ID: [103]	Study type: Case series Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: Exchange transfusion Setting: Hospital Sample Size: 141 Mean GA: Not reported. Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 8/141 (5.7%) Rh incompatibility: 13/141 (9.2%) G6PD deficiency: 24/141 (17.2%) Infection: 34/141 (24.1%) Idiopathic: 50/141 (35.4%)	Demographic data reported for all babies who received PT/ET (Cockington charts) and data Not reported for those with serum bilirubin > 256 micromol/litre

Evidence Table – Assessment Tests
Kernicterus

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Maisels J Year: 1995 Country: USA Ref ID: [113]	Study type: Case series Evidence level: 3	Diagnosis: Kernicterus Criteria: Not reported Setting: Not reported Sample Size: 14 GA (range): 37 – 42 weeks BW (range): Not reported) Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: All Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: (Not reported) ABO incompatibility: 1/14 (7.1%) Rh incompatibility: 0/14 (0 %) Incidence of G6PD deficiency: 3/14 (21.4%) Infection: 2/14 (14.3%) Idiopathic: 6/14 (42.8%)	
Author: Bhutani V Year: 2006 Country: USA Ref ID: [20]	Study type: Case series Evidence level: 3	Diagnosis: Kernicterus Criteria: Not reported Setting: Hospital Sample Size: 125 GA (range): 35 – 42 weeks BW (range): 2015 – 4730 gms Gender M/F: Not reported Ethnicity: White (58.4%), Black (26.4%), Hispanic (8.8%) and Asian (6.4%) Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: Not reported Rh incompatibility: Not reported Incidence of G6PD deficiency: 26/125 (20.8%) Infection: Not reported Idiopathic: 44/125 (35.2%)	Demographc data reported for all cases on Kernicterus Register not just the sample used here
Author: Ogunlesi T Year: 2007 Country: Nigeria Ref ID: [112]	Study type: Case series Evidence level: 3	Diagnosis: Bilirubin Encephalopathy Criteria: severe jaundice and tone abnormalities, abnormal cry and abnormal movements Setting: Hospital Sample Size: 115 GA: 97 (84,3%) were term BW: ≥ 77 (69.9%) > 500 g Gender M/F: 88/27 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels (unconjugated) TSB: 348 ± 113 micromol/litre ABO incompatibility: 22/115 (19.2%) Rh incompatibility: 7/115 (6.1%) Incidence of G6PD deficiency: 40/115 (34.8%) Infection: 12/115 (10.4%)	Also 2 had mixed ABO/Rh incompatibilities 4 had mixed ABO incompatibility and septicaemia

Evidence Table – Additional Tests

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Hulzebos C Year: 2008 Country: USA Ref ID: [114]	Study type: Systematic review Evidence level: 1^{++}	Inclusion criteria Studies of Preterm babies with hyperbilirubinaemia that used the Bilirubin/Albumin ratio to predict BIND	6 studies included. Higher B/A ratio was associated with abnormal ABR in 2 studies, lower IQ at 6 years in one study and with Kernicterus in one study One study found no difference One study found that binding capacities (expressed a B/A molar ratio) were lower in babies with kernicterus	
Author: Malik G Year: 1986 Country: India Ref ID: [115]	Study type: Case-series Evidence level: 3	Diagnosis: Jaundice Criteria: Not reported Exclusion: Respiratory distress, Sepsis, Hypothermia, Hypoglycaemia, Postasphysial seizure, bleeding diathesis Setting: Special baby care unit Sample Size: 53 Gender M/F: Not reported Mean GA: 37.9 ± 2.2 weeks Mean BW: 2780 ± 620 g Ethnicity: Not reported	Mean TsB levels 227 ± 80 micromol/litre Mean free bilirubin 8.7 ± 5.6 nmol/l Mean Albumin levels 3.6. ± 0. g/dl Mean Bilirubin/Albumin ratio 3.7 Mean Molar B/A ratio 0.41 correlation between free bilirubin and B-A ratio 0.74 ($P < 0.001$)	
Author: Chan G Year: 1980 Country: Canada Ref ID: [116]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: Jaundice Exclusion: Not reported Setting: Neonatal Intensive Care Unit Sample Size: 46 (55 samples used) Gender M/F: Not reported	Mean TsB levels Not reported Mean free bilirubin Not reported Mean Albumin levels Not reported Mean B/A ratio Not reported correlation between free bilirubin and	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
		Mean GA: 36 ± 4 weeks Mean BW: 2453 ± 813 g Ethnicity: Not reported	Bilirubin/Albumin molar ratio r = 0.75, *P* < 0.001	
Author: De Carvalho W Year: 1992 Country: Brazil Ref ID: [117]	Study type: Case series Evidence level: 3	Diagnosis: Non-haemolytic jaundice Criteria: Mothers who received prenatal care and no previous history of lues and with negative serologic test for syphilis, Birthweight ≥ 2500 g, Negative direct Coombs test, Gestational age between 37 and 41 weeks, < 7 days old, no history of neonatal anoxia and Apgar ≥ 8 at 1 and 5 minutes, normal infants no administration of substances competing for albumin binding site, no phototherapy, exchange transfusion or human albumin Exclusion: Not reported Setting: Neonatal service Sample Size: Not reported Gender M/F: 25/18 Mean GA: Not reported Mean BW: Not reported Ethnicity: Not reported	Mean TsB levels Not reported Mean free bilirubin 11.5 ± 6.0 nmol/litre 0.0115 ± 0.006 micromol/litre Mean Albumin levels 3.33 ± 0.3 g/dl correlation between free bilirubin and indirect bilirubin 0.69 (*P* < 0.01)	Serum albumin levels not taken in 6 babies
Author: Newman T Year: 1991 Country: USA Ref ID: [118]	Study type: Retrospective case series Evidence level: 3	Diagnosis: Jaundice Criteria: Not reported Exclusion: None Setting: Hospital Sample Size: 149 (9 from Stanford) Gender M/F: Not reported Mean GA: Not reported Mean BW: Not reported Ethnicity: Not reported	Mean TsB levels Not reported Mean free bilirubin Not reported Mean Albumin levels Not reported Mean B/A ratio Not reported Direct Bilirubin Not reported Direct bilirubin levels were unexplained in 52% of cases while 24% were laboratory errors. The remainder were as follows; Isoimmunisation = 19 (12.7%) Sepsis or pneumonia = 5 (3.6%)	Abnormal direct bilirubin = direct bilirubin above 95th percentile in each centre (UCSF = ≥ 39micromol/litre, Stanford = ≥ 17 micromol/litre)

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
			Congestive Heart failure = 5 (3.6%) Multiple anomalies = 2 (1.3%) Pyloric Stenosis = 2 (1.3%) Extreme small for gestational age (possible Rubella) = 1(0.7%) Hypothyroid = 1(0.7%) Choledochal cyst = 1(0.7%) Slightly high aminotransferase levels (100 U/litre) = 3(2.0%) Sludge in gallbladder = 1(0.7%)	
Author: Newman T Year: 1990 Country: USA Ref ID: [119]	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: Birthweight > 2500 g, Hyperbilirubinaemia Exclusion: Low birthweight Setting: Hospital Sample Size: 447 Gender M/F: Not reported Mean GA: Not reported Mean BW: 3440 ± 485 g Ethnicity: Not reported	Routine hyperbilirubinaemia tests Direct Bilirubin Blood type, Complete blood count, Differential cell count, Reticulocyte count, Platelet count, Morph, Urinalysis Usefulness of tests Possible cause of hyperbilirubinaemia identified from history, physical exam or routine haematocrit done at 4 hours 145/447 (32.4%) Other diagnosis related to hyperbilirubinaemia no made due to routine hyperbil. investigations 13/447 (2.9%) No specific diagnosis related to hyperbilirubinaemia: 214/447 (47.8%) Diagnoses possibly from routine hyperbil investigations not accompanied by other diagnoses 58/447 (12.9%) Diagnoses possibly from routine hyperbil investigations accompanied by other diagnoses 17/447 (3.8%)	
Author: Tiker F Year: 2006 Country:	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Conjugated Hyperbilirubinaemia Criteria: Direct bilirubin > 15% of total TsB Elevation in biliary enzymes (gamma glutamyl transpeptidase (GGT), alkaline pjosphatse (ALP), asparttate	Mean age at presentation 240 hours Mean peak TsB levels 292 ± 193 micromol/litre	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Turkey Ref ID: [121]		transaminase (AST) or alanine transaminase (ALT) Exclusion: Not reported Setting: Neonatal Intensive Care Unit Sample Size: 42 Gender M/F: Not reported Mean GA: 37 weeks Mean BW: Not reported Ethnicity: Not reported	Mean peak conjugated bilirubin 130 ± 130 micromol/litre Diagnoses in conjugated jaundice Culture-proven sepsis: 14/42 (35.7%) Perinatal hypoxia-ischemia: 7/42 (16.7%) Blood group incompatibility: 5/42 (11.9%) Trisomy 21: 3/42 (7.1%) TPN-associated cholestasis (3/42 (7.1%) Neonatal hepatitis: 2/42 (4.8%) Metabolic liver disease: 1/42 (2.4%) Biliary atresia: 1/42 (2.4%) Portal venous thrombosis: 1/42 (2.4%) Unknown: 4/42 (9.5%)	
Author: Sarlik Y Year: 2003 Country: Turkey Ref ID: [120]	Study type: Case series Evidence level: 3	Diagnosis: Prolonged Jaundice Criteria: Jaundiced at day 14 Setting: Neonatal Intensive Care Unit Sample Size: 26 Mean GA: 38 weeks Mean BW: 3164 g Gender M/F: 15/11 Ethnicity: Not reported Breastfeeding: 96% Mean age jaundice recognised: 19 days: Exclusion: Preterm babies	Prevalence of prolonged jaundice/hyperbilirubinaemia 31/381 (8.1%) Median bilirubin levels TSB: 246 micromol/litre Blood group incompatibility: 7/26 (26.9%) Breast milk jaundice: 14/26 (53.8%) Possible Biliary Atresia : 1/26 (3.8%) referred to pediatric gastroenterology due to direct bilirubin Inadequate caloric intake: 4/26 (15.4%)	
Author: Hannam S Year: 2000 Country: UK Ref ID: [122]	Study type: Case series Evidence level: 3	Diagnosis: Prolonged Jaundice Criteria: jaundiced at day 14 Setting: Outpatient Sample Size: 154 GA (range): 39(37 – 43) weeks BW (range): 3.2 (1.98 – 4.8 kg Gender M/F: 96/58 Ethnicity: 89 (57%) Caucasian, 36 (23%) Black, 20 (13%) Asian, 9 (6%) Mediterranean Breastfeeding: 96% Jaundice recognised: Older than 14 days: Exclusion: Not reported	Median bilirubin levels TSB: 179 micromol/litre ABO incompatibility: 0/154 (0%) Incidence of G6PD deficiency: 3/59 (5.1%) Infection (UTI): 2/154 (1.3%) Idiopathic: Not reported	G6PD testing done where indicated by ethnic background of baby Clinical Examination by a Paediatrician is vital Recommended Investigations in prolonged jaundice ☐ Total & unconugated bilirubin ☐ PCV & G6PD level (where appropriate) ☐ Urine microscopy & culture ☐ Inspection of recent stool sample for bile pigmentation

Phototherapy

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Author: NICHHD Year:1985 Country: USA ID: [129]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table, Sealed envelopes Evidence level: 1++	*n*: 1339 Inclusion: BW < 2000gms or BW between 2000 gms and 2500 gms and TSB > 171 micromol/litre in 96 hours or BW > 2500 and TSB > 222 micromol/litre in 96 hours Exclusion: Rh hemolysis TSB > 171 micromol/litre in 24 hours Babies with severe conditions/anomalies who care would be compromised by protocol Demographics: **BW less than 2000 gms** Gender (M/F) :Not reported Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: 24.2 ± 8.0 hours Mean TSB: 97 ± 33 micromol/litre **BW between 2000 gms and 2500 gms** Gender (M/F): 73/66 Mean GA: Not reported Mean BW: Not reported Age at entry to study: 62.6 ± 17.1 hours Mean TSB: 212 ± 37 micromol/litre	Group 1: Usual care Group 2: Conventional phototherapy Conventional Phototherapy (Air Shields) consisted of 96 hours (with 30 min breaks every 4 hours for feeding etc) Daylight fluorescent bulbs 35 – 55cm above the baby. Baby naked and with eye pads (changed every 8 hours) Irradiance measured with a light monitoring badge Babies received 25ml/kg of body weight extra fluids	ET: **BW less than 2000 g** Group 1: 22/462 Group 2: 110/460 **BW between 2000 gms and 2500 gms** Group 1: 3/70 Group 2: 18/71 **BW above 2500 gms** Group 1: 14/140 Group 2: 23/136 :	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		BW > 2500 Gender (M/F): 157/119 Mean GA: Not reported Mean BW: Not reported Age at entry to study: 64.8 ± 18.4 hours Mean TSB: 15.6 ± 2.49 MG/DL			
Author: Martinez J Year: 1993 Country: USA ID: [133]	Methodology: RCT Blinding: Not reported Randomisation: Computer-generated Evidence level: 1^+	*n*: 125 Inclusion: TSB > 291 micromol/litre Exclusion: Congenital anomalies Neonatal complications Birthweight below 10^{th} percentile or above 90^{th} percentile Venous hematocrit > 65% Significant bruising Large cephalhematoma Haemolytic disease Demographics: Gender (M/F):70/55 Mean GA: 39.2 ± 0.9 weeks Mean BW: 3404 ± 361gms Age at entry to study: Not reported Mean TSB: 306 ± 12 micromol/litre	Group 1: Continue breastfeeding Group 2: Discontinue breastfeeding, substitute formula feeds Group 3: Discontinue breastfeeding, substitute formula feeds, add Conventional phototherapy Group 4: Continue breastfeeding, add phototherapy Conventional phototherapy Conventional Phototherapy consisted of Quartz halide spot unit Irradiance = 10microW/cm^2 Light band = 400 – 480 nm Babies were naked in a bassinet with their eyes patched Phototherapy discontinued at TSB < 231 micromol/litre	ET: Group 1: 0/25 Group 2: 0/26 Group 3: 0/38 Group 4: 0/36 Treatment failure: Group 1: 6/25 Group 2: 5/26 Group 3: 1/38 Group 4: 5/36	TSB levels – change **Groups 1 + 2** 48 hours: -27 ± 43 micromol/litre **Groups 3 + 4** 48 hours: -72 ± 380 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Author: Sisson T Year: 1971 Country: USA ID: [130]	Methodology: RCT Blinding: Not reported Randomisation: Coin toss Evidence level: 1^-	*n*: 35 Inclusion: TSB > 162 micromol/litre Exclusion: Sepsis, Cephalhaematoma Massive ecchymosis Demographics: Gender (M/F) :16/19 Mean GA: Not reported Mean BW: 2567 ± 709 gms Age at entry to study: Not reported Mean TSB: 193 micromol/litre	Group 1: No treatment Group 2: Conventional phototherapy Conventional Phototherapy consisted of 10 (20 watt) fluorescent lamps Units were 45 cm above the baby and had a Plexiglas shields to block ultraviolet radiation. Canopies were vented so lamp heat was dissipated Babies removed for no more than 20 minutes a time for feeding etc Babies were naked except for eye shields and diapers Light band = 410 – 490 Phototherapy discontinued at TSB < 145 micromol/litre	ET: Group 1: 2/14 Group 2: 3/21 Treatment failure: Group 1: 9/16 Group 2: 2/19	TSB levels – change Incomplete data Mean change in TSB: Incomplete data Time to max TSB (hours): Incomplete data
Author: Meloni T Year: 1974 Country: Italy ID: [132]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	*n*: 24 Inclusion: TSB > 188 micromol/litre Exclusion: Unclear Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: 209 ± 24 micromol/litre	Group 1:No treatment Group 2: Conventional phototherapy Conventional Phototherapy consisted of continuous phototherapy for 96 - 120 hours 8 cool white fluorescent tubes which deliver (at mattress level) 13.5 ± 3.5 watts/m^2	ET: Group 1: 6/12 Group 2: 2/12 Treatment failure: Group 1: 6/12 Group 2: 2/12	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Author: Ju S Year: 1991 Country: Taiwan ID: [134]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	*n*: 29 Inclusion: TSB between 205 and 256 micromol/litre Full term singletons Normal pregnancy Normal birth/caesarean Birthweight between 10^{th} and 90^{th} percentile Apgar scores ≥ 7 at 1 and 5 minutes Exclusion: Perinatal complication Congenital anomalies Possible haemolysis Demographics: Gender (M/F): 12/14 Mean GA: 39.0 ± 0.8 weeks Mean BW: 3364 ± 334 gms Age at entry to study: 97.2 ± 22.4 hours Mean TSB: 221 ± 13 micromol/litre	Group 1: No treatment Group 2: Conventional phototherapy : Conventional Phototherapy consisted of a portable unit of 4 blue and 4 white 20-watt fluorescent lamps Irradiance at baby skin levels was 5–6microW/cm^2/nm Babies moved every 4 hours for feeding Phototherapy discontinued at TSB < 205 micromol/litre	ET: Group 1: 0/13 Group 2: 0/13 Treatment failure: Group 1: 4/17 Group 2: 0/13	
Author: Lewis H Year: 1982 Country: UK ID: [131]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table Evidence level: 1^+	*n*: 40 Inclusion: Birthweight > 2500gms, Gestational Age > 37 weeks, TSB ≥ 250 micromol/litre Exclusion: Perinatal asphyxia, Apgar score < 5 at 4 minutes, Positive DAT test Demographics: Gender (M/F): 27/13 Mean GA: Not reported Mean BW: 3200 ± 260 gms Age at entry to study: 84 hours	Group 1: Conventional Phototherapy Group 2: Conventional Phototherapy - Delayed (initiated if TSB rose to ≥ 320 micromol/litre : Conventional Phototherapy consisted of a Vickers 80 white light phototherapy unit mounted 50 cm above the baby. Babies were blindfolded, naked except for a napkin while nursing and were turned every 3 hours.	ET: Group 1: 0/20 Group 2: 0/20 Treatment failure: Group 1: 0/20 Group 2: 3/20	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Mean TSB: 263 micromol/litre	Phototherapy discontinued at TSB < 250 micromol/litre		
Author: Holtrop P Year: 1992 Country: USA ID: [151]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated Evidence level: 1^{+}	*n*: 70 Inclusion: Birthweight < 2500, Birthweight between 10^{th} and 90^{th} percentile, > 24 1 day old, no congenital anomalies, no Rh incompatibility TSB > 85 micromol/litre at BW < 1000gms TSB > 103 micromol/litre at BW 1000 - 1200gms TSB > 120 micromol/litre at BW 1200 - 1400gms TSB > 137 micromol/litre at BW 1400 - 1600gms TSB > 1071 micromol/litre at BW 1600 - 1800gms TSB > 12 at BW 1800 - 2200gms TSB 12 - 15 at BW 2200 - 2500gms Exclusion: Not reported Demographics:	Group 1: Conventional phototherapy Group 2: Double phototherapy (Conventional phototherapy + Fiberoptic phototherapy) Single Conventional phototherapy consisted of either 1/ if baby was in an incubator, a standard unit (Olympic Bili-lite) with 4 white and 4 blue fluorescent lamps 35 cm above the baby. Irradiance at skin level was 9.2microW/cm^2/nm Light range was 425 – 475 Or 2/ if baby was on a radiant warmer, 3 halogen lights on each side(Air Shields7850) with an irradiance of 7microW/cm^2/nm Double phototherapy consisted of single Conventional phototherapy as above combined with a 'Wallaby' fiberoptic blanket measuring 10 X 35 cm. Mean irradiance on the blanket's surface was 8.2microW/cm^2/nm Babies wore eye patches and wore disposable diapers cut to allow maximum skin exposure Fluids were administered on clinician advice	ET: Group 1: 0/37 Group 2: 0/33 Kernicterus: Group 1: 0/37 Group 2: 0/33 Mortality: Group 1: 0/37 Group 2: 0/33 Rebound jaundice: Group 1: 14/37 Group 2: 12/33	Mean duration Group 1: Not reported Group 2: Not reported Mean change in TSB: Group 1:- 45 ± 18 micromol/litre Group 2: - 28 ± 20 micromol/litre
Author: Nuntnarumit P Year: 2002 Country: Thailand ID: [136]	Methodology: RCT Blinding: Not reported Randomisation: Not reported	*n*: 51 Inclusion: BW > 2500gms GA > 37 weeks TSB ≥ 205 micromol/litre at 24–48 hours TSB ≥ 256 micromol/litre at 49–	Group 1: Single Conventional phototherapy Group 2: Double Conventional phototherapy Single Conventional phototherapy consisted of 3 daylights and 2 blue	ET: Group 1: 0/27 Group 2: 0/24 Rebound jaundice: Group 1: 1/27 Group 2: 0/24	Mean duration Group 1: 43.7 ± 17.5 hours Group 2: 34.9 ± 12.6 hours Mean change in TSB: Group 1: -98 ± 46 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
	Evidence level: 1-	72 hours TSB ≥ 291 micromol/litre at ≥ 72 hours Exclusion: Babies who had been on ventilator support or incubator, Babies who had been on phototherapy, Direct hyperbilirubinaemia Demographics: Gender (M/F) : 34/17 Mean GA: 38.7 ± 1.29 weeks Mean BW: 3104 ± 284 Age at entry to study 74.6 ± 27.4 Mean TSB: 316 ± 47 micromol/litre	lights 38 cm above the baby. Double Conventional phototherapy consisted of single phototherapy plus an additional bank of 8 20watt daylight fluorescents lamps 32 cm below the baby. A ventilated fan was used to prevent overheating Target irradiance was 9–10microW/cm^2/nm Phototherapy was discontinued when TSB < 205 micromol/litre at < 96 hours of age or TSB < 256 micromol/litre at > 96 hours of age		Group 2: - 156 ± 67 micromol/litre Stools/day: Group 1: 2.8 ± 1.7 Group 2: 2.2 ± 1.4
Author: Boonyarittipong P Year: 2008 Country: Thailand ID: [137]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	*n*: 60 Inclusion: Full term (37–42 weeks), Birthweight > 2500gms, Apgar > 6 T 1 and 5 minutes TSB between 222 - 340 micromol/litre, Nonhemolytic hyperbilirubinaemia Exclusively breastfed, Exclusion: Not reported Demographics: Gender (M/F): 32/28 Mean GA: 38.6 ± 1.15 weeks Mean BW: 3130 ± 311 gms Age at entry to study Not reported Mean TSB: 260 ± 30 micromol/litre	Group 1: Single Conventional phototherapy Group 2: Double Conventional phototherapy Single Conventional phototherapy consisted of 4 blue and 2 daylight fluorescent lamps at least 30 cm above the baby Mean irradiance was 32.7 ± 2.6microW/cm^2/nm Baby wore eye patches and cotton diapers Double Conventional phototherapy (Neonatal Jaundice phototherapy apparatus/XHZ) was single phototherapy and an additional bank of 4 blue fluorescent lamps 25 cm beneath the bassinet. A fan was used to prevent overheating Mean irradiance of overhead unit was	ET: Group 1: 0/30 Group 2: 0/30 Treatment failure: Group 1: 0/30 Group 2: 0/30	Mean change in TSB: Group 1: -111 ± 39 micromol/litre Group 2: -144 ± 36 micromol/litre Stools/day: Group 1: 2.8 ± 1.7 Group 2: 2.2 ± 1.4

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
			33.7 ± 1.6microW/cm^2/nm and not reported for the unit underneath the baby Phototherapy was discontinued at TSB < 222 micromol/litre or phototherapy > 48 hours		
Author: Sarici S Year: 2001 Country: Turkey ID: [139]	Methodology: RCT Blinding: Blind allocation Randomisation: Sequential Evidence level: 1+	N: 100 Inclusion: Birthweight > 2500 gms, Nonhemolytic indirect hyperbilirubinaemia, Normal Reticulocyte count, Negative DAT, No evidence of blood group isoimmunisation TSB ≥ 256 micromol/litre Exclusion: Direct hyperbilirubinaemia, Enclosed haemorrhage, Infection, congenital malformations Demographics: Gender (M/F): 54/46 Mean GA: 39.0 ± 0.7 weeks Mean BW: 3380 ± 359 gms Age at entry to study 105.4 ± 42.8 hours Mean TSB: 308 ± 47 micromol/litre	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy (Ohio Medical Products) consisted of a bank of 5 daylight fluorescent lamps 30cm above the baby Fiberoptic phototherapy (Walley II Phototherapy System) consisted of a single pad (7.6 X 35.5 cm) Babies in both groups were placed in a prone position and all babies wore disposable diapers. Babies in the phototherapy group wore eye patches Irradiance and light range were not reported Phototherapy considered to have failure if two consecutive measures showed an increase in TSB	ET: Group 1: 0/50 Group 2: 0/50 : Erythema: Group 1: 1/50 Group 2: 1/50 Watery stools: Group 1: 3/50 Group 2: 3/50 Rebound jaundice: Group 1: 3/50 Group 2: 2/50 Treatment failure: Group 1: 0/50 Group 2: 4/50	Mean duration: Group 1: 49.4 ± 14.4 hours Group 2: 61.0 ± 13.1 hours Mean change in TSB: Group 1: 125 ± 39 micromol/litre Group 2: 111 ± 42 micromol/litre
Author: Gale R Year: 1990 Country: USA ID: [140]	Methodology: RCT Blinding: Not reported Randomisation: Not reported	N: 42 Inclusion: Full-term (> 37 weeks), No haemolytic jaundice TSB > 200 micromol/litre but if babies had rapidly increasing TSB levels they could be entered into the study before	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy (Air Shields PT 53–3) consisted of a standard phototherapy unit (both daylight and	ET: Group 1: 0/22 Group 2: 0/20	Mean duration of phototherapy Group 1: Not reported Group 2: Not reported

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
	Evidence level: 1-	they reached 200 micromol/litre Exclusion: Evidence of hemolysis Demographics: Gender (M/F): Not reported Mean GA: 39.6 ± 1.6 weeks Mean BW: 3197 ± 475 Age at entry to study Not reported Mean TSB: 186 ± 86 micromol/litre	blue lamps) positioned above the baby. Babies were naked, with eyes covered, and were alternate between prone and supine position every 6 hours. Irradiance at blanket level was 7.0 ± 0.5microW/cm^2/nm. Fiberoptic phototherapy (Wallaby Phototherapy System) consisted of a single fiberoptic pad linked to a lightbox with 150-watt halogen lamp and a fan with 150.ft^2/minute air volume. Irradiance spectrum was between 425 and 475 nm. Irradiance at blanket level was 7.0 ± 0.5microW/cm^2/nm. Babies were placed naked on the blanked. While nursing the mother could hold the baby wrapped in the blanket In both group babies were kept on phototherapy for 48 hours but could be withdrawn at any stage.		
Author: Dani C Year: 2004 Country: Italy ID: [153]	Methodology: RCT Blinding: Not reported Randomisation: Allocation method not reported but sealed envelopes used Evidence level: 1-	N: 23 Inclusion: Preterm (GA < 34 weeks), No haemolytic jaundice, not on respiratory support, Clinically stable. Exclusion: Major congenital malformations, patent ductus arteriosus, intracranial haemorrhage, Perinatal asphyxia, receiving cardiovascular drugs Demographics: Gender (M/F): Not reported Mean GA: 31.0 ± 1.8 weeks Mean BW: 1468 ± 400 gms Age at entry to study	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy consisted of a Photo-Therapie 800 system. Baby was naked except for eye patches and in a supine position. Irradiance and light range not reported Fiberoptic phototherapy (BiliBlanket) consisted of a mat that covered the baby up to the upper abdomen. Irradiance and light range not reported To avoid trans-epidermal water loss the babies were placed in incubators with a thermo-monitoring system to maintain normal body temperature (46.5^{o}C) at a	ET: Group 1: 0/12 Group 2: 0/11	Mean duration of phototherapy Group 1: 43.0 ± 3.1 hours Group 2: 38.7 ± 4.5 hours Mean change in TSB: Group 1: -69 ± 13 micromol/litre Group 2: -62 ± 17 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		63.2 ± 15.0 hours Mean TSB: 241 ± 9 micromol/litre	relative humidity of 60%.		
Author: Al-Alaiyan S Year: 1996 Country: Saudi Arabia ID: [135]	Methodology: RCT Blinding: Not reported Randomisation: Allocation method not reported but shuffled, sealed envelopes used Evidence level: 1-	N: 46 Inclusion: GA > 36 weeks, Nonhemolytic jaundice Age > 1 day, Normal hemoglobin, No evidence of blood group incompatibility, Exclusion: Not reported Demographics: Gender (M/F): 23/23 Mean GA: 37.9 ± 2.08 weeks Mean BW: 2921 ± 696 gms Age at entry to study 37.9 ± 24.1 hours Mean TSB: 185 ± 56 micromol/litre	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Group 3: Combined phototherapy and fiberoptic phototherapy Conventional Phototherapy (Air Shields Fluoro-Lite) consisted of a standard unit of blue and white fluorescent bulbs 50 cm from the baby. Mean irradiance was 11.6 ± 2.2microW/cm^2/nm Light range = 425 – 475 nm Phototherapy was interrupted for feeding etc for an average of 115 minutes per day. Babies were naked except for eye patches. Fiberoptic phototherapy (BiliBlanket) consisted of a halogen lamp linked to a fiberoptic blanket. Mean irradiance was 22.3 ± 2.2microW/cm^2/nm Light range = 400 – 500 nm Fiberoptic phototherapy was continuous. Combined therapy consisted of both conventional and fiberoptic phototherapy as above.	ET: Group 1: 0/15 Group 2: 0/16 Group 3: 0/15 Rebound jaundice: Group 1: 0/15 Group 2: 0/16 Group 3: 0/15	Mean duration of phototherapy Group 1: 52.8 ± 24.8 hours Group 2: 47.5 ± 24.8 hours Group 3: 50.7 ± 24.8 hours Mean change in TSB: Group 1: -14 ± 28 micromol/litre Group 2: 19 ± 35 micromol/litre Group 3: -23 ± 39 micromol/litre :
Author: Pezzati M Year: 2000 Country: Italy	Methodology: RCT Blinding: Clinician blinded Randomisation: Allocation method	N: 39 Inclusion: Preterm babies with hyperbilirubinaemia > 171 micromol/litre Exclusion:	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy (Photo grph	ET: Group 1: 0/19 Group 2: 0/20	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
ID: [157]	not reported but shuffled, sealed envelopes used Evidence level: 1^{+}	Malformations, Perinatal asphyxia, Respiratory distress, renal or gastrointestinal abnormalities, Patent ductus arteriosus, hypotension, Hypertension, Infection, Anaemia, polycythemia Demographics: Gender (M/F): 21/18 Mean GA: 34.3 weeks Mean BW: 2101 g Age at entry to study Not reported Mean TSB: Not reported	– Therapie 800) consisted of a standard unit of blue lamp with two filters (infrared and uiltraviolet) . Babies were naked except for eye patches. Fiberoptic phototherapy (BiliBlanket)		
Author: Holtrop P Year: 1992 Country: USA ID: [141]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated Evidence level: 1^{+}	N: 26 Inclusion: Birthweight > 2500 gms, Age > 1 day, No Rh incompatibility, Clinical need for phototherapy Exclusion: Not reported Demographics: Gender (M/F): 17/9 Mean GA: 38.1 ± 2.5 weeks Mean BW: 3377 ± 541 gms Age at entry to study 66.3 ± 19.4 hours Mean TSB: 231 ± 24 micromol/litre	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy (Olympic Bili-lite) consisted of an overhead bank of 4 white and 4 blue 35 cm above the baby. Babies were naked except for diapers and eye patches. Babies were removed for feeding. Mean irradiance was 9.2 ± 0.9microW/cm^2/nm Fiberoptic phototherapy (Wallaby Phototherapy System) consisted of a cummerbund which was wrapped around the torso. Babies wore eye patches. Mean irradiance was 8.2 ± 1.2microW/cm^2/nm Babies were removed form the study if the TSB rose by more than 9 micromol/litre/h	ET: Group 1: 0/14 Group 2: 0/12 Treatment failure: Group 1: 1/14 Group 2: 3/12	Mean duration of phototherapy Group 1: Not reported Group 2: Not reported :
Author: Pezzati M	Methodology:	N: 41	Group 1:	ET:	Mean duration of phototherapy

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Year: 2002 Country: Italy ID: [142]	RCT Blinding: Not reported Randomisation: Not report but sealed envelopes used Evidence level: 1^+	Inclusion: Exclusion: Demographics: Gender (M/F) : Not reported Mean GA: 39.6 ± 1.2 weeks Mean BW: 3236 ± 425 gms Age at entry to study Not reported Mean TSB: 296 ± 32 micromol/litre	Conventional Phototherapy Group 2: Fiberoptic Phototherapy Conventional phototherapy ('Photo-Therapie 800') consisted of a unit incorporating a metal vapour discharge blue lamp with 2 filters (an infrared filter and a Plexiglas ultraviolet filter). A fan was fitted to remove heat generated by lamp. Fiberoptic phototherapy (BiliBlanket PT) consisted of a 140W quartz halogen lamp with a built-in dichroic reflector with low infrared and ultraviolet radiation reflectivity. Light range was restricted to 400 – 550 nm. All babies were naked in a supine position at a stabilised room temperature.	Group 1: 0/21 Group 2: 0/20	Group 1: Not reported Group 2: Not reported Mean change in TSB: Group 1: -55 ± 16 micromol/litre Group 2: -51 ± 23 micromol/litre
Author: Romagnoli C Year: 2006 Country: Italy ID: [152]	Methodology: RCT Blinding: No reported Randomisation: Not reported but sealed envelopes used Evidence level: 1^+	N: 136 Inclusion: TSB> 103 micromol/litre GA ≤ 30 weeks Exclusion: Not reported Demographics: Gender (M/F): 72/64 Mean GA: 27.9 ± 1.4 weeks Mean BW: 1019 ± 283 gms Age at entry to study 38.3 ± 7.1 hours Mean TSB: 109 ± 5 micromol/litre	Group 1: Conventional phototherapy Group 2: Fiberoptic (Wallaby) phototherapy Group 3: Fiberoptic (BiliBlanket) phototherapy Group 4: Combined conventional and Fiberoptic (Wallaby) phototherapy Conventional phototherapy consisted of standard phototherapy composed of 4 fluorescent lamps and 4 blue lamps 40cm above the baby. Irradiance at skin level was 22 – 24 microW/cm^2/nm. Babies were naked except for eye patches and disposable diapers. Baby position was changed from prone to supine and vice versa every 6 hours. Fiberoptic Wallaby phototherapy	ET: Group 1: 2/33 Group 2: 2/35 Group 3: 1/35 Group 4: 0/33 Erythema: Group 1: 10/33 Group 2: 9/35 Group 3: 8/35 Group 4: 12/33 Treatment failure: Group 1: 2/33 Group 2: 4/35 Group 3: 1/35 Group 4: 0/33	Mean duration of phototherapy Group 1: 90.2 ± 24.3 hours Group 2: 92.1 ± 43.3 hours Group 3: 94.4 ± 43.3 hours Group 4: 75.1 ± 23.6 hours Max TSB: Group 1: 157 ± 43 micromol/litre Group 2: 169 ± 56 micromol/litre Group 3: 161 ± 44 micromol/litre Group 4: 130 ± 22 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
			consisted of a 10.1 X 15.2 cm pad linked to a 150W quartz halogen lamp. A light filter is placed between the lamp and the fiberoptic bundle to allow only 400 – 550 nm range through. Irradiance at skin level was 8 – 10 microW/cm^2/nm. Baby position was changed from prone to supine and vice versa every 6 hours. Fiberoptic BiliBlanket phototherapy consisted of an 11 X 13 cm pad linked to a 150W tungsten halogen lamp. A light filter is placed between the lamp and the fiberoptic bundle to allow only 400 – 550 nm range through. Irradiance at skin level was 35microW/cm^2/nm. Baby position was changed from prone to supine and vice versa every 6 hours. Combined phototherapy consisted of conventional phototherapy as above and the fiberoptic Wallaby system as above.		
Author: Tan K Year: 1997 Country: Singapore ID: [138]	Methodology: RCT Blinding: Not reported Randomisation: Lottery method Evidence level: 1$^+$	N: 171 Inclusion: Nonhemolytic jaundice, TSB > 256 micromol/litre or > 222 micromol/litre before 48 hours, Exclusion: Not reported Demographics: Gender (M/F): 96/75 Mean GA: 38.5 ± 1.5 weeks Mean BW: 3114 ± 415 gms Age at entry to study 96.9 ± 30.9 days Mean TSB: 262 ± 17 micromol/litre	Group 1: Conventional Phototherapy Group 2: Fiberoptic phototherapy - Standard Group 3: Fiberoptic phototherapy – Large Group 4: Fiberoptic phototherapy - Double Conventional phototherapy consisted of seven overhead daylight fluorescent lamps arrange din an arc 35cm above the baby. The baby was kept unclothed except for eye coverings. Irradiance was 6.73 microW/cm^2/nm The standard fiberoptic (BiliBlanket) phototherapy consisted of a pad, 11 X 20 cm (illuminated part was 11 X 13cm) which was used without its sheath and	ET: Group 1: 0/44 Group 2: 0/42 Group 3: 0/43 Group 4: 0/42 Rebound jaundice: Group 1: 1/44 Group 2: 0/42 Group 3: 0/43 Group 4: 1/42 Treatment failure: Group 1: 0/44 Group 2: 4/42 Group 3: 3/43 Group 4: 0/42	Mean duration of phototherapy Group 1: 62.6 ± 24.8 hours Group 2: 87.0 ± 39.5 hours Group 3: 82.6 ± 38.3 hours Group 4: 64.8 ± 35.2 hours :

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
			at maximal power. Irradiance was an average of 19.01 microW/cm^2/nm when measured at the centre and at the four corners. The standard fiberoptic phototherapy consisted of a pad, 11 X 24 cm (illuminated part was 11 X 16cm) which was used without its sheath and at maximal power. The irradiance was calculated to be 23% more than that of the standard fiberoptic pad. The double fiberoptic phototherapy consisted of two standard pads one on the back and one the front of the baby. Phototherapy was terminated when TSB < 188 micromol/litre on at least two occasions Phototherapy was deemed to have failed when TSB values exceeded start level on at least two occasions and when direct bilirubin was minimal < 0.6 MG/DL		
Author: Van Kamm A Year: 1998 Country: Netherlands ID: [154]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed envelopes used Evidence level: 1$^+$	N: 124 Inclusion: Preterm babies with birthweight < 2000gms, Nonhaemolytic jaundice Exclusion: Prior phototherapy, Met criteria for exchange transfusion Demographics: Gender (M/F) : 72/52 Mean GA: 29.7 ± 2.4 weeks Mean BW: 1250 ± 353 gms Age at entry to study 26.5 ± 17.5 Mean TSB: 94 ± 36 micromol/litre	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy consisted of 4 overhead fluorescent lamps arranged in an arc 40 cm above the baby. Baby was naked except for eye patches. The light range is in the 380 – 480 nm range. Irradiance level was 16 microW/cm^2/nm Fiberoptic phototherapy (Ohmeda BiliBlanket) consisted of a halogen lamp illuminating a flat mat using a fiberoptic attachment containing 2400 optic givers woven into the mat. Baby was naked. The illuminating part of the mat is 11 X	ET: Group 1: 3/68 Group 2: 4/56 Treatment failure: Group 1: 27/68 Group 2: 29/56	Mean duration of phototherapy Group 1: Not reported Group 2: Not reported: Mean change in TSB: Group 1: -2 ± 25 micromol/litre Group 2: -2 ± 20 micromol/litre :

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
			13 cm. The light range is in the 400 – 550 nm range. Irradiance level was 35 microW/cm^2/nm If TSB levels increased above predetermined cut-offs double phototherapy was started using conventional phototherapy as above.		
Author: Dani C Year: 2001 Country: Italy ID: [155]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed envelopes used Evidence level: 1$^+$	N: 20 Inclusion: Aged ≤ 3 days, Gestational age between 31 and 36 weeks, Clinically stable, No major congenital malformations Exclusion: Non-haemolytic jaundice Demographics: Gender (M/F): Not reported Mean GA: 34.4 ± 1.2 weeks Mean BW: 2600 ± 382 Age at entry to study 49.5 ± 2.9 hours Mean TSB: 227 ± 10 micromol/litre	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy consisted of a Photo-Therapie 800 Fiberoptic phototherapy was an Ohmeda BiliBlanket which was wrapped around the baby's torso. Babies were naked except for eye patches and were in a supine position. Phototherapy was initiated when TSB > 220micromol/litre and discontinued when TSB ≤ 170 micromol/litre.	ET: Group 1: 0/10 Group 2: 0/10	Mean duration of phototherapy Group 1: 25.8 ± 3.4 hours Group 2: 24.0 ± 2.5 hours Mean change in TSB: Group 1: Incomplete data Group 2: Incomplete data
Author: Morris B Year: 2008 Country: USA ID: [145]	Methodology: RCT Blinding: Single-blind – outcome assessors were unaware of allocation Randomisation: Computer-generated Evidence level: 1^{++}	N: 1974 Inclusion: Birthweight between 5001 and 1000 g Between 12 and 36 hurs of age Exclusion: Terminal condition (Ph < 6.8 or persistent bradycardia with hypoxaemia for > 2 hours), Previous phototherapy, Major congenital anomaly, Hydrops fetalis, Severe haemolytic disease,	Group 1: Early Phototherapy – begun when Day 1 – 7 TSB > 85 micromol/litre Day 8 – 14 TSB > 120 micromol/litre Group 2: Phototherapy at TSB ≥ 137 micromol/litre for BW 501 – 750 g Or 171 micromol/litre for BW 751 – 1000 g TSB was measured daily. Irradiance was 15 – 40 microW/cm^2/nm	ET: Group 1: 2/990 Group 2: 3/984 Intensive phototherapy: Group 1: 3/990 Group 2: 13/984 Mortality: Group 1: 209/990 Group 2: 201/984 **18 – 22 months** Mortality Group 1: 230/946 Group 2: 218/944	Max TSB: Group 1: 120 ± 31 micromol/litre Group 2: 168 ± 36 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Congenital nonbacterial infection, Judgement at parents may be able to return for final assessment at 18 – 22 months Demographics: Gender (M/F) : 1013/961 Mean GA: 26.0 ± 2.0 weeks Mean BW: 777 ± 134 g Mean age at entry to study: Not reported Mean TSB: Not reported for all babies	and was increased if TSB > 222 micromol/litre in BW 501 – 750 g or TSB > 256 in BW 751 – 1000 g Exchange transfusion was indicated TSB exceeded threshold after 8 hours of intensive phototherapy	RR = 1.05 (95% CI: 0.90, 1.22) Neurodevelopmental impairment Group 1: 235/902 Group 2: 275/902 RR = 0.86 (95% CI: 0.74, 0.99)	
Author: Valdes O Year: 1971 Country: USA ID: [146]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 75 Inclusion: Birthweight < 2500 g Exclusion: Positive Coombs test, ABO incompatibility, Sepsis Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 1766 g Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Phenobarbital Group 2: Phototherapy Group 3: Phenobarbital + Phototherapy Group 4: No treatment		Max TSB: Group 1: 96 ± 57 micromol/litre Group 2: 58 ± 52 micromol/litre Group 3: 63 ± 58 micromol/litre Group 4: 140 ± 53 micromol/litre
Author: Costello S Year: 1994 Country: Australia ID: [156]	Methodology: RCT Blinding: Not reported Randomisation: Lottery method Evidence level: 1^+	N: 44 Inclusion: Gestational age between 27 and 36 weeks TSB > 125 micromol/litre) (increased with age (hours) and birthweight Exclusion: Not reported Demographics: Gender (M/F): Not reported	Group 1: Conventional Phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy consisted of a standard system of four white and 4 blue fluorescent lamps 50cm above the baby with an intensity of 8 microW/cm^2/nm Fiberoptic phototherapy (BiliBlanket) with a constant setting of	ET: Group 1: 0/24 Group 2: 0/20 Treatment failure: Group 1: 3/24 Group 2: 1/20	Mean duration of phototherapy Group 1: 44.0 ± 42.8 hours Group 2: 42.0 ± 39.1 hours Max TSB: Group 1: 210 ± 58 micromol/litre Group 2: 198 ± 53 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Mean GA: 32.0 ± 0.54 weeks Mean BW: 1614 ± 140 gms Age at entry to study 56.6 ± 37.0 hours Mean TSB: Not reported	35microW/cm^2/nm. Baby was nursed in an open cot or isolette and turned at regular intervals from prone to supine positions. Eyes pads were used for babies < 1500gms.		
Author: Bertini G Year: 2008 Country: Italy ID: [159]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed envelopes used Evidence level: 1+	N: 31 Inclusion: TSB ≥ 171 micromol/litre, Gestational ages < 34 weeks, Age ≤ 7days, Did not require respiratory support, Clinically stable Exclusion: Malformations, Perinatal asphyxia, Patent ductus arteriosus, intracranial haemorrhage, hypotension, Hypertension, Infection, Anemia (venous Hb< 10g/dl), Polycythemia (venous Hb> 22 g/dl), Infants receiving cardiovascular drugs. Demographics: Gender (M/F): Not reported Mean GA: 30.7 ± 2.0 weeks Mean BW: 1192 ± 238 gms Age at entry to study 64.4 ± 15.2 hours Mean TSB: 200 ± 16 micromol/litre	Group 1: Conventional phototherapy Group 2: LED Phototherapy Conventional phototherapy (Photo-Therapie 800) incorporating a metal vapour discharge blue lamp with two filters (an infrared cut-off filter and a Plexiglas ultraviolet cut-off filter). 20 cm above the baby. LED phototherapy (Natus NeoBlue system). Light range 450–470nm spectrum. Irradiance was at the intensive setting at 30– 35 microW/cm^2/nm. Unit was placed 30cm above the baby. All babies were placed in incubators with a thermo-monitoring system to maintain a normal body temperature (36.5^{o}C) at a relative humidity of 60%. Babies received full enteral feeding with human milk. Babies were naked except for eye patches and were in a supine position. Phototherapy discontinued at < 145 micromol/litre	ET: Group 1: 0/14 Group 2: 0/17	Mean duration of phototherapy Group 1: 38.7 ± 5.0 hours Group 2: 34.0 ± 12.0 hours TSB levels – change Group 1: -62 ± 24 micromol/litre Group 2: -55 ± 5 micromol/litre :
Author: Seidman D Year: 2000 Country: Israel	Methodology: RCT Blinding: Open label study Randomisation:	N: 69 Inclusion: Full-term (Gestational age > 37 weeks), Jaundice according to AAP criteria for phototherapy	Group 1: Conventional phototherapy Group 2: LED phototherapy Conventional phototherapy (Micro-lites	ET: Group 1: 0/35 Group 2: 0/34	Mean duration of phototherapy Group 1: 32.0 ± 17.0 hours Group 2: 31.0 ± 17.0 hours Mean change in TSB: Group 1: -44 ± 58 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
ID: [143]	Computer generated Evidence level: 1^+	Exclusion: None reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: 251 ± 77 micromol/litre	PTL 68–1) units equipped with 3 halogen quartz bulbs. Irradiance was 5–6 microW/cm^2/nm. LED phototherapy consisted of 6 focussed arrays each with 100 3-mm blue LED's. Unit was placed 50cm above the baby, to achieve an irradiance of 5–6microW/cm^2/nm. All babies were placed in a crib and were naked except for diapers and eye coverings.		Group 2: -44 ± 46 micromol/litre
Author: Seidman D Year: 2003 Country: Israel ID: [144]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated Evidence level: 1^+	N: 114 Inclusion: AAP criteria for phototherapy, Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: 39.5 ± 1.5 weeks Mean BW: Not reported Age at entry to study 53.9 ± 37.8 hours Mean TSB: 251 ± 73 micromol/litre	Group 1: Conventional phototherapy Group 2: LED phototherapy - Blue Group 3: LED Phototherapy - Blue-Green Conventional phototherapy (Air Shields Micro-lites PTL 68–1) units equipped with 3 halogen quartz bulbs. Irradiance was 5–6 microW/cm^2/nm. Blue LED phototherapy consisted of 6 focussed arrays each with 100 3-mm blue LED's. Peak wavelength was 459nm with a half spectral width of 22nm. Unit was placed 50cm above the baby, to achieve an irradiance of 5–6microW/cm^2/nm. Blue-Green LED phototherapy consisted of 6 focussed arrays each with 100 3-mm blue-green LED's. Peak wavelength was 505nm with a half spectral width of 38nm. Unit was placed 50cm above the baby, to achieve an irradiance of 5–6microW/cm^2/nm. All babies were placed in open cribs and were naked except for diapers and eye	ET: Group 1: 0/57 Group 2: 0/25 Group 3: 0/22 Erythema: Group 1: 0/57 Group 2: 0/25 Group 3: 0/22	Mean duration of phototherapy Group 1: 35.4 ± 20.2 hours Group 2: 31.6 ± 19.6 hours Group 3: 39.2 ± 25.5 hours Mean change in TSB: Group 1: -44 ± 33 micromol/litre Group 2: -39 ± 46 micromol/litre Group 3: -41 ± 48 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
			coverings.		
Author: Martins B Year: 2007 Country: Brazil ID: [158]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 88 Inclusion: Need for phototherapy according to birthweight Exclusion: Direct bilirubin > 34 micromol/litre Haemolytic jaundice, Ecchymosis, Malformations, Congenital infection Demographics: Gender (M/F):58/30 Mean GA: 33.6 ± 1.9 weeks Mean BW: 1998 ± 541 gms Age at entry to study 68.1 ± 25.5 hours Mean TSB: 179 ± 38 micromol/litre	Group 1: Conventional Phototherapy Group 2: LED phototherapy Conventional phototherapy consisted of a single quartz-halogen lamp, with a dichroic reflector, positioned 50cm from the baby and illuminating a circle of 18cm diameter. Mean irradiance was 21 ± 6microW/cm^2/nm LED phototherapy consisted of the Super LED system positioned 30cm from the patient and illuminating an elliptical area of 38cm x 27cm diameter. Mean irradiance was 37 ± 9microW/cm^2/nm Phototherapy discontinued when TSB levels decreased 30% from original levels Treatment was considered to have failed if TSB continued to rise and reached a level 30% below TSB levels required for exchange transfusion.	ET: Group 1: 0/44 Group 2: 0/44 Erythema: Group 1: 0/44 Group 2: 0/44 Treatment failure: Group 1: 0/44 Group 2: 0/44	Mean duration of phototherapy Group 1: 63.8 ± 37 hours Group 2: 36.8 ± 21 hours TSB levels – change 24 hours Group 1: -22 ± 25 micromol/litre Group 2: -50 ± 26 micromol/litre
Author: Ebbesen F Year: 2007 Country: Denmark ID: [160]	Methodology: RCT Blinding: Not reported Randomisation: Not stated but sealed envelopes used Evidence level: 1^+	N: 141 Inclusion: Preterm infants (28 – 36.6 weeks), Age > 24 hours, No previous phototherapy, Non-haemolytic hyperbilirubinaemia Exclusion: Not reported Demographics: Gender (M/F): 80/61	Group 1: Blue phototherapy Group 2: Turquoise phototherapy Treatment duration was fixed (24 hours) Phototherapy consisted of either 8 blue fluorescent lamps (20 W, 60 x 3.7cm) 41 cm above the baby or 8 turquoise fluorescent lamps (18 W, 60 x 2.6cm) 41 cm above the baby. Distance from baby was different to ensure irradiance was identical in both groups	ET: Group 1: 0/69 Group 2: 0/72	Mean change in TSB: Group 1: -78 ± 31 micromol/litre Group 2: -92 ± 31 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Mean GA: 33.8 ± 2.49 weeks Mean BW: 2078 ± 605 gms Age at entry to study 74.0 ± 31.9 hours Mean TSB: 221 ± 60 micromol/litre	Phototherapy was continuous with breaks for feeding etc Babies were naked except for eye patches and diapers		
Author: Ebbesen F Year: 2003 Country: Denmark ID: [161]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 85 Inclusion: Preterm infants (28 – 36.8 weeks), Age > 24 hours, Non-haemolytic hyperbilirubinaemia Exclusion: Not reported Demographics: Gender (M/F): 49/36 Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: Not reported	Group 1: Blue phototherapy Group 2: Turquoise phototherapy Treatment duration was fixed (48 hours) Phototherapy consisted of either 6 blue + 2 daylight fluorescent lamps 32 cm above the baby or 6 turquoise + 2 daylight fluorescent lamps 32 cm above the baby. Irradiance for turquoise lamps was 2.72 ± 0.25 mW/cm^2 Irradiance for blue lamps was 3.52 ± 0.33 mW/cm^2 Irradiance for white lamps was 0.56 ± 0.07 mW/cm^2 Phototherapy was continuous with breaks for feeding etc Babies were naked except for eye patches and diapers		:
Author: Ayyash H Year: 1987 Country: Greece ID: [162]	Methodology: RCT Blinding: Not reported Randomisation: Not reported	Study 1: Full-term N: 200 Inclusion: Idiopathic jaundice Exclusion: Haemolytic jaundice	Group 1: Blue Phototherapy Group 2: Green Phototherapy Phototherapy consisted of 5, either green or blue, fluorescent tubes mounted on a conventional		**Study 1 – Full-term** Mean duration of phototherapy Group 1: 49.88 ± 3.02 hours Group 2: 42.68 ± 2.74 hours Mean change in TSB: Group 1: -39 ± 2 micromol/litre Group 2: -43± 2 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
	Evidence level: 1^-	Demographics: Gender (M/F): Not reported Mean GA: 38.9 ± 0.14 weeks Mean BW: 3394 ± 43 gms Age at entry to study 101.8 ± 4.32 hours Mean TSB: 286 ± 60 micromol/litre Study 2: Preterm N: 62 Inclusion: Idiopathic jaundice Exclusion: Haemolytic jaundice Demographics: Gender (M/F): Not reported Mean GA: 34.6 ± 0.36 weeks Mean BW: 2361 ± 102 gms Age at entry to study 85.6 ± 5.52 hours Mean TSB: 239 ± 16 micromol/litre	phototherapy unit.		**Study 2 – Preterm** Mean duration of phototherapy Group 1: 53.29 ± 5.9 hours Group 2: 53.26 ± 5.52 hours Mean change in TSB: Group 1: -34 ± 6 micromol/litre Group 2: -38 ± 8 micromol/litre
Author: Amato M Year: 1991 Country: Switzerland ID: [163]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table Evidence level: 1^+	N: 30 Inclusion: Idiopathic hyperbilirubinaemia TSB ≥ 250 micromol/litre Exclusion: Perinatal asphyxia, Apgar < 4 at 1 minute and < 6 at 5 minutes, Signs of haemolytic disease, secondary hyperbilirubinaemia Demographics: Gender (M/F): 13/17	Group 1: Blue Phototherapy Group 2: Green Phototherapy Phototherapy consisted of either blue or green fluorescent tubes 30cm above the mattress. The baby was placed naked, except for eye patches and gonadal protection, on a Plexiglas surface. Light spectral range of green tubes was 350–650 nm and 300–600 for the blue tubes	ET: Group 1: 0/15 Group 2: 0/15 Rebound jaundice: Group 1: 12/15 Group 2: 3/15	Mean duration of phototherapy Group 1: 34 ± 10 hours Group 2: 70 ± 23 hours Mean change in TSB: Group 1: -157 ± 22 micromol/litre Group 2: -154 ± 31 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Mean GA: 39.0 ± 1.03 weeks Mean BW: 3395 ± 547 gms Age at entry to study 70.5 ± 23,1 hours Mean TSB: 291± 35 micromol/litre	Babies were supplemented with 5% glucose (15 mg/kg per day) Phototherapy discontinued at TSB < 200 micromol/litre Rebound jaundice was a rise of 17 micromol/litre after phototherapy discontinuation		
Author: Vecchi C Year: 1986 Country: Italy ID: [164]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 84 Inclusion: Hyperbilirubinaemia Exclusion: Blood group incompatibility, Haemolytic disease, Respiratory distress, Sepsis Demographics: Gender (M/F): Not reported Mean GA: 35 weeks Mean BW: 1930 gms Age at entry to study Not reported Mean TSB: 227 ± 40 micromol/litre	Group 1: Blue Phototherapy Group 2: Green Phototherapy Phototherapy units consisted of 8 (blue or green) fluorescent tubes positioned 46 cm above the mattress. The total power irradiance reaching the baby through two plastic shields was 2.3 mW/cm^2 for green phototherapy and 3.2 mW/cm^2 for blue phototherapy Phototherapy was continuous except for feeding etc Babies were placed in an incubator		TSB levels – change 24 hours: Group 1: -50 ± 23 micromol/litre Group 2: -48 ± 26 micromol/litre
Author: Sisson T Year: 1972 Country: USA ID: [165]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers Evidence level: 1-	N: 72 Inclusion: TSB ≥ 150 micromol/litre Exclusion: Sepsis, Respiratory distress, Blood group incompatibility, Haemolytic disease Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 2097 gms Age at entry to study Not reported Mean TSB: 190 micromol/litre	Group 1: Blue Phototherapy Group 2: Special Blue phototherapy Group 3: White phototherapy Each phototherapy unit consisted of 10 fluorescent tubes. Irradiance for blue lamps was 0.91 mW/cm^2 Irradiance for special blue lamps was 2.9 mW/cm^2 Irradiance for white lamps was 0.32 mW/cm^2	Incomplete data for all outcomes	Mean duration of phototherapy Group 1: 46 ± 15.7 hours Group 2: 40 ± 18.3 hours Group 3: 75 ± 29.4 hours

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
			Babies wore eye patches Phototherapy was continuous except for breaks for feeding etc Phototherapy discontinued at a steady rate and reached TSB ≤ 137 micromol/litre		
Author: Shinwell E Year: 2002 Country: Israel ID: [166]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed, opaque envelopes used Evidence level: 1^+	N: 32 Inclusion: Full-term, Birthweight > 2500gms, TSB > 308 micromol/litre Exclusion: Congenital malformation Demographics: Gender (M/F): 8/22 Mean GA: 38 ± 1 weeks Mean BW: 3500 ± 478 gms Age at entry to study 104.2 ± 33.7 hours Mean TSB: 320 ± 17 micromol/litre	Group 1: Supine position Group 2: Changing positions All babies received identical phototherapy for periods of 150 minutes followed by 30 minute breaks for feeding and routine nursing care. Babies in changing position group were alternated between supine and prone Phototherapy discontinued after two consecutive measurements TSB < 239 micromol/litre	ET: Group 1: 0/16 Group 2: 1/16 Rebound jaundice: Not reported Treatment failure: Group 1: 0/16 Group 2: 1/16	Mean duration of phototherapy Group 1: 28 ± 9 hours Group 2: 40 ± 15 hours Mean change in TSB: Group 1: -114 ± 23 micromol/litre Group 2: -108 ± 11 micromol/litre
Author: Chen C Year: 2002 Country: Taiwan ID: [167]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed envelopes used. Evidence level: 1^+	N: 51 Inclusion: TSB > 256 micromol/litre, Absence of blood group incompatibility, Normal G6PD status, Haemoglobin > 14g/dl Exclusion: Congenital anomalies, Significant bruising, Large cephalhematoma Demographics: Gender (M/F): 19/32 Mean GA: 38.2 ± 1.14 weeks Mean BW:3137 ± 384 gms	Group 1: Supine position Group 2: Changing position Phototherapy initiated at TSB ≥ 256 micromol/litre and discontinued at TSB ≤ 171 micromol/litre Babies in changing position group were alternated between supine and prone every 120 minutes		Mean duration of phototherapy Group 1: 53.3 ± 17.9 hours Group 2: 52.8 ± 20.2 hours Mean change in TSB: Group 1: -128 ± 54 micromol/litre Group 2: -126 ± 45 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Age at entry to study 143.4 ± 48.5 hours Mean TSB: Not reported			
Author: Mohammadzadeh A Year: 2004 Country: Iran ID: [168]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 50 Inclusion: TSB ≥ 256 micromol/litre (49–72 hours) TSB ≥ 291 micromol/litre (> 72 hours) Exclusion: Haemolytic disease, Congenital anomalies, Cephalhaematoma, Metabolic disease Demographics: Gender (M/F) : Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: 321 ± 39 micromol/litre	Group 1: Supine position Group 2: Changing position All babies received identical phototherapy for periods of 150 minutes followed by 30 minute breaks for feeding and routine nursing care. Babies in changing position group were alternated between supine and prone Phototherapy discontinued after two consecutive measurements TSB < 239 micromol/litre		Mean change in TSB: Group 1: -68 ± 27 micromol/litre Group 2: -62 ± 21 micromol/litre
Author: Lau S Year: 1984 Country: Hong Kong ID: [172]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 34 Inclusion: Full-term, Birthweight > 2500gms, TSB between 190 – 205 micromol/litre Exclusion: Jaundice with known causes Demographics: Gender (M/F): Not reported Mean GA: 39.9 ± 1.5 weeks Mean BW: 3229 ± 394 gms Age at entry to study Not reported Mean TSB: 198 ± 25 micromol/litre	Group 1: Continuous Phototherapy Group 2: Intermittent Phototherapy – 4 hours on - 4 hours off Group 3: Intermittent Phototherapy – 1 hour on - 3 hours off Phototherapy was discontinued when TSB < 171 micromol/litre		Mean duration of phototherapy Group 1: 89.9 ± 54.2 hours Group 2: 86.7 ± 28.9 hours Group 3: 100.0 ± 61.0 hours

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Author: Vogl T Year: 1978 Country: USA ID: [173]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 76 Inclusion: Birthweight between 1200 and 2400gms, TSB > 137 micromol/litre Exclusion: Haemolytic anaemia, Positive Coombs tests, Respiratory distress syndrome Demographics: Gender (M/F) : Mean GA: 34.7 ± 2.0 weeks Mean BW: 1836 ± 299 gms Age at entry to study 56.8 ± 10.8 hours Mean TSB: 150 ± 19 micromol/litre	Group 1: Continuous Phototherapy Group 2: Intermittent Phototherapy – 15 minutes on – 15 minutes off Group 3: Intermittent Phototherapy – 15 minutes on – 30 minutes off Group 4: Intermittent Phototherapy – 15 minutes on – 60 minutes off Therapy was discontinued when TSB < 137 micromol/litre on two successive occasions		Mean duration of phototherapy Group 1: 64 ± 50 hours Group 2: 57 ± 45 hours Group 3: 79 ± 40 hours Group 4: 80 ± 50 hours
Author: Fok T Year: 1995 Country: Hong Kong ID: [169]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated random numbers Evidence level: 1^+	N: 203 Inclusion: Gestational age > 35 weeks, Birthweight > 2300 gms, Exclusion: Other systemic illness, Eye infection, Haemolysis, Treatment with antibiotics, History of infection, Demographics: Gender (M/F): 106/97 Mean GA: 38.6 ± 2.56 weeks Mean BW: 3087 ± 611 gms Age at entry to study 89.5 ± 27.6 hours Mean TSB: 258 ± 27 micromol/litre	Group 1: Eye patches Group 2: Headbox Eye patches were obtained commercially, were removed during feeding and were replaced daily Headbox consisted of an opaque plastic box (20 x 20 x 16cm). Holes were used for ventilation.	Prurient eye discharge Group 1: 23/102 Group 2: 9/101 Features of Conjunctivitis Group 1: 13/102 Group 2: 2/101	Mean duration of phototherapy Group 1: 67.2 ± 33.6 hours Group 2: 64.5 ± 26.6 hours HC Professional satisfaction: 76 (70.4%) of nurse preferred the headbox while 17 (15.7%) preferred the eye patches.
Author: Paludetto R	Methodology:	N:	Group 1:		Mean duration of phototherapy

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Year: 1985 Country: Italy ID: [171]	RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	38 Inclusion: Healthy normal labour and delivery, Single birth, No congenital malformation, Apgar > 7 at 5 minutes, Birthweight > 2500 gms, Full-term, Breast –feeding, No perinatal complications Exclusion: Babies in Special Care Unit, Haemolytic disease, Hypocalcaemia, Polycythemia Demographics: Gender (M/F): 24/14 Mean GA: 39 weeks Mean BW: 3395 gms Age at entry to study 66.5 hours Mean TSB 232 micromol/litre	Eye patches Group 2: Screen Screen consisted of an opaque fabric suspended from the head end of the bassinet with ribbons attached to both upper sides of the crib so that the head is covered and the fabric falls freely upon the shoulders and neck of the baby. Two other ribbons tied to the lower part of the fabric are attached with adhesive tape behind the neck in a way that the bay is free to move and the fabric does not create any tension in the neck.		Group 1: 23.9 hours Group 2: 22.6 hours
Author: Wu P Year: 1974 Country: USA ID: [148]	Methodology: RCT Blinding: Not reported Randomisation: Randomised cards Evidence level: 1-	N: 120 Inclusion: Preterm babies with birthweight between 1250 and 2000 g Exclusion: Gross congenital anomalies, Haemolytic anaemias, Severe respiratory distress syndrome Demographics: Gender (M/F): 59/61 Mean GA: 34.0 ± 2.5 weeks Mean BW: 1736 ± 199 g Mean age at entry to study: Not reported Mean TSB: Not reported	Group 1: No treatment Group 2: Phototherapy - continuous Group 3: Phototherapy – Intermittent Babies in phototherapy group received 5 days of phototherapy while in incubators Phototherapy consisted of 10 20w cool-white fluorescent lamps suspended 45cm above the baby. Average irradiance during day was 0.05microW/cm^2/nm and at night was 0.01microW/cm^2/nm in the 400 – 500 nm wave band.	ET: Group 1: 0/40 Group 2: 0/40 Group 3: 0/40 Mortality: Group 1: 2/40 Group 2: 2/40 Group 3: 0/40	Max TSB: Group 1: 161 ± 51 micromol/litre Group 2: 115 ± 34 micromol/litre Group 3: 134 ± 32 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Author: Curtis-Cohen M Year: 1985 Country: USA ID: [149]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 22 Inclusion: Preterm babies Exclusion: Haemolytic disease, Direct hyperbilirubinaemia, sepsis Demographics: Gender (M/F) : Not reported Mean GA: 27.4 ± 1.4 weeks Mean BW: 858 ± 214 g Mean age at entry to study: Not reported Mean TSB: Not reported	Group 1: Early Phototherapy Group 2: Delayed start of treatment – Phototherapy started at TsB > 85.5micromol/litre Phototherapy consisted of a broad spectrum white light from a tungsten-halogen lamp in a Model 1400 phototherapy unit. Irradiance was maintained at 12microW/cm^2/nm at 450nm	ET: Group 1: 0/11 Group 2: 0/11 Mortality: Group 1: 0/11 Group 2: 0/11	Max TSB: Group 1: 112 ± 27 micromol/litre Group 2: 123 ± 20 micromol/litre
Author: Leite M Year: 2004 Country: Brazil ID: [150]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 81 Inclusion: Birthweight < 2000 g Exclusion: Haemolysis, G6PD deficiency, Malformations, Intestinal obstructions, Cholestasis, congenital infections, Maternal or neonatal use of Phenobarbital, TCB > 256.5micromol/litre Demographics: Gender (M/F) : 37/33 Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: Not reported	Group 1: Early Phototherapy Group 2: Phototherapy at TsB ≥ 136.8micromol/litre Phototherapy discontinued at TsB ≤ 85.5micromol/litre Phototherapy consisted of fanem Mod 007 units equipped with 7 Philips fluorescent lamps (special blue), 400 – 540 nm Average irradiance was 14.4microW/cm^2/nm	ET: Group 1: 0/35 Group 2: 0/35	Max TSB: Group 1: 113 ± 49 micromol/litre Group 2: 147 ± 36 micromol/litre
Author: Maurer H Year:	Methodology: RCT Blinding:	N: 69 Inclusion:	Group 1: Agar – 125mg in first 4ml of formula beginning at 18 hours and continued at 3 hourly intervals for 4 days		Max TSB: Group 1: 118 ± 40 micromol/litre Group 2: 108 ± 36 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
1973 Country: USA ID: [147]	Not reported Randomisation: Not reported Evidence level: 1-	Birthweight < 2500 g Exclusion: Positive Coombs test, Potential ABO incompatibility, sepsis Demographics: Gender (M/F) : 39/30 Mean GA: 34.2 ± 3.8 weeks Mean BW: 1860 ± 344 g Age at entry to study: < 24 hours Mean TSB: Not reported	 Group 2: Early phototherapy – Intermittent – 12 hours daily for 4 days Group 3: Early phototherapy – Continuous – 24 hours daily for 4 days Group 4: No treatment Phototherapy consisted of 8 blue fluorescent lamps (200 – 300 foot candles) 40 cm above the baby		Group 3: 60 ± 42 micromol/litre Group 4: 147 ± 57 micromol/litre
Author: Wananukul S Year: 2002 Country: Thailand ID: [188]	Methodology: RCT Blinding: Not reported Randomisation: Nor reported Evidence level: 1-	N: 40 Inclusion: Preterm babies requiring phototherapy for hyperbilirubinaemia Exclusion: Skin disease, Respiratory distress Demographics: Gender (M/F) : 22/18 Mean GA: 33.1 ± 2.6 weeks Mean BW: 1444 ± 196 g Mean age at entry to study: Not reported Mean TSB: 171 ± 39 micromol/litre	Group 1: Clear topical ointment 3.0 ml (Vaseline:liquid paraffin = 1:1) Group 2: No ointment All babies were placed in incubators. Ointment was applied to the whole body, measurements taken from upper arms, back and legs. Evaporation rate was measured by a method based on the determination of the water vapour pressure gradient in the air layer closed to the skin surface. (Tewameter TM 210)		TEWL – at 5 hours Group 1: 7.5 ± 1.5 g/m^2/h Group 2: 8.9 ± 1.6 g/m^2/h
Author: Eggert P Year: 1988 Country: Germany ID: [191]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level:	N: 101 Inclusion: Uncomplicated hyperbilirubinaemia Exclusion: Age < 40 hours with ABO or Rh incompatibility,	Group 1: Conventional Phototherapy Group 2: Conventional Phototherapy + white curtains Group 3: Halide Phototherapy		Mean change in TsB (24 hours) Group 1: -56 ± 26 micromol/litre Group 2: -80 ± 27 micromol/litre Group 3: -55 ± 22 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
	1^{-}	Babies who received antibiotics Demographics: Gender (M/F): 62/39 Median GA: 40 weeks Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: 243 ± 28 micromol/litre	All babies were treated in intensive care incubators. Conventional phototherapy consisted of a Drager 76 unit equipped with 6 blue standard fluorescent lights (light range 410 – 520 nm) In the second group the four outer walls of the incubator were draped in white cloth The halide phototherapy consisted of a Drager 8000 halide lamp (light range 400 – 580 nm) All phototherapy units were 34cm above the mattress. Babies were naked except for a bikini diaper and blindfolds and were their position was changed every 4 hours. Phototherapy could be interrupted for nursing care and feedings. Babies received oral feedings of either mother's milk or adapted formula and dextrose solution.		
Author: Djokomuljanto S Year: 2006 Country: Malaysia ID: [190]	Methodology: RCT Blinding: Investigators blinded to allocation Randomisation: Block randomisation Evidence level: 1^{+}	N: 100 Inclusion: Term babies with uncomplicated jaundice requiring phototherapy Exclusion: TsB approaching criteria for exchange transfusion Demographics: Gender (M/F): 56/44 Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: 105 ± 35 hours Mean TSB: 264 ± 59 micromol/litre	Group 1: Conventional phototherapy Group 2: Conventional phototherapy + white curtains Conventional phototherapy consisted of Phoenix Medical Systems unit of 6 compact blue fluorescent lamps 45 cm above the baby. Curtains were hung on both sides if the phototherapy unit.		Mean change in TsB (4 hours) Group 1: -4 ± 24 micromol/litre Group 2: -28 ± 25 micromol/litre

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Author: Sivanandan S Year: 2009 Country: India ID: [192]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed opaque envelopes use Evidence level: 1^+	N: 84 Inclusion: Term babies with non-haemolytic jaundice on a postnatal ward of a tertiary level neonatal unit Age ≥ 24 hours and ≤ 20 days, 5 minute Apgar > 6, TSB < 359 micromol/litre Exclusion: Hyperbilirubinaemia requiring exchange transfusion, Rh haemolysis, G6PD deficiency, Evidence of haemolysis, Positive Coombs' test, Major congenital malformation, Culture-positive sepsis, Need of intensive care Demographics: Gender (M/F): 47/35 Mean GA: 37.5 ± 1.3 weeks Mean BW: 2856 ± 345 g Mean age at entry to study: 69 ± 36 hours Mean TSB: 280 ± 39 micromol/litre	Group 1: Conventional phototherapy Group 2: Conventional phototherapy + white curtains Conventional phototherapy consisted of Phoenix Medical Systems unit of 4 blue and 2 white compact fluorescent lamps 45 cm above the baby. Light range was425 – 475 nm White plastic sheets could be attached to the sides of the unit Treatment failure was defined as TSB > 342 micromol/litre Phototherapy was discontinued if If started after 72 hours of age after two consecutive TSB < 256 micromol/litre If started before 72 hours of age after two consecutive were less than age-specific threshold for phototherapy TSB was measured for rebound after 8 hours	Phototherapy failure Group 1: 52 Group 2: 4/42 ET: Group 1: 0/10 Group 2: 0/10 Mortality: Group 1: 0/10 Group 2: 0/10	Mean change in TsB (24 hours) Group 1: -34 ± 63 micromol/litre Group 2: -39 ± 56 micromol/litre Mean duration of phototherapy Group 1: 24.9 ± 15.4 hours Group 2: 23.3 ± 12.9 hours
Author: Grunhagen D Year: 2002 Country: Netherlands ID: [187]	Methodology: Case series Blinding: None Randomisation: None Evidence level: 3	N: 18 Inclusion: Preterm with non-haemolytic hyperbilirubinaemia Exclusion: None Demographics: Gender (M/F): / Mean GA: 30.6 ± 1.6 weeks	All babies received phototherapy which consisted of a single quartz spotlight (Bililight Ohmeda) 55 cm above the baby. The irradiance was 12.5 microwatt/cm² per nm. Light range was 420 – 480 nm. TEWL was measured with a Tewameter TM210 (YSI Inc) and measurements taken on chest or back of the baby. TEWL was measured when hyperbilirubinaemia was diagnosed and 60 minutes after initiation of		Mean change in TEWL 2.9 ± 3.9 $g/m^2/h$ TEWL retuned to pre-phototherapy levels within 1 hour of discontinuation of phototherapy

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Mean BW: 1412 ± 256 g Mean age at entry to study: 120 ± 72 hours Mean TSB: Not reported	phototherapy.		
Author: Wananukul S Year: 2001 Country: Thailand ID: [185]	Methodology: Comparative study Blinding: None Randomisation: None Evidence level: 2-	N: 80 (40 with hyperbilirubinaemia who received phototherapy and 40 healthy controls) Inclusion: Term babies Exclusion: None Demographics: Gender (M/F): 44/36 Mean GA: 39.0 ± 1.2 weeks Mean BW: 3166 ± 435 g Mean age at entry to study: Not reported Mean TSB: Not reported	Babies with hyperbilirubinaemia received conventional phototherapy in open cribs. Phototherapy consisted of 6 white and 2 blue fluorescent bulbs in a plexiglass-bottomed box 30cm above the baby. Irradiance was 10 microwatt/cm² per nm. TEWL was measured with a Tewameter TM 2/0 (Courage & Khazama) and measurements were taken at chest, interscapular and buttocks of the baby. Measurements were taken before phototherapy and repeated at 30 minutes and 6 hours during phototherapy.	ET: Group 1: Group 2: Mortality: Group 1: Group 2:	Mean change in TEWL PT: 1.2 ± 3.9 g/m^2/h Control: 0.2 ± 0.9 g/m^2/h TEWL retuned to pre-phototherapy levels within 1 hour of discontinuation of phototherapy
Author: Maayan-Metzeger A Year: 2001 Country: Israel ID: [186]	Methodology: Case series Blinding: None Randomisation: None Evidence level: 3	N: 31 Inclusion: Preterm with hyperbilirubinaemia Exclusion: Respiratory distress, Sepsis, Need for ventilatory support Demographics: Gender (M/F): 15/16 Mean GA: 31.2 weeks Mean BW: 1447 g Mean age at entry to study: 106 hours Mean TSB: Not reported	All babies were nursed naked, except for eye pads, in incubators and received phototherapy.. Conventional phototherapy consisted of (Air Shields Micro-Lite) Light range was 400 – 500 nm. TEWL was measured usinga combined Tewameter and corneometer (Courage and Khazka) TEWL was measure in seven body areas; forehead, upper back, cubital fossa, palms, abdomen, soles, and inguinal region. Measurement were taken before start of phototherapy and repeated during phototherapy (at least 4 and up to 24 hours)		Mean change in TEWL PT: 4.3 ± 4.7 g/m^2/h
Author: Rosenfeld W	Methodology: RCT	N: 74	Group 1: Phototherapy	Patent Ductus Arteriosus Group 1: 23/38 Group 2: 11/36	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Year: 1986 Country: USA ID: [184]	Blinding: Not reported Randomisation: Randomisation chart Evidence level: 1^{+}	Inclusion: Preterm babies with gestational age between 26 and 32 weeks Exclusion: None Demographics: Gender (M/F):Not reported Mean GA: 29.4 weeks Mean BW: 2034 g Mean age at entry to study: Not reported Mean TSB: micromol/litre	Group 2: Phototherapy with Chest shields All babies were receiving early phototherapy to prevent hyperbilirubinaemia and were nursed under radiant warmers, receive mechanical ventilation for respiratory distress syndrome. Standard phototherapy units (Air Shields) were used Mean light intensity was 4.77 microwatt/cm² per nm Chest shields were folded (doubled) piece of aluminium foil covered in a gauze pad and taped over the left chest.	Late mortality Group 1: 4/38 Group 2: 10/36	
Author: Tatli M Year: 2008 Country: Turkey ID: [178]	Methodology: Comparative study with healthy controls Blinding: None Randomisation: None Evidence level: 2^{-}	N: 47 (14 were healthy controls) Inclusion: Term babies with non-haemolytic hyperbilirubinaemia Exclusion: None Demographics: Gender (M/F):29/18 Mean GA: 39.3 ± 0.9 weeks Mean BW: 3021 ± 450 g Mean age at entry to study: 113 ± 46 hours Mean TSB: Not reported	Phototherapy consisted of standard unit of 4 blue and 2 white fluorescent tubes (Air Shields) with a light range of 480 – 520 nm and an irradiance of 12 microwatt/cm² per nm. Phototherapy lasted 72 hours, babies whose TsB declined to normal levels before 72 hours were excluded.		Mean change in Lymphocyte-DNA damage PT: 29.1 ± 1.9 Control: 2.7 ± 2.9
Author: Berg P Year: 1997 Country: Sweden ID: [180]	Methodology: Retrospective matched case–control study Blinding: None Randomisation: None Evidence level:	N: 150 Inclusion: 30 cases of childhood cancer before 20 years of age and 120 controls Exclusion: None Demographics:		PT Cases: 0/30 Controls: 11/120	No increased risk of developing childhood malignant melanoma in skin of babies who received phototherapy

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
	2-	Gender (M/F):Not reported Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: Not reported			
Author: Matichard E Year: 2006 Country: France ID: [182]	Methodology: Case control study Blinding: Not reported Randomisation: Not reported Evidence level: 2-	N: 58 Inclusion: Primary school children (age 8 – 9) Exclusion: Not reported Demographics: Gender (M/F) 30/28 Mean GA: N/A Mean BW: NA Mean age at entry to study: N/A Mean TSB: N/A	Collected information included, Phototype (Fitzpatrick's classification), Behaviour in the sun, Sun protection policy, History of phototherapy for neonatal jaundice A melanocytic nevus count was conducted by a dermatologistpy The size of nevi was recorded < 2mm, 2–5mm, > 5mm	Received phototherapy = 18 Controls = 40	Mean melanocytic coun (nevus ≥ 2mm): Phototherapy 3.5 ± 3.05 Controls:1.45 ± 1.99
Author: Turan O Year: 2004 Country: Turkey ID: [183]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 98 Inclusion: Term and preterm babies receiving phototherapy for hyperbilirubinaemia Exclusion: Congenital malformations, Sepsis, babies receiving positive inotropic drugs Demographics: Gender (M/F):Not reported Mean GA: 36.7 ± 3.2 weeks Mean BW: 2880 ± 803 g Mean age at entry to study: Not reported Mean TSB: Not reported			No significant correlation found between heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure and serum nitric oxide and vascular endothelial growth factor.
Author: Speck W Year: 1979	Methodology: Review Blinding: Not reported	Review of *in vivo* studies of effects of phototherapy on cell DNA			

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Country: USA ID: [177]	Randomisation: Not reported Evidence level: 1-				
Author: Weissman A Year: 2009 Country: Israel ID: [189]	Methodology: Before–after study Blinding: None Randomisation: None Evidence level: 3	N: 30 Inclusion: Jaundice GA = 37 – 42 weeks Apgar (1 min) > 7 Apgar (5 min) > 8 Exclusion: Haemolysis, G6PD, Fever, Maternal use of narcotic analgesic drugs during labour, Ruptured membranes > 18ours Demographics: Gender (M/F)16/14 Mean GA: 39.1 ± 1.5 weeks Mean BW: 3116 ± 392 g Mean age at entry to study: 53 ± 31 hours Mean TSB: 238 ± 43 micromol/litre	Phototherapy consisted of an overhead LED unit (neoBLUE) Irradiance was 34 microwatt/cm² per nm.		Heart Rate variability – SD1 Before: 12 ± 8 ms After : 8 ± 4ms *P* < 0.02 Heart Rate variability – SD2 Before: 33 ± 16 ms After : 22 ± 10 ms *P* < 0.01 Heart Rate variability – SDDN Before: 30 ± 14 ms After : 18 ± 7 ms *P* < 0.01 Heart Rate variability – RMSSD Before: 18 ± 12 ms After : 11 ± 6 ms *P* < 0.02
Author: Mahe E Year: 2009 Country: France ID: [181]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1+	N: 828 Inclusion: Primary school children (age 8 – 9) Exclusion: Not reported Demographics: Gender (M/F) 415/413 Mean GA: N/A	Collected information included, Phototype (Fitzpatrick's classification), Behaviour in the sun, Sun protection policy, History of phototherapy for neonatal jaundice A melanocytic nevus count was conducted by trained nurses who was blind to whether the child had received phototherapy The size of exposed body parts (arm and	Received phototherapy = 180 Controls = 648	There was no difference in nevus counts as a function of exposure to neonatal phototherapy. Mean melanocytic count: Phototherapy 16.8 ± 9.8 Controls:16.7 ± 10.5

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
		Mean BW: NA Mean age at entry to study: N/A Mean TSB: N/A	back)was record < 2mm, 2–5mm, > 5mm		
Author: Ayclcek A Year: 2008 Country: Turkey ID: [179]	Methodology: Case control study Blinding: Not reported Randomisation: Not reported Evidence level: 2-	N: 65 Inclusion: Indirect hyperbilirubinaemia TSB > 222 micromol/litre Exclusion: Severe congenital malformation, Preterm birth or postmaturity, Maternal diabetes, Birth asphyxia, Sepsis, Haemolysis due to ABO/Rh incompatibility, Phototherapy before blood was collected, Bilirubin rising by more than 85 micromol./litre day in first 24 hour, Tsb > 410 micromol/litre Demographics: Gender (M/F) 35/28 Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: Not reported	Group 1: Intensive phototherapy Group 2: Conventional phototherapy Group 3: No phototherapy Phototherapy consisted of six white fluorescent tubes 40cm above the baby. 12–16 microwatt/cm² per nm. Intensive phototehrpay consisted of 12 white fluorescent tubes 20cm above and below the baby. 30–34 microwatt/cm² per nm. DNA damage was measured in blood samples taken after phototherapy. The images of 100 randomly selected nuclei (50 from each of two replicate slides) were analysed visually.		Mean duration of phototherapy: Group 1: 54 ± 6 hours Group 2: 61 ± 10 hours Group 3: N/A DNA damage (arbitrary units): Group 1: 32 ± 9 Group 2: 28 ± 9 Group 3: 21 ± 10 $P < 0.001$

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

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Tontisirin K Year: 1989 Country: Thailand ID: [176]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^{-}	N: 25 Inclusion: Hyperbilirubinaemia TSB ≥ 256.5 micromol/litre Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3185 ± 288 gms Age at entry to study: 95 ± 17.7 hours Mean TSB: Not reported	Group 1: Formula feed – *Enfamil (Energy = 20 kcal/oz, contains 1.5 g/dl protein, 3.7 g/dl fat, 7 g/dl carbohydrate, mineral 0.34 g/dl, water 87.4 g/dl)* Group 2: Lactose-free Formula feed – *Enfamil ProSobee(Energy = 20 kcal/oz, contains 2 g/dl protein, 3.6 g/dl fat, 6.6 g/dl carbohydrate, mineral 0.3 g/dl, water 87.4 g/dl)* Babies were fed ad libitum with formula (3 ounces) 8 times/day.		Mean decrease in TsB: Group 1: -97 ± 41 micromol/litre Group 2: -92 ± 46 micromol/litre Weight gain/loss: Group 1: 33 ± 65 gms Group 2: -7 ± 55 gms	
Author: Mehta S Year: 2005 Country: India ID: [174]	Methodology: RCT Blinding: Not reported Randomisation: Stratified block randomisation (based on TsB levels) using sealed opaque envelopes Evidence level: 1^{++}	N: 74 Inclusion: Hyperbilirubinaemia TsB > 308 micromol/litre Exclusion: TsB > 427 micromol/litre, Kernicterus, Evidence of hemolysis, Signs of dehydration, Major congenital malformations, Babies on IV fluids Demographics: Gender (M/F): 52/22 Mean GA: 37.6 ± 0.9 weeks Mean BW: 2936 ± 473 gms Age at entry to study 130 ± 31 hours Mean TSB: 350 ± 31micromol/litre	Group 1: Phototherapy + Usual feeds Group 2: Phototherapy + Usual Feeds + Extra fluids Extra fluids consisted of IV fluid supplementation with N/5 saline in 5% dextrose for a period of 8 hours before phototherapy. After babies were offered 30mL/kg/day of extra oral feeds (expressed breast milk or formula) until phototherapy discontinued Phototherapy was discontinued when two TsB values obtain 12 hours apart were < 256 micromol/litre Exchange transfusion was done if at 4 hours into the study TsB increased by > 34 micromol/litre or if at 8 hours TsB remained > 342 micromol/litre	Exchange Transfusions Group 1: 20/37 Group 2: 6/37	Mean decrease in TsB (24 hours): Group 1: -69 ± 28 micromol/litre *n* = 17 Group 2: -95 ± 22 micromol/litre *n* = 31 Mean duration of treatment: Group 1: 73 ± 31 hours Group 2: 52 ± 18 hours	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Boo N Year: 2002 Country: Malaysia ID: [175]	Methodology: RCT Blinding: Not reported Randomisation: Stratified randomisation (type of feed, hydration status, and TsB levels) using sealed envelopes Evidence level: 1^{+}	N: 54 Inclusion: TsB > 300 micromol/litre with conjugated bilirubin ≤15% of TsB Exclusion: Sick babies, Major congenital malformations, Conjugated hyperbilirubinaemia, prolonged jaundice Demographics: Gender (M/F): 28/26 Mean GA: 39.4 ± 0.9 weeks Mean BW: 3075 ± 429 gms Age at entry to study: 139 ± 47 hours Mean TSB: 377 ± 66 micromol/litre	Group 1: Phototherapy + Enteral feeds alone Group 2: Phototherapy + 50 % Enteral feeds + 50 % Intravenous feeds All babies received a daily maintenance fluid level of 90 mL/kg on day 2, 1290 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 the fluid loss. Enteral feeds group Formula-fed babies were given 8 divided feeds at 3 hour intervals. Breastfed babies were breastfed on demand. In addition they were given half of the calculated volume of formula feeds given to the formula-fed babies. Enteral + Intravenous group Formula-fed babies were given half of their 24hour fluid requirement at eight divided feeds at 3hour intervals. The remaining half of their daily fluid requirement was given as continuous intravenous1/5 normal saline and 5% dextrose infusion via a peripheral vein over 24 hours. Breastfed babies were breastfed on demand. Half of their daily fluid requirement was given as continuous intravenous1/5 normal saline and 5% dextrose infusion via a peripheral vein over 24 hours.	Exchange Transfusions Group 1: 5/27 Group 2: 8/27 Mortality Group 1: 0/27 Group 2: 0/27	Mean decrease in TsB (4 hours): Group 1: -37 ± 44 micromol/litre Group 2: -43 ± 37 micromol/litre	
Author: Martinez J Year: 1993 Country: Argentina ID: [133]	Methodology: RCT Blinding: Not reported Randomisation: Computer-generated Evidence level:	N: 125 Inclusion: TSB > 291micromol/litre Exclusion: Congenital anomalies Neonatal complications Birthweight below 10^{th}	Group 1: Continue breastfeeding Group 2: Discontinue breastfeeding, substitute formula feeds Group 3: Discontinue breastfeeding, substitute formula feeds, add Conventional	ET: Group 1: 0/25 Group 2: 0/26 Group 3: 0/38 Group 4: 0/36 Treatment failure: Group 1: 6/25 Group 2: 5/26 Group 3: 1/38	Mean decrease in TsB (48 hours): Group 3: -77 ± 41 micromol/litre Group 4: -65 ± 34 micromol/litre	Only data from groups 3 and 4 used

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
	1^{+}	percentile or above 90th percentile Venous hematocrit > 65% Significant bruising Large cephalhematoma Haemolytic disease Demographics: Gender (M/F):70/55 Mean GA: 39.2 ± 0.9 weeks Mean BW: 3404 ± 361gms Age at entry to study: Not reported Mean TSB: 306 ± 12 micromol/litre	phototherapy Group 4: Continue breastfeeding, add Conventional Phototherapy Conventional Phototherapy consisted of Quartz halide spot unit Irradiance = 10 microwatt/cm² Light band = 400 – 480 nm Babies were naked with eyes patched in a bassinet Phototherapy discontinued at TSB < 231 micromol/litre	Group 4: 5/36		

How to monitor a baby with jaundice?

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

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments	Bibliographic details
Author: Kaplan M Year: 2005 Country: Israel ID: [126]	Study Type: Clinical study Evidence Level: 3	Diagnosis Hyperbilirubinaemia Criteria: Need for phototherapy: according to AAP 1997 Setting Medical Center Demographics: Sample size: 226 Gender (M/F): 134/92 Mean GA: 39 ± 2 weeks Mean BW: 3204 ± 445 g	Phototherapy criteria < 24 hours 170 micromol/litre 24–38 hours 205 micromol/litre 48–72 hours 256 micromol/litre > 72 hours 291–308 micromol/litre Babies with risk factors at 17 – 34 micromol/litre below these levels For readmitted babies TsB ≥ 308 – 342 micromol/litre Bilirubin routinely measured every 12 hours (checked more if clinical need) Phototherapy discontinued at 205 micromol/litre or if TsB did not reach 205 once TsB stabilised and became lower than 75th centile on the hour specific nomogram Rebound Jaundice criteria TsB measured between 2 and 36 hours after discontinuation of phototherapy If TsB was ≥ 120% of post-phototherapy or ≥ 239 micromol/litre were followed at 12–24 hour intervals Phototherapy was r-continued at clinician discretion but usually not below 256 micromol/litre	**Primary phototherapy** Mean TsB at onset: 251 ± 53 micromol/litre Age at onset 53 ± 29 hours Mean duration 43 ± 23 hours Mean TsB at discontinuation 182 ± 20 micromol/litre Rebound Jaundice 30/196 (15.3%) **Phototherapy after readmission** Mean TsB at onset: 318 ± 22 micromol/litre Age at onset 122 ± 38 hours Mean duration 30 ± 9 hours Mean TsB at discontinuation 182 ± 18 micromol/litre Rebound Jaundice 0/30 (0.0%)	

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments	Bibliographic details
Author: Barak M Year: 2009 Country: Israel ID: [125]	Study Type: RCT Evidence Level: 1++	Diagnosis Hyperbilirubinaemia Criteria: GA > 36 weeks BW > 2500 g Setting Medical Center Randomisation method: Computer-generated block randomisation. Sequence was concealed until allocation was completed Blinding: Parents Demographics: Sample size: 52 Gender (M/F): 27/25 Mean GA: 38.7 ± 1.6 weeks Mean BW: 3302 ± 453 g Mean TsB: 252 ± 36 micromol/litre	Once TsB reached criteria for phototherapy (AAP 2004)[19] the baby was given phototherapy to two group for when phototherapy should be discontinued Group 1 TsB ≥ 17 micromol/litre below threshold Group 2 TsB ≥ 51 micromol/litre below threshold	Duration of phototherapy: Group 1: 22 ± 13 hours Group 2: 27 ± 12 hours Rebound level – 10 hours: Group 1: 1.8 ± 25.6 micromol/litre Group 2: 4.8 ± 22.2 micromol/litre Rebound level – 28 hours: Group 1: 19.1 ± 29.1 micromol/litre Group 2: 11.6 ± 36.4 micromol/litre Number requiring PT Group 1: 5/25 (20.0%) Group 2: 5/27 (18.5%)	

Exchange transfusion

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Tan K Year: 1975 Country: Singapore ID: [197]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 52 Inclusion: Non-hemolytic jaundice Exclusion: Not reported Demographics: Gender (M/F): 28/24 Mean GA: 37.0 ± 2.78 weeks Mean BW: 2501 ± 576 gms Age at entry to study 84 ± 12 hours Mean TSB: 297 ± 25 micromol/litre	Group 1: Double Volume Exchange transfusion Group 2: Phototherapy Both treatments initiated at 256.micromol/litre in preterm babies and at 308 micromol/litre in term babies Exchange transfusion was performed in the morning using the umbilical vein. Acid Citrate Dextrose blood (warmed to 37^{O}C) less than 5 days old was used. Volume was 170ml/kg body weight Daily TSB values from capillary blood were determined until stabilisation at a safe level or an obviously decreasing trend were observed. Phototherapy consisted of seven fluorescent lamps Light spectral range = 400 – 500 nm Energy output range = 250 – 330 microwatt/cm² Phototherapy discontinued at TSB < 188 micromol/litre	Mortality: Group 1: 0/26 Group 2: 0/26 Treatment failure (repeated treatment) Group 1: 8/26 Group 2: 0/26 TSB < 188 micromol/litre Group 1: 3/26 Group 2: 25/26	Mean decrease in TSB (24 hours): Group 1: -26 ± 24 micromol/litre Group 2: -77 ± 17 micromol/litre	
Author: Amato M Year: 1988 Country: Switzerland ID: [196]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table Evidence level: 1-	N: 20 Inclusion: ABO incompatibility, Hyperbilirubinaemia Exclusion: Perinatal asphyxia, Congenital anomalies, Documented congenital infection, Suspected or proven bacterial infection,	Group 1: Double Volume Exchange Transfusion Group 2: Single Volume Exchange Transfusion Blood preparation A unit of packed red cells was used. Mean blood volume of each unit was 280 ± 40 ml (2/3 red cell volume and 1/3 plasma volume) Mean sodium was 168 ± 43 micromol/litre	Mortality: Group 1: 0/10 Group 2: 0/10	Mean decrease in TSB: Group 1: -73 ± 33 micromol/litre Group 2: -69 ± 20 micromol/litre Duration of phototherapy (hours): Group 1: 38.1 ± 16.4 hours Group 2: 45.4 ± 17.7 hours Rebound level: Group 1: 74 ± 41 micromol/litre Group 2: 65 ± 17 micromol/litre	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
		Respiratory distress, Secondary hyperbilirubinaemia (due to medications, polycythemia, skin hematomas or cephalhematoma) Demographics: Gender (M/F): 15/5 Mean GA: 39.5 ± 1.0 weeks Mean BW: 3305 ± 392 gms Age at entry to study 17.9 ± 6.13 hours Mean TSB: 207 ± 45 micromol/litre	Mean potassium 6.8 ± 1.4 micromol/litre No immunoglobulin or clotting factors were present. Hemoglobin and hematocrit values were equally distributed between the two samples. Exchange transfusion was performed through the umbilical vein in 1 hour using a disposable exchange transfusion set in 10 ml portions. No additional calcium or human albumin given All babies received double phototherapy after exchange transfusion. Phototherapy consisted of a double blue light united (2 x 30 microwatt/cm²) mounted 30 cm above and under the mattress. Babies were nursed with 10%(120ml/kg) glucose Phototherapy discontinued at TSB < 205 micromol/litre on two successive occasions. Rebound jaundice was defined as a rise of 17 micromol/litre or more after treatment was discontinued.			
Author: Chan G Year: 1976 Country: Canada ID: [198]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 42 Inclusion: Need for exchange transfusion Exclusion: Not reported Demographics: Gender (M/F): 25/17 Mean GA: 36.0 ± 0.7 weeks Mean BW: 2455 ± 153 gms Age at entry to study Not reported Mean TSB:	Group 1: Double Volume Exchange Transfusion Group 2: Double Volume Exchange Transfusion + Albumin priming Double Volume Exchange Transfusion consisted of Acid Citrate Dextrose blood less than 48 hours old Albumin priming consisted 1 gm/kg of salt-poor human albumin given intravenously 1 hour prior to the exchange transfusion	Mortality: Group 1: 0/27 Group 2: 0/15	Mean decrease in TSB: Group 1: -193 ± 56 micromol/litre Group 2: -168 ± 63 micromol/litre Rebound level: Group 1: 74 ± 32 micromol/litre Group 2: 92 ± 56 micromol/litre	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
		263 ± 82 micromol/litre				
Author: Grajwer L Year: 1976 Country: USA ID: [199]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 43 Inclusion: Need for exchange transfusion Exclusion: Not reported Demographics: **> 2500 g** Gender (M/F): Not reported Mean GA: 39.1 ± 1.8 weeks Mean BW:3234 ± 494 gms Age at entry to study Not reported Mean TSB: 328 ± 25 micromol/litre **< 2500 g** Gender (M/F): Not reported Mean GA: 32.6 ± 3.2 weeks Mean BW:1670 ± 434 gms Age at entry to study Not reported Mean TSB: 304 ± 48 micromol/litre	**> 2500gms** Group 1: Double Volume Exchange Transfusion of whole blood less than 5 days old Group 2: Frozen erythrocytes diluted in plasma **< 2500gms** Group 1: Exchange transfusion of whole blood less than 5 days old Group 2: Frozen erythrocytes diluted in plasma Exchange transfusion criteria were 1/ Cord blood bilirubin > 85.5 micromol/litre and rapidly increasing by more than 8.5 micromol/litre an hour) 2/ Increase of TSB > 17.1 micromol/litre per hour during first 24 hours if cord blood bilirubin is unknown 3/ Two repeated values of 342 micromol/litre indirect bilirubin for babies > 2500 gms or 273.6 micromol/litre in babies < 2500gms 4/ In sick preterm babies with asphyxia or acidosis or receiving ventilatory assistance ET was performed at two repeated values of 356.5 micromol/litre Exchange transfusion was repeated after two repeated values of 342 micromol/litre indirect bilirubin for babies > 2500gms and 273.6 micromol/litre for babies < 2500gms	**> 2500gms** Mortality: Group 1: 0/5 Group 2: 1/8 **< 2500gms** Mortality: Group 1: 1/14 Group 2: 3/16 **> 2500gms** Repeat ET: Group 1: 1/5 Group 2: 1/8 **< 2500gms** Repeat ET: Group 1: 4/14 Group 2: 7/16	**> 2500gms** Mean decrease in TSB: Group 1: -144 ± 17 micromol/litre Group 2: -149 ± 22 micromol/litre **< 2500gms** Mean decrease in TSB: Group 1: -156 ± 51 micromol/litre Group 2: -177 ± 24 micromol/litre	Sample was divided into 2 groups < 2500gms and > 2500gms before randomisation
Author: Locham K Year: 2002 Country: India	Methodology: CCT Blinding: None Randomisation: None	N: 30 Inclusion: Jaundice requiring exchange transfusion Exclusion:	Group 1: Double Volume Exchange Transfusion Group 2: Double Volume Exchange Transfusion + Supplementary calcium		No jaundice related outcomes	Noted increased instances of bradycardia and fluctuations in heart rate after calcium injections. One baby had cardiac arrest.

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
ID: [201]	Evidence level: 1-	Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Hrs: Not reported Mean TSB: Not reported				
Author: Ahmed S Year: 2005 Country: India ID: [202]	Methodology: Case series Blinding: None Randomisation: None Evidence level: 3	N: 198 Inclusion: Need for exchange transfusion Exclusion: None Demographics: Gender (M/F): 65/3 Mean GA: 34.5 weeks Mean BW: Not reported Age at entry to study Not reported Mean TSB: Not reported	Peripheral exchange transfusion Brachial or radial artery was cannulated with a 24G cannula under all aseptic conditions. A good peripheral or antecubital vein on the other side was cannulated with a 22G or a 24G angiocath. Citrate phosphate dextrose fresh blood was used for the procedure & and phototherapy was used pre & post exchange. Two operators carried out the procedure using aliquots of 5–10 ml on withdrawal; and infusion. Three way stop-cocks were used on either side and arterial catheter flushed with 0.5ml of heparin solution (5units/ml) after every 50ml. Procedure was performed under radiant warmer with monitoring of heart rate, respiratory rate, body temperature and oxygen saturation.	Reported decreased chances of sepsis, complete exchange and more safety in peripheral exchange transfusion/ It is also cost-effective as only two angiocaths, two stop-cocks and two 10ml syringes are needed compared to a complete exchange set used in umbilical route.	:	
Author: NICHHD Year: 1985 Country: USA ID: [129]	Methodology: Randomised controlled trial Blinding: None Randomisation: None Evidence level: 1++	N: 190 Inclusion: Received an exchange transfusion Exclusion: None Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: Not reported		Adverse effects: :Transient bradycardia: 8 (4.2%) - 6 with calcium Transient cyanosis: 3 (1.6%) Transient vasospasm: 2 (1.0%) Vasospasm with thrombosis: 2 (1.0%) Apnea and/or bradycardia requiring treatment: 7 (3.7%)	Mean decrease in TSB after ET: 139 ± 30 micromol/litre	This report includes data from exchanges transfusions carried out during a RCT of phototherpay.

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
				Mortality: One baby died with 6 hours of ET Three died with 24 hours of ET		
Author: Mollison P Year: 1952 Country: UK ID: [194]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers, Sealed envelopes used Evidence level: 1^+	N: 137 Inclusion: Haemolytic disease of the newborn, Term babies Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: Not reported	Group 1: Exchange transfusion Group 2: Simple transfusion All exchange transfusion were carried out with 9 hours of birth, using a concentrated suspension of Rh-negative red cells (60ml/lb)	Mortality: Group 1: 8/62 Group 2: 21/57 Deaths due to kernicterus Group 1: 6/62 Group 2: 18/57 Kernicterus Group 1: 12/62 Group 2: 22/57		Data from one centre 'N' used
Author: Armitage P Year: 1953 Country: UK ID: [195]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers, Sealed envelopes used Evidence level: 1^+					Secondary publication of [194]
Author: Patra K Year: 2004 Country: USA ID: [203]	Methodology: Retrospective chart review Blinding: Not reported Randomisation: Not reported	N: 55 Inclusion: Babies who had an exchange transfusion, Hyperbilirubinaemia Exclusion: Poplycythemia,		Adverse Effects/ET Mortality: 1/66 Hypotension: 5/66 Seizures: 1/66 Platelets < 50 000 microlitre/litre : 29/66 Calcium < 8mg/dl: 19/66 Catheter malfunction: 6/66 Hypoglycemia: 2/66		

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
	Evidence level: 3	anaemia Demographics: Gender (M/F): 30/25 Mean GA: 35 ± 4 weeks Mean BW:2388 ± 973 g Age at entry to study: Not reported Mean TSB: 307.8 ± 136.8 micromol/litre		Respiratory distress: 2/66 Bradycardia: 1/66 Hypokalemia: 1/66 Acute renal failure: 1/66 Omphalitis: 1/66		
Author: Wishingrad L Year: 1965 Country: USA ID: [193]	Methodology: RCT Blinding: Not reported Randomisation: Stratified randomisation And sealed envelopes used Evidence level: 1^+	N: 100 Inclusion: Indirect serum Bilirubin > 307.8 micromol/litre No anomalies, Less than 7 days old Exclusion: Not reported Demographics: Gender (M/F): Unclear Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Double volume exchange transfusion Group 2: No treatment The double volume exchange transfusion (based on an estimated blood volume of 75ml/kg) was carried out with type specific blood, less than 72 hours old, and warmed to room temperature. The umbilical vein was cannulated with a plastic catheter and plastic disposable equipment used. 10ml aliquots were used. Small amounts (0.5ml) of 10% calcium gluconate were given after each 100ml of donor blood with continuous auscultation of the heart. All babies in exchange transfusion group received penicillin and streptomycin.	Mortality: Group 1: 3/50 Group 2: 3/50 Abnormal neurological examination (1 – 2 years) Group 1: 7/50 Group 2: 6/50		
Author: Jackson J Year: 1997 Country: USA ID: [204]	Methodology: Retrospective chart review Blinding: None Randomisation: None Evidence level:	N: 106 Inclusion: Babies who had an exchange transfusion Exclusion: None Demographics:	Group 1: Exchange transfusion	Mortality:due to ET 2/106 (1.9 %) Permament serious sequelae due to ET 4/106 (3.8%) Serious prolonged sequelae due to ET 5/106 (4.7%)		

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
	3	Gender (M/F): Not reported Mean GA: 36.6 ± 3.6 weeks Mean BW: 2846 ± 806 g Age at entry to study Not reported Mean TSB: Not reported		Serious transient sequelae due to ET 18/106 (17.0%) Asymptomatic treated complications 27/106 (25.5%) Asymptomatic laboratory complications 11/106 (10.4%)		

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

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Pascale J Year: 1976 Country: USA ID: [217]	Methodology: RCT Blinding: Not reported Randomisation: Random numerical selection Evidence level: 1^{+}	N: 24 Inclusion: Hyperbilirubinaemia Exclusion: Not reported Demographics: Gender (M/F): 12/12 Mean GA: Not reported Mean BW: Not reported Age at entry to study: 71.3 ± 24.1 hours Mean TSB: Not reported	Group 1: Phototherapy Group 2: Low-irradiance Phototherapy + Riboflavin Group 3: Phototherapy + Riboflavin Riboflavin was given for 6 hours prior to phototherapy and was discontinued after 24 hours of phototherapy. Riboflavin consisted of sodium phosphate 1.5mg/kg every 12 hours Phototherapy irradiance was 8 – 10 microwatt/cm² Low irradiance was Phototherapy irradiance was 6 – 7 microwatt/cm²	:	Mean decrease in TSB (24 hours): Group 1: -53 ± 13.5 micromol/litre Group 2: -52 ± 10.2 micromol/litre Group 3: -89 ± 18.8 micromol/litre	
Author: Pataki L Year: 1985 Country: Hungary ID: [218]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^{-}	N: 28 Inclusion: ABO – Incompatible jaundice Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3338 ± 425 g Age at entry to study: 50.2 ± 27.2 hours Mean TSB: 358 ± 71micromol/litre	Group 1: Phototherapy Group 2: Phototherapy + Riboflavin Riboflavin (Vitamin B_2) was diluted by a three-fold volume of physiological saline and a single intravenous dose of 10mg/kg was given slowly.		Mean decrease in TSB (3 hours) Group 1: 32 ± 55 micromol/litre Group 2: -87 ± 40 micromol/litre	Subjects were awaiting exchange transfusion
Author: Yurdakok M	Methodology: RCT	N: 124	Group 1: Phototherapy		Mean decrease in TSB: Group 1: -55 ± 67.2 micromol/litre	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Year: 1988 Country: Turkey ID: [219]	Blinding: Not reported Randomisation: Not reported Evidence level: 1^{-}	Inclusion: Indirect hyperbilirubinaemia Exclusion: Those who received exchange transfusions Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3230 ± 502 g Age at entry to study: 61.9 ± 11.0 hours Mean TSB: Not reported	Group 2: Phototherapy + Riboflavin Riboflavin (Vitamin B_2) was given as a single oral dose of 3mg/kg within 30 minutes of start of phototherapy.		Group 2: -85 ± 42.1 micromol/litre Mean duration of treatment: Group 1: 45.7 ± 27.5 hours Group 2: 55.0 ± 31.1 hours	
Author: Ashkan M Year: 2007 Country: Iran ID: [212]	Methodology: RCT Blinding: Not reported Randomisation: Computerised using sealed opaque envelopes Evidence level: 1^{++}	N: 90 Inclusion: Term babies, Birthweight between 2500 and 3500 g, TsB between 292 and 425 micromol/litre Exclusion: Congenital anomaly, Haemolytic disease, Infection, Dehydration, G6PD deficiency, Conjugated hyperbilirubinaemia Demographics: Gender (M/F): 47/43 Mean GA: 38.8 ± 1.6 weeks Mean BW: 2542 ± 547 g Age at entry to study: 125 ± 45.6 hours Mean TSB: 301 ± 23.4 micromol/litre	Group 1: Phototherapy Group 2: Phototherapy + Low-dose clofibrate Group 2: Phototherapy + Moderate-dose clofibrate Clofibrate was administered in a single dose (either low-dose = 25 mg/kg body weight or moderate dose = 50 mg/kg body weight) orally in a mixture of corn oil 30 minutes before breastfeeding.	No side-effects were noted	Mean decrease in TSB (24 hours) : Group 1: -104 ± 14 micromol/litre Group 2: -186 ± 13 micromol/litre Group 3: -186 ± 16 micromol/litre Mean duration of treatment: Group 1: 25.3 ± 4.4 hours Group 2: 14.2 ± 1.2 hours Group 3: 14.7 ± 1.5 hours	Clofibrate groups were combined
Author: Mohammadzadeh A Year:	Methodology: RCT Blinding:	N: 60 Inclusion:	Group 1: Phototherapy Group 2:	No adverse effects noted	Mean decrease in TSB: Group 1: -210 ± 44 micromol/litre Group 2: -184 ± 37 micromol/litre	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
2005 Country: Iran ID: [213]	Not reported Randomisation: Random numbers table Evidence level: 1+	Term, breastfed babies, TsB between 291 and 512micromol/litre Exclusion: Congenital anomaly, Haemolytic disease, Dehydration, G6PD deficiency, Conjugated hyperbilirubinaemia Demographics: Gender (M/F):34/26 Mean GA: 38.7 ± 0.9 weeks Mean BW: 3259 ± 481 g Age at entry to study: 216 ± 94.8 hours Mean TSB: 395 ± 58 micromol/litre	Phototherapy + Clofibrate Clofibrate was administered in a single oral dose (100 mg/kg)		Mean duration of treatment: Group 1: 54 ± 18.8 hours Group 2: 30 ± 12.9 hours	
Author: Zahedpasha Y Year: 2007 Country: Iran ID: [215]	Methodology: RCT Blinding: No reported Randomisation: Not reported Evidence level: 1-	N: 60 Inclusion: Gestational age between 38 and 41 weeks, TsB between 256 and 427micromol/litre Exclusion: Haemolytic disease, Rh or ABO incompatibility, G6PD deficiency, dehydration, Infection, Conjugated hyperbilirubinaemia, History of Phenobarbital intake by mother or infant Demographics: Gender (M/F): 28/32 Mean GA: Not reported Mean BW: Not reported Age at entry to study: 144 ± 71 hours	Group 1: Phototherapy + Placebo Group 2: Phototherapy + Clofibrate Subject in the clofibrate group received a single oral dose of clofibrate (100 mg/kg body weight) while the control group received distilled water in the same amount and colour.	No adverse effects were noted	Mean decrease in TSB: Group 1: -108 ± 24 micromol/litre Group 2: -148 ± 20 micromol/litre	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
		Mean TSB: 305 ± 36micromol/litre				
Author: Zahedpasha Y Year: 2008 Country: Iran ID: [216]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 40 Inclusion: G6PD deficiency, Gestation age between 38 and 41 weeks, Birthweight > 2500 g TsB between 256 and 342 micromol/litre Exclusion: Haemolytic disease, conjugated hyperbilirubinaemia, dehydration, infection, history of Phenobarbital intake by mother or infant Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3257 ± 479 g Age at entry to study: 123 ± 55 hours Mean TSB: 307 ± 33micromol/litre	Group 1: Phototherapy Group 2: Phototherapy + Clofibrate Subject in the clofibrate group received a single oral dose of clofibrate (100 mg/kg body weight)	No adverse effects were noted	Mean decrease in TSB: Group 1: -104 ± 29 micromol/litre Group 2: -142 ± 26 micromol/litre	
Author: Eghbalian F Year: 2007 Country: Iran ID: [214]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table Evidence level: 1+	N: 60 Inclusion: Term, breastfed babies, Birthweight > 2500 g, TsB between 256 and 427micromol/litre Exclusion: Congenital anomalies, Haemolytic disease, Sepsis, Dehydration, Exchange transfusion Demographics:	Group 1: Phototherapy Group 2: Phototherapy + Clofibrate Subject in the clofibrate group received a single dose of clofibrate (100 mg/kg body weight)	No adverse effects were noted	Mean decrease in TSB: Group 1: -137 ± 45 micromol/litre Group 2: -171 ± 30 micromol/litre Mean duration of treatment: Group 1: 68.8 ± 21.6 hours Group 2: 53.6 ± 15 hours	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Miqdad A Year: 2004 Country: Saudi Arabia ID: [206]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 112 Inclusion: Hyperbilirubinaemia due to ABO incompatibility Exclusion: Low birthweight, Rh haemolytic disease,, Perinatal asphyxia, severe congenital malformations Demographics: Gender (M/F): 70/42 Mean GA: 38 weeks Mean BW: Not reported Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Phototherapy Group 2: Phototherapy + IVIG 500 mg/kg body weight over 4 hours	Mortality: Group 1: 4/56 Group 2: 16/56	Mean duration of treatment: Group 1: 106 ± 29 hours Group 2: 92 ± 29 hours	
Author: Voto L Year: 1997 Country: Argentina ID: [205]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 40 Inclusion: Rh positive blood type and Positive Coombs' test Exclusion: Rh positive blood and negative Coombs' test, Histroy of prenatal therapy (Imaternal IVIG/IUT) ABO incompatibility, Other causes of haemolyisis Demographics: Gender (M/F): Not reported Mean GA: 37.2 ± 2.7 Mean BW: 2834 ± 569 g Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Phototherapy Group 2: Phototherapy + IVIG 800 mg/kg body weight per day for 3 days	Exchange transfusion: Group 1: 8/19 Group 2: 12/18 No adverse effects were noted		
Author: Rubo J Year:	Methodology: RCT Blinding:	N: 32 Inclusion:	Group 1: Phototherapy Group 2:	Exchange transfusion: Group 1: 11/16 Group 2: 2/16	Max TsB: Group 1: 240 ± 78 micromol/litre Group 2: 254 ± 86 micromol/litre:	Prevention study One baby in each group excluded for

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
1992 Country: Germany ID: [207]	Not reported Randomisation: Not reported Evidence level: 1-	Babies with Rh antigens born to mothers lacking Rh antigens, Positive Coombs' test Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: Not reported	Phototherapy + IVIG 500 mg/kg body weight over 2 hours	No adverse effects were noted		protocol violations
Author: Dagoglu T Year: 1995 Country: Turkey ID: [208]	Methodology: RCT Blinding: None Randomisation: Random numbers table with sealed envelopes Evidence level: 1++	N: 41 Inclusion: Babies with Rh antigens born to mothers lacking Rh antigens, Positive Coombs' test Exclusion: Not reported Demographics: Gender (M/F): 25/16 Mean GA: 36.1 ± 2.0 weeks Mean BW: 2776 ± 419 g Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Phototherapy Group 2: Phototherapy + IVIG 500 mg/kg body weight as soon as possible after birth	Exchange transfusion: Group 1: 15/19 Group 2: 4/22	Max TSB: Group 1: 224 ± 99 micromol/litre Group 2: 198 ± 106 micromol/litre	
Author: Nasseri F Year: 2006 Country: Iran ID: [209]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 34 Inclusion: Gestation age > 37 weeks, Positive Coombs' test, Significant hyperbilirubinaemia rising at 8.5micromol/litre per hour, TsB below exchange transfusion levels, Exclusion:	Group 1: Phototherapy Group 2: Phototherapy + IVIG IVIG (500 mg/kg body weight) was given with 2–4 hours of admission for 3 consecutive doses each 12 hours	Exchange transfusion: Group 1: 11/17 Group 2: 3/17 No adverse effects were noted	Mean duration of treatment: Group 1: 154 ± 48 hours Group 2: 119 ± 23 hours	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
		Risk factors for hyperbilirubinaemia, i.e. sepsis, G6PD deficiency Demographics: Gender (M/F): 14/20 Mean GA: Not reported Mean BW: 2683 ± 292 g Age at entry to study: 20.2 ± 9.5 hours Mean TSB: 254 ± 57micromol/litre				
Author: Farhat A Year: 2006 Country: Iran ID: [225]	Methodology: RCT Blinding: Double-blind Randomisation: Not reported Evidence level: 1-	N: 104 Inclusion: TsB between 308 and 496micromol/litre Exclusion: Birthweight < 2500 g, Renal failure, Systemic infections, Already taken Shirkhest Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: 401 ± 53 micromol/litre	Group 1: Phototherapy + Placebo Group 2: Phototherapy + Shirkhest Shirkhest (6 g) was diluted in 8mL of distilled water while the control group were given a starch solution (0.1%, 8mL) coloured with 1 drop of caramel solution to appear identical to Shirkhest solution. Phototherapy was discontinued at 256micromol/litre	No adverse effects were noted	Mean decrease in TsB: Group 1: -164 Group 2: -154	
Author: Nicolopoulos D Year: 1978 Country: Greece ID: [220]	Methodology: CCT Blinding: Not reported Randomisation: Alternation Evidence level: 2-	N: 40 Inclusion: Jaundice Exclusion: Babies of diabetic mothers, Rh incompatibility, Perinatal asphyxia, Large cephalhaematoma Demographics:	Group 1: Phototherapy Group 2: Phototherapy + Cholestyramine Babies received 1.5 g/kg per day of cholestyramine powder mixed in milk No Phenobarbital, other medications, or parenteral fluids were administered.	No adverse effects were noted	Mean duration of treatment: **Term babies** Group 1: 84.4 ± 12 hours Group 2: 41.8 ± 5.5 hours **Preterm babies** Group 1: 73.3 ± 9 hours Group 2: 47.0 ± 6 hours	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
		Term babies Gender (M/F): 6/14 Mean GA: 39.1 ± 0.3 weeks Mean BW: 3286 ± 39 g Age at entry to study: 90 ± 1.5 hours Mean TSB: 298 ± 5 micromol/litre **Preterm babies** Gender (M/F): 9/11 Mean GA: 33.4 ± 0.3 weeks Mean BW: 2077 ± 88 g Age at entry to study: 76 ± 2.9 hours Mean TSB:198 ± 5micromol/litre			
Author: Tan K Year: 1984 Country: Singapore ID: [221]	Methodology: CCT Blinding: Not reported Randomisation: Alternation Evidence level: 2-	N: 84 Inclusion: Term babies with non-haemolytic hyperbilirubinaemia (TsB ≥ 256.5micromol/litre) Normal G6PD status, No isoimmunisation, no cephalhaematoma Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: 38.9 ± 0.2 weeks Mean BW: 3154 ± 139 g Age at entry to study: 84 ± 2.9 hours Mean TSB: 298 ± 5micromol/litre	Group 1: Phototherapy Group 2: Phototherapy + Cholestyramine Babies received 1.5 g/kg per day of cholestyramine powder mixed in milk		Mean decrease in TSB: Group 1: -168 ± 24 micromol/litre Group 2: -150 ± 20 micromol/litre	
Author: Martin J	Methodology: CCT	N: 100	Group 1: Usual nursery care	ET: Group 1: 3/35	Mean duration of phototherapy Group 1: NA	No significant differences

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Year: 1974 Country: New Zealand ID: [224]	Blinding: Not reported Randomisation: 'allocated in rotation' Evidence level:2-	Inclusion: physiological jaundice Exclusion: Not reported Demographics: Gender (M/F) : 49/51 Mean GA: 34.8 ± 2.7 weeks Mean BW: 2155 ± 632 gms Age at entry to study 48.1 ± 14.7 hours Mean TSB: 174 ± 40 micromol/litre	Group 2: Usual nursery care + Conventional phototherapy Group 3: Usual nursery care + phototherapy + phenobarbitone (for babies with birthweight ≥ 3kg, 8mg x 3 per day, For babies with birthweight < 3kg, 2mg/kg x 3 per day) Conventional Phototherapy consisted of a single bank of eight 30 watt fluorescent tubes behind a Perspex screen 50cm above the baby in a bassinet Light intensity = 2500 lux Light band = 441 nm Baby naked and with eyes covered No deliberate attempt to sequentially rotate the baby	Group 2: 0/34 Group 3: 1/31 Mortality: Group 1: 2/35 Group 2: 0/34 Group 3: 1/31	Group 2: 67 ± 33 hours Group 3: 72 ± 31 hours Mean rise to max TSB: Group 1: 80.4 ± 49.6 micromol/litre Group 2: 22.2 ± 29.1 micromol/litre Group 3: 18.8 ± 29.1 micromol/litre Time to max TSB (hours): Group 1: 51 ± 23 hours Group 2: 14 ± 19 hours Group 3: 13 ± 18 hours	between groups No reason given for mortality
Author: Odell G Year: 1983 Country: USA ID: [222]	Methodology: CCT Blinding: Not reported Randomisation: By patient number Evidence level: 2-	N: 52 Inclusion: Hyperbilirubinaemia requiring phototherapy Exclusion: Not reported Demographics: Gender (M/F): 31/21 GA: Not reported BW:2767 ± 69 g Mean age at entry to study: 80.6 ± 28.7 hours Mean TSB: 234 ± 46.8 micromol/litre	Group 1: Phototherapy Group 2: Phototherapy + Agar 250mg orally every 8 hours during phototherapy Phototherapy initiated at 239.4 micromol/litre for term babies and 171 micromol/litre for preterm babies Phototherapy discontinued 188.1 micromol/litre for term babies and 171 micromol/litre for preterm babies		Mean duration of Phototherapy Group 1: 48.1 ± 23.0 hours Group 2: 37.6 ± 18.0 hours	15 babies excluded retrospectively
Author: Ebbesen F Year: 1977	Methodology: CCT Blinding: Not reported	N: 49 Inclusion: Hyperbilirubinaemia requiring phototherapy	Group 1: Phototherapy Group 2: Phototherapy + Agar 250mg orally at feedings every three hours		Mean decrease in TsB Group 1: 87 ± 39 micromol/litre Group 2: 85 ± 40 micromol/litre Mean duration of Phototherapy	

Bibliographic Information	Study Type & Evidence Level	Number of Patients/Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Country: Denmark ID: [223]	Randomisation: By patient number Evidence level: 2-	Exclusion: Not reported Demographics: Gender (M/F): 26/23 GA: 36.8 ± 2.5 weeks BW:2729 ± 538 g Mean age at entry to study: 87 ± 26 hours Mean TSB: 274 ± 51 micromol/litre	Phototherapy initiated at 274 micromol/litre Phototherapy discontinued when TsB fell continuously for 24 hours		Group 1: 60 ± 30 hours Group 2: 61 ± 28 hours	

What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia?

Author: Salem-Schatz S Year: 2004 Country: USA ID: [228]	Study Type: Focus group study Evidence Level: III	Four focus groups 1 for physicians (*n* = 9) 1 for nurses (*n* = 9) 2 for parents/carers (*n* = 14) Aim: To identify barriers to timely follow-up of hyperbilirubinaemia in 1st 7 days Focus had between 7 and 9 participants and lasted for between 90 and 120 minutes Content was the importance of 1st week newborn follow-up and key questions relating to physican and parent/carer experiences	Barriers - communication Conflicting advice from HCP's on readiness for discharge - MD Communication gaps between handover from hospital to community - MD, RN Key information missing MD, RN Barriers – systems and process Delays in outpatient bilirubin testing and reporting - MD, RN Barrier to home visits – MD, RN, P Barriers to office visits in week 1 – MD, RN, P Barriers – systems and process Shorter hospital stays leave less time for parent education –RN Clinicians may be reluctant to educate about hyperbilirubinaemia prenatally – MD, RN Poor understanding by clinicians of risks of near-terms – MD Lack of clinician awareness of the recommendations of early follow-up visits – MD HCP recommendations forgotten once parent is home – P	Solutions - communication Improve communication between HCP - MD Notify community HCP by email when baby born – MD, RN Provide easy-access (on-line or form parent) for community HCP for lab results – MD, RN Give parents/carers 'early warning signs' to report – MD, P Continued contact from birth hospital to parent/carer – P Solutions – systems and process Home visit by a physician – P Encourage home visits, RN, P Choose paediatrician before discharge/book appointment before discharge – MD Separate visiting toom for well children – P More flexible visiting time – P Community HCP to visit pre-discharge – RN, P Ensure quick easy access to labs – MD, RN Solutions – systems and process Increase professional awareness – MD, RN Parental education through continuum of care – MD, RN, P Support groups for new and expectant parents – MD, RN	MD = physician RN = Nurse P = Parent

Author: Willis S Year: 2002 Country: USA ID: [229]	Study Type: Qualitative study Evidence Level: III	Population Mother of newborn babies with jaundice Criteria: Breastfeeding babies with TsB > 170 micromol/litre Setting Hospital Demographics: Sample size: 47 Mean age: 27 years More than half of multiparous mother had a previous baby with jaundice and ¾ had breastfed a previous child. Mothers interview between 2.5 and 14.5 weeks postpartum	Half of the mothers described how jaundice had influenced, positive or negatively their breastfeeding patterns.		

Appendix I

Search strategies

Question: Recognising jaundice and predicting hyperbilirubinaemia

Ovid MEDLINE 1950 to April Week 2 2008

JAUN_recognise_predict_medline_230408

#	Searches	Results
1	INFANT, PREMATURE/	31751
2	preterm$.tw.	28005
3	INFANT, NEWBORN/	412490
4	(newborn$ or neonate$).tw.	134938
5	BLOOD GROUP INCOMPATIBILITY/	4748
6	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	3708
7	or/1-6	475270
8	HYPERBILIRUBINEMIA/	3350
9	HYPERBILIRUBINEMIA, NEONATAL/	139
10	hyperbilirubin?emia$.ti.	2141
11	bilirubin?emia$.ti.	148
12	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	273
13	exp JAUNDICE/	9646
14	jaundice$.ti.	9495
15	KERNICTERUS/	876
16	kernicterus$.ti.	358
17	or/8-16	19912
18	DIAGNOSIS/	15621
19	(prediction or predicting or recogniz$ or detection).ti.	179778
20	history.ti.	47128
21	PHYSICAL EXAMINATION/	23129
22	((clinical$ or visual$ or physical$) adj3 examin$).tw.	72628
23	SKIN PIGMENTATION/	3966
24	((skin or urine or stool$) adj3 colo?r$).tw.	2521
25	((urine or stool$) adj3 examin$).tw.	3883
26	BILIRUBIN/bl [Blood]	11105
27	UMBILICAL CORD/	7145
28	FETAL BLOOD/	20781
29	BLOOD GROUP ANTIGENS/	14212

30	COOMBS' TEST/	3929
31	((coomb$ or antiglobulin$) adj3 test$).tw.	2462
32	((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	19944
33	transcutaneous$.tw.	8166
34	bilirubinomet$.tw.	140
35	icteromet$.tw.	29
36	(jaundice?met$ or jaundice met$).tw.	130
37	CARBON MONOXIDE/	11864
38	end tidal.tw.	5796
39	etco.tw.	141
40	NOMOGRAMS/	310
41	nomogram$.tw.	2996
42	(bilirubin$ adj3 percentile$).tw.	9
43	(hour$ adj3 bilirubin$).tw.	81
44	RISK ASSESSMENT/	89761
45	(risk$ adj3 (assess$ or index or model$)).tw.	37348
46	(total adj3 serum adj3 bilirubin$).tw.	1227
47	(serum adj3 bilirubin$ adj3 level$).tw.	1785
48	tsb.tw.	489
49	or/18-48	541944
50	and/7,17,49	1741

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

JAUN_recognise_predict_cctr_230408

#	Searches	Results
1	INFANT, PREMATURE/	1658
2	preterm$.tw.	3020
3	INFANT, NEWBORN/	8235
4	(newborn$ or neonate$).tw.	4126
5	BLOOD GROUP INCOMPATIBILITY/	41
6	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	25
7	or/1-6	11232
8	HYPERBILIRUBINEMIA/	58
9	HYPERBILIRUBINEMIA, NEONATAL/	6
10	hyperbilirubin?emia$.ti.	146
11	bilirubin?emia$.ti.	4
12	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
13	exp JAUNDICE/	245
14	jaundice$.ti.	191
15	KERNICTERUS/	2
16	kernicterus$.ti.	3

17 or/8-16	525
18 DIAGNOSIS/	26
19 (prediction or predicting or recogniz$ or detection).ti.	2758
20 history.ti.	707
21 PHYSICAL EXAMINATION/	482
22 ((clinical$ or visual$ or physical$) adj3 examin$).tw.	4706
23 SKIN PIGMENTATION/	106
24 ((skin or urine or stool$) adj3 colo?r$).tw.	133
25 ((urine or stool$) adj3 examin$).tw.	223
26 BILIRUBIN/bl [Blood]	472
27 UMBILICAL CORD/	109
28 FETAL BLOOD/	398
29 BLOOD GROUP ANTIGENS/	14
30 COOMBS' TEST/	17
31 ((coomb$ or antiglobulin$) adj3 test$).tw.	31
32 ((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	548
33 transcutaneous$.tw.	1256
34 bilirubinomet$.tw.	6
35 icteromet$.tw.	0
36 (jaundice?met$ or jaundice met$).tw.	17
37 CARBON MONOXIDE/	258
38 end tidal.tw.	1265
39 etco.tw.	34
40 NOMOGRAMS/	4
41 nomogram$.tw.	143
42 (bilirubin$ adj3 percentile$).tw.	0
43 (hour$ adj3 bilirubin$).tw.	24
44 RISK ASSESSMENT/	2723
45 (risk$ adj3 (assess$ or index or model$)).tw.	1532
46 (total adj3 serum adj3 bilirubin$).tw.	104
47 (serum adj3 bilirubin$ adj3 level$).tw.	176
48 tsb.tw.	22
49 or/18-48	17006
50 and/7,17,49	134

CDSR, DARE

JAUN_recognise_predict_cdsrdare_230408

#	Searches	Results
1	INFANT, PREMATURE.kw.	181
2	preterm$.tw.	519
3	INFANT, NEWBORN$.kw.	541

4	(newborn$ or neonate$).tw.	890
5	BLOOD GROUP INCOMPATIBILIT$.kw.	5
6	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENC$.kw.	0
7	or/1-6	1028
8	HYPERBILIRUBINEMIA.kw.	3
9	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
10	hyperbilirubin?emia$.ti.	2
11	bilirubin?emia$.ti.	0
12	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	5
13	JAUNDICE.kw.	13
14	jaundice$.ti.	10
15	KERNICTERUS.kw.	1
16	kernicterus$.ti.	0
17	or/8-16	18
18	DIAGNOSIS.kw.	821
19	(prediction or predicting or recogniz$ or detection).ti.	69
20	history.ti.	22
21	PHYSICAL EXAMINATION$.kw.	56
22	((clinical$ or visual$ or physical$) adj3 examin$).tw.	931
23	SKIN PIGMENTATION.kw.	3
24	((skin or urine or stool$) adj3 colo?r$).tw.	25
25	((urine or stool$) adj3 examin$).tw.	13
26	BILIRUBIN.kw.	4
27	UMBILICAL CORD.kw.	7
28	FETAL BLOOD.kw.	2
29	BLOOD GROUP ANTIGEN$.kw.	0
30	COOMBS' TEST.kw.	0
31	((coomb$ or antiglobulin$) adj3 test$).tw.	4
32	((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	121
33	transcutaneous$.tw.	195
34	bilirubinomet$.tw.	0
35	icteromet$.tw.	0
36	(jaundice?met$ or jaundice met$).tw.	1
37	CARBON MONOXIDE.kw.	5
38	end tidal.tw.	10
39	etco.tw.	1
40	NOMOGRAM$.kw.	0
41	nomogram$.tw.	6
42	(bilirubin$ adj3 percentile$).tw.	0
43	(hour$ adj3 bilirubin$).tw.	2
44	RISK ASSESSMENT$.kw.	213
45	(risk$ adj3 (assess$ or index or model$)).tw.	1095
46	(total adj3 serum adj3 bilirubin$).tw.	13

47	(serum adj3 bilirubin$ adj3 level$).tw.	21
48	tsb.tw.	1
49	or/18-48	2884
50	and/7,17,49	9

EMBASE 1980 to 2008 Week 16

JAUN_recognise_predict_embase_230408

#	Searches	Results
1	PREMATURITY/	27937
2	preterm$.tw.	25261
3	NEWBORN/	174081
4	(newborn$ or neonate$).tw.	94136
5	exp BLOOD GROUP INCOMPATIBILITY/	2541
6	GLUCOSE 6 PHOSPHATE DEHYDROGENASE DEFICIENCY/	1474
7	or/1-6	235354
8	HYPERBILIRUBINEMIA/	5333
9	hyperbilirubin?emia$.ti.	1025
10	bilirubin?emia$.ti.	15
11	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	237
12	JAUNDICE/	9237
13	NEWBORN JAUNDICE/	1660
14	jaundice$.ti.	3561
15	KERNICTERUS/	683
16	kernicterus$.ti.	146
17	or/8-16	17140
18	DIAGNOSIS/	465073
19	(prediction or predicting or recogniz$ or detection).ti.	141323
20	HISTORY/	16157
21	FAMILY HISTORY/	24813
22	history.ti.	24050
23	PHYSICAL EXAMINATION/	56183
24	((clinical$ or visual$ or physical$) adj3 examin$).tw.	60247
25	SKIN PIGMENTATION/	4446
26	((skin or urine or stool$) adj3 colo?r$).tw.	2234
27	((urine or stool$) adj3 examin$).tw.	2748
28	BLOOD LEVEL/	36543
29	BILIRUBIN BLOOD LEVEL/	6158
30	CORD SERUM/	234
31	UMBILICAL CORD BLOOD/	9443
32	FETUS BLOOD/	1630
33	BLOOD GROUP/	1596

34	COOMBS TEST/	1552
35	((coomb$ or antiglobulin$) adj3 test$).tw.	1598
36	((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	16636
37	transcutaneous$.tw.	6774
38	bilirubinomet$.tw.	109
39	icteromet$.tw.	11
40	(jaundice?met$ or jaundice met$).tw.	118
41	CARBON MONOXIDE/	12990
42	end tidal.tw.	5299
43	etco.tw.	52
44	NOMOGRAM/	1225
45	nomogram$.tw.	2280
46	(bilirubin$ adj3 percentile$).tw.	8
47	(hour$ adj3 bilirubin$).tw.	61
48	RISK ASSESSMENT/	163822
49	(risk$ adj3 (assess$ or index or model$)).tw.	35319
50	NEWBORN ASSESSMENT/	114
51	(total adj3 serum adj3 bilirubin$).tw.	1120
52	(serum adj3 bilirubin$ adj3 level$).tw.	1512
53	tsb.tw.	363
54	or/18-53	1010463
55	and/7,17,54	1537

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to April Week 3 2008

JAUN_recognise_predict_cinahl_230408

#	Searches	Results
1	INFANT, PREMATURE/	5759
2	preterm$.tw.	4893
3	INFANT, NEWBORN/	36675
4	(newborn$ or neonate$).tw.	9202
5	BLOOD GROUP INCOMPATIBILITY/	154
6	(glucose$ adj5 deficien$).tw.	73
7	or/1-6	41328
8	HYPERBILIRUBINEMIA/	200
9	hyperbilirubin?emia$.ti.	134
10	bilirubin?emia$.ti.	1
11	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	23
12	JAUNDICE/	192
13	jaundice$.ti.	279
14	KERNICTERUS/	92
15	kernicterus$.ti.	36

16 or/8-15	663
17 DIAGNOSIS/	1110
18 (prediction or predicting or recogniz$ or detection).ti.	9865
19 FAMILY HISTORY/	1191
20 history.ti.	5984
21 PHYSICAL EXAMINATION/	8809
22 ((clinical$ or visual$ or physical$) adj3 examin$).tw.	7584
23 SKIN PIGMENTATION/	134
24 ((skin or urine or stool$) adj3 colo?r$).tw.	187
25 ((urine or stool$) adj3 examin$).tw.	118
26 BILIRUBIN/bl [Blood]	231
27 UMBILICAL CORD/	420
28 FETAL BLOOD/	749
29 BLOOD GROUPS/	164
30 COOMBS' TEST/	31
31 ((coomb$ or antiglobulin$) adj3 test$).tw.	54
32 ((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	692
33 transcutaneous$.tw.	867
34 bilirubinomet$.tw.	19
35 icteromet$.tw.	1
36 (jaundice?met$ or jaundice met$).tw.	14
37 CARBON MONOXIDE/	410
38 end tidal.tw.	350
39 etco.tw.	32
40 nomogram$.tw.	157
41 (bilirubin$ adj3 percentile$).tw.	1
42 (hour$ adj3 bilirubin$).tw.	8
43 RISK ASSESSMENT/	13435
44 (risk$ adj3 (assess$ or index or model$)).tw.	6295
45 NEONATAL ASSESSMENT/	875
46 (total adj3 serum adj3 bilirubin$).tw.	69
47 (serum adj3 bilirubin$ adj3 level$).tw.	61
48 tsb.tw.	30
49 or/17-48	53123
50 and/7,16,49	162

CINAHL EBSCO

JAUN_recognise_predict_cinahl_230408_6

Wednesday, May 06, 2009 9:25:37 AM

#	Query	Limiters/Expanders	Last Run Via	Results

S63	S5 and S17 and S62	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S62	S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S61	TI tsb or AB tsb	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S60	TI serum N3 bilirubin* N3 level* or AB serum N3 bilirubin* N3 level*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S59	TI total N3 serum N3 bilirubin* or AB total N3 serum N3 bilirubin*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S58	MH NEONATAL ASSESSMENT	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S57	TI risk N3 model* or AB risk N3 model*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S56	TI risk N3 index* or AB risk N3 index*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S55	TI risk N3 assessment* or AB risk N3 assessment*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	Display

			Database - CINAHL with Full Text	
S54	MH RISK ASSESSMENT	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S53	TI hour* N3 bilirubin* or AB hour* N3 bilirubin*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S52	TI bilirubin* N3 percentile* or AB bilirubin* N3 percentile*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S51	TI nomogram* or AB nomogram*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S50	TI etco or AB etco	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S49	TI end tidal or AB end tidal	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S48	MH CARBON MONOXIDE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S47	TI jaundice met* or AB jaundice met*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S46	TI icteromet* or AB icteromet*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S45	TI bilirubinomet* or AB	Search modes -	Interface - EBSCOhost	Display

	bilirubinomet*	Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S44	TI transcutaneous* or AB transcutaneous*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S43	TI (foetus N3 blood*) or AB (foetus N3 blood*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S42	TI (fetus N3 blood*) or AB (fetus N3 blood*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S41	TI (foetal N3 blood*) or AB (foetal N3 blood*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S40	TI (fetal N3 blood*) or AB (fetal N3 blood*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S39	TI (cord N3 blood*) or AB (cord N3 blood*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S38	TI (antiglobulin* N3 test*) or AB (antiglobulin* N3 test*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S37	TI (coomb* N3 test*) or AB (coomb* N3 test*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S36	MH COOMBS' TEST	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with	Display

			Full Text	
S35	MH BLOOD GROUPS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S34	MH FETAL BLOOD	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S33	MH UMBILICAL CORD	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S32	(MH 'BILIRUBIN/BL')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S31	TI (examin* N3 stool*) or AB (examin* N3 stool*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S30	TI (examin* N3 urine) or AB (examin* N3 urine)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S29	TI (stool* N3 color*) or AB (stool* N3 colour*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S28	TI (urine N3 color*) or AB (urine N3 colour*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S27	TI (skin N3 color*) or AB (skin N3 colour*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S26	MH SKIN PIGMENTATION	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	Display

			Advanced Search Database - CINAHL with Full Text	
S25	TI (physical* N3 examin*) or AB (physical* N3 examin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S24	TI (visual* N3 examin*) or AB (visual* N3 examin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S23	TI (clinical* N3 examin*) or AB (clinical* N3 examin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S22	MH PHYSICAL EXAMINATION	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S21	TI history	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S20	MH FAMILY HISTORY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S19	TI (prediction or predicting or recogni* or detection)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S18	MH DIAGNOSIS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S17	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

S16	(TI 'kernicterus*')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S15	MH KERNICTERUS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	(TI jaundice*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S12	(AB 'hyperbilirubin*' N3 'encephalopath*')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S11	(TI 'hyperbilirubin*' N3 'encephalopath*')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(AB 'bilirubin*' N3 'encephalopath*')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S9	(TI 'bilirubin*' N3 'encephalopath*')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI 'bilirubinaemia' OR 'bilirubinemia')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S7	(TI 'hyperbilirubinemia' or 'hyperbilirubinaemia')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	Display

			Database - CINAHL with Full Text	
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI 'newborn*' or 'neonate*') or (AB 'newborn*' or 'neonate*')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI 'preterm*') or (AB 'preterm*')	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

Ovid MEDLINE 1950 to June Week 4 2008

JAUN_recognise_predict_economic_medline_090708

#	Searches	Results
1	costs.tw.	75877
2	cost effective$.tw.	43549
3	economic.tw.	65215
4	or/1-3	160435
5	(metabolic adj cost).tw.	480
6	((energy or oxygen) adj cost).tw.	2016
7	4 not (5 or 6)	160205
8	INFANT, PREMATURE/	32498

9	preterm$.tw.	28724
10	INFANT, NEWBORN/	420292
11	(newborn$ or neonate$).tw.	137294
12	BLOOD GROUP INCOMPATIBILITY/	4831
13	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	3757
14	or/8-13	484157
15	HYPERBILIRUBINEMIA/	3398
16	HYPERBILIRUBINEMIA, NEONATAL/	157
17	hyperbilirubin?emia$.ti.	2174
18	bilirubin?emia$.ti.	148
19	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	282
20	exp JAUNDICE/	9967
21	jaundice$.ti.	9785
22	KERNICTERUS/	891
23	kernicterus$.ti.	361
24	or/15-23	20452
25	DIAGNOSIS/	15941
26	(prediction or predicting or recogniz$ or detection).ti.	183186
27	history.ti.	48172
28	PHYSICAL EXAMINATION/	23519
29	((clinical$ or visual$ or physical$) adj3 examin$).tw.	74495
30	SKIN PIGMENTATION/	4079
31	((skin or urine or stool$) adj3 colo?r$).tw.	2598
32	((urine or stool$) adj3 examin$).tw.	3968
33	BILIRUBIN/bl [Blood]	11319
34	UMBILICAL CORD/	7264
35	FETAL BLOOD/	21153
36	BLOOD GROUP ANTIGENS/	14483
37	COOMBS' TEST/	3978
38	((coomb$ or antiglobulin$) adj3 test$).tw.	2486
39	((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	20418
40	transcutaneous$.tw.	8286
41	bilirubinomet$.tw.	144
42	icteromet$.tw.	29
43	(jaundice?met$ or jaundice met$).tw.	135
44	CARBON MONOXIDE/	12056
45	end tidal.tw.	5867
46	etco.tw.	144
47	NOMOGRAMS/	346
48	nomogram$.tw.	3080
49	(bilirubin$ adj3 percentile$).tw.	10
50	(hour$ adj3 bilirubin$).tw.	82
51	RISK ASSESSMENT/	93027

52	(risk$ adj3 (assess$ or index or model$)).tw.	38546
53	(total adj3 serum adj3 bilirubin$).tw.	1256
54	(serum adj3 bilirubin$ adj3 level$).tw.	1820
55	tsb.tw.	497
56	or/25-55	554568
57	and/14,24,56	1800
58	and/7,57	17
59	limit 58 to english language	15

EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2008

JAUN_recognise_predict_economic_cctr_090708

#	Searches	Results
1	costs.tw.	5343
2	cost effective$.tw.	4066
3	economic.tw.	2244
4	or/1-3	8799
5	(metabolic adj cost).tw.	38
6	((energy or oxygen) adj cost).tw.	178
7	4 not (5 or 6)	8789
8	INFANT, PREMATURE/	1688
9	preterm$.tw.	3060
10	INFANT, NEWBORN/	8341
11	(newborn$ or neonate$).tw.	4171
12	BLOOD GROUP INCOMPATIBILITY/	41
13	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	25
14	or/8-13	11364
15	HYPERBILIRUBINEMIA/	58
16	HYPERBILIRUBINEMIA, NEONATAL/	8
17	hyperbilirubin?emia$.ti.	147
18	bilirubin?emia$.ti.	4
19	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
20	exp JAUNDICE/	247
21	jaundice$.ti.	192
22	KERNICTERUS/	2
23	kernicterus$.ti.	3
24	or/15-23	531
25	DIAGNOSIS/	26
26	(prediction or predicting or recogniz$ or detection).ti.	2797
27	history.ti.	718
28	PHYSICAL EXAMINATION/	487
29	((clinical$ or visual$ or physical$) adj3 examin$).tw.	4818

30 SKIN PIGMENTATION/	107
31 ((skin or urine or stool$) adj3 colo?r$).tw.	136
32 ((urine or stool$) adj3 examin$).tw.	228
33 BILIRUBIN/bl [Blood]	478
34 UMBILICAL CORD/	112
35 FETAL BLOOD/	404
36 BLOOD GROUP ANTIGENS/	14
37 COOMBS' TEST/	17
38 ((coomb$ or antiglobulin$) adj3 test$).tw.	31
39 ((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	555
40 transcutaneous$.tw.	1266
41 bilirubinomet$.tw.	6
42 icteromet$.tw.	0
43 (jaundice?met$ or jaundice met$).tw.	19
44 CARBON MONOXIDE/	264
45 end tidal.tw.	1279
46 etco.tw.	34
47 NOMOGRAMS/	7
48 nomogram$.tw.	146
49 (bilirubin$ adj3 percentile$).tw.	0
50 (hour$ adj3 bilirubin$).tw.	24
51 RISK ASSESSMENT/	2861
52 (risk$ adj3 (assess$ or index or model$)).tw.	1568
53 (total adj3 serum adj3 bilirubin$).tw.	108
54 (serum adj3 bilirubin$ adj3 level$).tw.	179
55 tsb.tw.	24
56 or/25-55	17382
57 and/14,24,56	139
58 and/7,57	3

EBM Reviews - Health Technology Assessment 3rd Quarter 2008

JAUN_recognise_predict_economic_hta_090708

#	Searches	Results
1	costs.tw.	1155
2	cost effective$.tw.	915
3	economic.tw.	682
4	or/1-3	1657
5	(metabolic adj cost).tw.	0
6	((energy or oxygen) adj cost).tw.	0
7	4 not (5 or 6)	1657
8	INFANT, PREMATURE/	9

9	preterm$.tw.	22
10	INFANT, NEWBORN/	65
11	(newborn$ or neonate$).tw.	99
12	BLOOD GROUP INCOMPATIBILITY/	1
13	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	0
14	or/8-13	122
15	HYPERBILIRUBINEMIA/	4
16	HYPERBILIRUBINEMIA, NEONATAL/	1
17	hyperbilirubin?emia$.ti.	3
18	bilirubin?emia$.ti.	0
19	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	1
20	exp JAUNDICE/	1
21	jaundice$.ti.	3
22	KERNICTERUS/	1
23	kernicterus$.ti.	0
24	or/15-23	8
25	DIAGNOSIS/	4
26	(prediction or predicting or recogniz$ or detection).ti.	113
27	history.ti.	7
28	PHYSICAL EXAMINATION/	4
29	((clinical$ or visual$ or physical$) adj3 examin$).tw.	55
30	SKIN PIGMENTATION/	0
31	((skin or urine or stool$) adj3 colo?r$).tw.	1
32	((urine or stool$) adj3 examin$).tw.	0
33	BILIRUBIN/bl [Blood]	0
34	UMBILICAL CORD/	1
35	FETAL BLOOD/	11
36	BLOOD GROUP ANTIGENS/	0
37	COOMBS' TEST/	0
38	((coomb$ or antiglobulin$) adj3 test$).tw.	0
39	((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	15
40	transcutaneous$.tw.	13
41	bilirubinomet$.tw.	1
42	icteromet$.tw.	0
43	(jaundice?met$ or jaundice met$).tw.	0
44	CARBON MONOXIDE/	1
45	end tidal.tw.	0
46	etco.tw.	0
47	NOMOGRAMS/	0
48	nomogram$.tw.	0
49	(bilirubin$ adj3 percentile$).tw.	0
50	(hour$ adj3 bilirubin$).tw.	0
51	RISK ASSESSMENT/	34

52	(risk$ adj3 (assess$ or index or model$)).tw.	84
53	(total adj3 serum adj3 bilirubin$).tw.	0
54	(serum adj3 bilirubin$ adj3 level$).tw.	1
55	tsb.tw.	1
56	or/25-55	286
57	and/14,24,56	3
58	and/7,57	1

EBM Reviews - NHS Economic Evaluation Database 2nd Quarter 2008

JAUN_recognise_predict_economic_nhseed_090708

#	Searches	Results
1	costs.tw.	17123
2	cost effective$.tw.	8445
3	economic.tw.	23126
4	or/1-3	23406
5	(metabolic adj cost).tw.	0
6	((energy or oxygen) adj cost).tw.	0
7	4 not (5 or 6)	23406
8	INFANT, PREMATURE/	74
9	preterm$.tw.	78
10	INFANT, NEWBORN/	849
11	(newborn$ or neonate$).tw.	915
12	BLOOD GROUP INCOMPATIBILITY/	5
13	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	2
14	or/8-13	943
15	HYPERBILIRUBINEMIA/	2
16	HYPERBILIRUBINEMIA, NEONATAL/	1
17	hyperbilirubin?emia$.ti.	1
18	bilirubin?emia$.ti.	0
19	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	0
20	exp JAUNDICE/	5
21	jaundice$.ti.	8
22	KERNICTERUS/	1
23	kernicterus$.ti.	1
24	or/15-23	14
25	DIAGNOSIS/	10
26	(prediction or predicting or recogniz$ or detection).ti.	185
27	history.ti.	34
28	PHYSICAL EXAMINATION/	48
29	((clinical$ or visual$ or physical$) adj3 examin$).tw.	305
30	SKIN PIGMENTATION/	0

31 ((skin or urine or stool$) adj3 colo?r$).tw.	4
32 ((urine or stool$) adj3 examin$).tw.	12
33 BILIRUBIN/bl [Blood]	4
34 UMBILICAL CORD/	1
35 FETAL BLOOD/	9
36 BLOOD GROUP ANTIGENS/	0
37 COOMBS' TEST/	1
38 ((coomb$ or antiglobulin$) adj3 test$).tw.	1
39 ((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	14
40 transcutaneous$.tw.	20
41 bilirubinomet$.tw.	1
42 icteromet$.tw.	0
43 (jaundice?met$ or jaundice met$).tw.	0
44 CARBON MONOXIDE/	0
45 end tidal.tw.	6
46 etco.tw.	0
47 NOMOGRAMS/	0
48 nomogram$.tw.	6
49 (bilirubin$ adj3 percentile$).tw.	0
50 (hour$ adj3 bilirubin$).tw.	0
51 RISK ASSESSMENT/	481
52 (risk$ adj3 (assess$ or index or model$)).tw.	624
53 (total adj3 serum adj3 bilirubin$).tw.	5
54 (serum adj3 bilirubin$ adj3 level$).tw.	5
55 tsb.tw.	0
56 or/25-55	1192
57 and/14,24,56	3
58 and/7,57	3

EMBASE 1980 to 2008 Week 27

JAUN_recognise_predict_economic_embase_090708

#	Searches	Results
1	costs.tw.	62745
2	cost effective$.tw.	39866
3	economic.tw.	51827
4	or/1-3	130966
5	(metabolic adj cost).tw.	369
6	((energy or oxygen) adj cost).tw.	1661
7	4 not (5 or 6)	130794
8	PREMATURITY/	28363
9	preterm$.tw.	25709

10 NEWBORN/	175463
11 (newborn$ or neonate$).tw.	95167
12 exp BLOOD GROUP INCOMPATIBILITY/	2563
13 GLUCOSE 6 PHOSPHATE DEHYDROGENASE DEFICIENCY/	1496
14 or/8-13	237679
15 HYPERBILIRUBINEMIA/	5455
16 hyperbilirubin?emia$.ti.	1039
17 bilirubin?emia$.ti.	15
18 ((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	243
19 JAUNDICE/	9422
20 NEWBORN JAUNDICE/	1688
21 jaundice$.ti.	3593
22 KERNICTERUS/	692
23 kernicterus$.ti.	148
24 or/15-23	17469
25 DIAGNOSIS/	465076
26 (prediction or predicting or recogniz$ or detection).ti.	143262
27 HISTORY/	16293
28 FAMILY HISTORY/	25370
29 history.ti.	24359
30 PHYSICAL EXAMINATION/	58090
31 ((clinical$ or visual$ or physical$) adj3 examin$).tw.	61169
32 SKIN PIGMENTATION/	4549
33 ((skin or urine or stool$) adj3 colo?r$).tw.	2276
34 ((urine or stool$) adj3 examin$).tw.	2785
35 BLOOD LEVEL/	36799
36 BILIRUBIN BLOOD LEVEL/	6389
37 CORD SERUM/	237
38 UMBILICAL CORD BLOOD/	9570
39 FETUS BLOOD/	1638
40 BLOOD GROUP/	1604
41 COOMBS TEST/	1573
42 ((coomb$ or antiglobulin$) adj3 test$).tw.	1608
43 ((cord or fetal or foetal or fetus or foetus) adj3 blood$).tw.	16829
44 transcutaneous$.tw.	6839
45 bilirubinomet$.tw.	111
46 icteromet$.tw.	11
47 (jaundice?met$ or jaundice met$).tw.	120
48 CARBON MONOXIDE/	13178
49 end tidal.tw.	5354
50 etco.tw.	52
51 NOMOGRAM/	1273
52 nomogram$.tw.	2336

53 (bilirubin$ adj3 percentile$).tw.	9
54 (hour$ adj3 bilirubin$).tw.	63
55 RISK ASSESSMENT/	167602
56 (risk$ adj3 (assess$ or index or model$)).tw.	36102
57 NEWBORN ASSESSMENT/	130
58 (total adj3 serum adj3 bilirubin$).tw.	1145
59 (serum adj3 bilirubin$ adj3 level$).tw.	1544
60 tsb.tw.	372
61 or/25-60	1020724
62 and/14,24,61	1568
63 and/7,62	24

Question: Risk Factors

Ovid MEDLINE(R) 1950 to July Week 5 2008

JAUN_risk_factors_medline_070808

#	Searches	Results
1	INFANT, PREMATURE/	32701
2	preterm$.tw.	28961
3	INFANT, NEWBORN/	422670
4	(newborn$ or neonate$).tw.	137993
5	BLOOD GROUP INCOMPATIBILITY/	4845
6	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	3767
7	or/1-6	486794
8	HYPERBILIRUBINEMIA/	3407
9	HYPERBILIRUBINEMIA, NEONATAL/	163
10	hyperbilirubin?emia$.ti.	2187
11	bilirubin?emia$.ti.	149
12	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	283
13	exp JAUNDICE/	10019
14	jaundice$.ti.	9818
15	KERNICTERUS/	893
16	kernicterus$.ti.	363
17	or/8-16	20536
18	or/13-14	15665
19	or/8-10	4640
20	and/18-19	602
21	and/7,20	258
22	or/15-16	986
23	or/18-19	19703
24	or/12,22	1163
25	and/23-24	422
26	and/7,25	328
27	RISK FACTORS/	364028
28	risk factor$.ti.	44766
29	COMORBIDITY/	36477
30	"CONFOUNDING FACTORS (EPIDEMIOLOGY)"/	6456
31	or/27-30	402101
32	and/7,17,31	251
33	or/21,26,32	747
34	from 33 keep 1-10	10

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

JAUN_risk_factors_cctr_070808

#	Searches	Results
1	INFANT, PREMATURE/	1709
2	preterm$.tw.	3074
3	INFANT, NEWBORN/	8435
4	(newborn$ or neonate$).tw.	4189
5	BLOOD GROUP INCOMPATIBILITY/	41
6	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY/	25
7	or/1-6	11437
8	HYPERBILIRUBINEMIA/	58
9	HYPERBILIRUBINEMIA, NEONATAL/	10
10	hyperbilirubin?emia$.ti.	148
11	bilirubin?emia$.ti.	4
12	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
13	exp JAUNDICE/	251
14	jaundice$.ti.	191
15	KERNICTERUS/	2
16	kernicterus$.ti.	3
17	or/8-16	536
18	or/13-14	383
19	or/8-10	191
20	and/18-19	48
21	and/7,20	48
22	or/15-16	5
23	or/18-19	526
24	or/12,22	14
25	and/23-24	5
26	and/7,25	5
27	RISK FACTORS/	10464
28	risk factor$.ti.	1717
29	COMORBIDITY/	1233
30	"CONFOUNDING FACTORS (EPIDEMIOLOGY)"/	224
31	or/27-30	12242
32	and/7,17,31	1
33	or/21,26,32	53

CDSR, DARE

JAUN_risk_factors_cdsrdare_070808

#	Searches	Results
1	INFANT, PREMATURE.kw.	194
2	preterm$.tw.	550
3	INFANT, NEWBORN.kw.	579
4	(newborn$ or neonate$).tw.	946
5	BLOOD GROUP INCOMPATIBILITY.kw.	1

6	GLUCOSEPHOSPHATE DEHYDROGENASE DEFICIENCY.kw.	0
7	or/1-6	1091
8	HYPERBILIRUBINEMIA.kw.	3
9	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
10	hyperbilirubin?emia$.ti.	2
11	bilirubin?emia$.ti.	0
12	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	5
13	JAUNDICE.kw.	13
14	jaundice$.ti.	10
15	KERNICTERUS.kw.	1
16	kernicterus$.ti.	0
17	or/8-16	18
18	or/13-14	15
19	or/8-10	4
20	and/18-19	3
21	and/7,20	3
22	or/15-16	1
23	or/18-19	16
24	or/12,22	6
25	and/23-24	4
26	and/7,25	4
27	RISK FACTORS.kw.	577
28	risk factor$.ti.	24
29	COMORBIDITY.kw.	39
30	"CONFOUNDING FACTORS (EPIDEMIOLOGY)".kw.	0
31	or/27-30	611
32	and/7,17,31	0
33	or/21,26,32	5

EMBASE 1980 to 2008 Week 31

JAUN_risk_factors_embase_070808

#	Searches	Results
1	PREMATURITY/	28534
2	preterm$.tw.	25873
3	NEWBORN/	175887
4	(newborn$ or neonate$).tw.	95506
5	exp BLOOD GROUP INCOMPATIBILITY/	2570
6	GLUCOSE 6 PHOSPHATE DEHYDROGENASE DEFICIENCY/	1508
7	or/1-6	238435
8	HYPERBILIRUBINEMIA/	5505
9	hyperbilirubin?emia$.ti.	1045
10	bilirubin?emia$.ti.	15
11	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	243

12	JAUNDICE/	9491
13	NEWBORN JAUNDICE/	1705
14	jaundice$.ti.	3602
15	KERNICTERUS/	699
16	kernicterus$.ti.	148
17	or/8-16	17595
18	or/13-14	4831
19	or/8-10	5731
20	and/18-19	775
21	and/7,20	571
22	or/15-16	702
23	or/18-19	9787
24	or/12,22	10101
25	and/23-24	2359
26	and/7,25	650
27	RISK FACTOR/	227978
28	risk factor$.ti.	37560
29	COMORBIDITY/	47834
30	confounding factor$.ti.	177
31	or/27-30	277617
32	and/7,17,31	290
33	or/21,26,32	1237

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to August Week 1 2008

JAUN_risk_factors_cinahl_070808

#	Searches	Results
1	INFANT, PREMATURE/	5661
2	preterm$.tw.	4757
3	INFANT, NEWBORN/	36594
4	(newborn$ or neonate$).tw.	9089
5	BLOOD GROUP INCOMPATIBILITY/	151
6	(glucose$ adj5 deficien$).tw.	71
7	or/1-6	**41326**
8	HYPERBILIRUBINEMIA/	201
9	hyperbilirubin?emia$.ti.	127
10	bilirubin?emia$.ti.	1
11	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	22
12	JAUNDICE/	205
13	jaundice$.ti.	282
14	KERNICTERUS/	86
15	kernicterus$.ti.	35
16	or/8-15	**667**
17	or/12-13	400

18	or/8-9	265
19	and/17-18	42
20	and/7,19	31
21	or/14-15	89
22	or/17-18	623
23	or/11,21	101
24	and/22-23	58
25	and/7,24	57
26	RISK FACTORS/	30074
27	risk factor$.ti.	6903
28	COMORBIDITY/	9000
29	confounding factor$.ti.	27
30	or/26-29	42220
31	and/7,16,30	25
32	or/20,25,31	98

CINAHL EBSCO

JAUN_risk_factors_cinahl_ebsco_070808

Friday, May 15, 2009 4:01:43 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S33	S21 or S25 or S32	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	113
S32	S7 and S17 and S31	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	32
S31	S27 or S28 or S29 or S30	Search modes -	Interface -	51515

		Boolean/Phrase	EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	
S30	TI confounding factor*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	30
S29	MH COMORBIDITY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	11607
S28	TI risk factor*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	8349
S27	MH RISK FACTORS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	36180
S26	S7 AND S25	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	71
S25	S18 AND S24	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	84
S24	S23 or S22	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	416
S23	S8 or S9 or S10 or S11 or S12	Search modes - Boolean/Phrase	Interface - EBSCOhost	343

			Search Screen - Advanced Search Database - CINAHL with Full Text	
S22	S15 or S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	119
S21	S7 and S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	43
S20	S18 and S19	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	56
S19	S8 or S9	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	328
S18	S13 or S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	476
S17	S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	808
S16	TI kernicterus	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	49
S15	MH KERNICTERUS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	116

			Advanced Search Database - CINAHL with Full Text	
S14	TI jaundice*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	329
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	255
S12	TI (hyperbilirubin* N3 encephalopath*) or AB (hyperbilirubin* N3 encephalopath*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3
S11	TI (bilirubin* N3 encephalopath*) or AB (bilirubin* N3 encephalopath*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	33
S10	TI (bilirubinemi*) or TI (bilirubinaemi*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1
S9	TI (hyperbilirubinemi*) or TI (hyperbilirubinaemi*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	163
S8	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	246
S7	S1 or S2 or S3 or S4 or S5 or S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	48069

			Database - CINAHL with Full Text	
S6	TI (glucose N5 deficien*) or AB (glucose N5 deficien*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	95
S5	MH BLOOD GROUP INCOMPATIBILITY+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	640
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	10924
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	41919
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5983
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6767

Question: What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia?

Ovid MEDLINE(R) 1950 to August Week 4 2008

JAUN_assess_tests_hyperbil_medline_050908

#	Searches	Results
1	INFANT, PREMATURE/	32828
2	preterm$.tw.	29140
3	INFANT, NEWBORN/	424141
4	(newborn$ or neonate$).tw.	138590
5	or/1-4	481742
6	HYPERBILIRUBINEMIA/	3415
7	HYPERBILIRUBINEMIA, NEONATAL/	167
8	hyperbilirubin?emia$.ti.	2193
9	bilirubin?emia$.ti.	149
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	285
11	exp JAUNDICE/	10042
12	jaundice$.ti.	9833
13	or/6-12	20019
14	THYROID FUNCTION TESTS/	11340
15	TSH.tw.	20277
16	(thyroid adj3 stimulating adj3 hormone$).tw.	6085
17	(thyroidstimulating adj3 hormone$).tw.	11
18	thyrotropin.ti.	7579
19	(urine adj3 reducing adj3 substance$).tw.	8
20	ASPARTATE AMINOTRANSFERASES/bl	14602
21	AST.ti.	206
22	ALANINE TRANSAMINASE/bl	15564
23	ALT.ti.	344
24	ALAKALINE PHOSPHATASE/bl	0
25	ALP.ti.	133
26	GAMMA-GLUTAMYLTRANSFERASE/bl	3768
27	GGT.ti.	126
28	HEMOGLOBINS/	51157
29	h?emoglobin$.ti.	30783
30	HEMATOCRIT/	29026
31	h?ematocrit$.ti.	2251
32	(peripheral adj3 blood adj3 smear$).tw.	1229
33	RETICULOCYTE COUNT/	704
34	(reticulocyte$ adj3 (count$ or number$)).tw.	2173
35	BLOOD GAS ANALYSIS/	17340

36	(blood adj3 gas$).ti.	5204
37	(ABG and arterial).tw.	243
38	SERUM ALBUMIN/	35634
39	((serum or plasma) adj3 albumin).tw.	42168
40	(total adj3 serum adj3 bilirubin$).tw.	1268
41	(serum adj3 bilirubin$ adj3 level$).tw.	1838
42	tsb.tw.	510
43	BILIRUBIN/bl [Blood]	11384
44	(unconjugated adj3 bilirubin).tw.	855
45	(split adj3 bilirubin).tw.	3
46	URINALYSIS/	2820
47	(urine adj3 (test$ or check$ or analys?s or level$)).tw.	12349
48	or/14-47	252812
49	and/5,13,48	1573
50	limit 49 to humans	1490
51	limit 50 to english language	1171

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

JAUN_assess_tests_hyperbil_cctr_050908

#	Searches	Results
1	INFANT, PREMATURE/	1709
2	preterm$.tw.	3074
3	INFANT, NEWBORN/	8435
4	(newborn$ or neonate$).tw.	4189
5	or/1-4	11391
6	HYPERBILIRUBINEMIA/	58
7	HYPERBILIRUBINEMIA, NEONATAL/	10
8	hyperbilirubin?emia$.ti.	148
9	bilirubin?emia$.ti.	4
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
11	exp JAUNDICE/	251
12	jaundice$.ti.	191
13	or/6-12	533
14	THYROID FUNCTION TESTS/	168
15	TSH.tw.	875
16	(thyroid adj3 stimulating adj3 hormone$).tw.	294
17	(thyroidstimulating adj3 hormone$).tw.	1
18	thyrotropin.ti.	231
19	(urine adj3 reducing adj3 substance$).tw.	0
20	ASPARTATE AMINOTRANSFERASES/bl	584
21	AST.ti.	18

22 ALANINE TRANSAMINASE/bl	876
23 ALT.ti.	56
24 ALKALINE PHOSPHATASE/bl	763
25 ALP.ti.	2
26 GAMMA-GLUTAMYLTRANSFERASE/bl	169
27 GGT.ti.	2
28 HEMOGLOBINS/	1869
29 h?emoglobin$.ti.	502
30 HEMATOCRIT/	1204
31 h?ematocrit$.ti.	88
32 (peripheral adj3 blood adj3 smear$).tw.	13
33 RETICULOCYTE COUNT/	94
34 (reticulocyte$ adj3 (count$ or number$)).tw.	227
35 Blood GAS ANALYSIS/	831
36 (blood adj3 gas$).ti.	357
37 (ABG and arterial).tw.	27
38 SERUM ALBUMIN/	742
39 ((serum or plasma) adj3 albumin).tw.	1295
40 (total adj3 serum adj3 bilirubin$).tw.	110
41 (serum adj3 bilirubin$ adj3 level$).tw.	183
42 tsb.tw.	24
43 BILIRUBIN/bl [Blood]	483
44 (unconjugated adj3 bilirubin).tw.	19
45 (split adj3 bilirubin).tw.	0
46 URINALYSIS/	102
47 (urine adj3 (test$ or check$ or analys?s or level$)).tw.	1091
48 or/14-47	10361
49 and/5,13,48	129

DARE, CDSR

JAUN_assess_tests_hyperbil_cdsrdare_050908

#	Searches	Results
1	INFANT, PREMATURE.kw.	207
2	preterm$.tw.	560
3	INFANT, NEWBORN.kw.	595
4	(newborn$ or neonate$).tw.	954
5	or/1-4	1104
6	HYPERBILIRUBINEMIA.kw.	3
7	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
8	hyperbilirubin?emia$.ti.	2
9	bilirubin?emia$.ti.	0

10 ((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	5
11 JAUNDICE.kw.	13
12 jaundice$.ti.	10
13 or/6-12	18
14 THYROID FUNCTION TESTS.kw.	1
15 TSH.tw.	27
16 (thyroid adj3 stimulating adj3 hormone$).tw.	24
17 (thyroidstimulating adj3 hormone$).tw.	0
18 thyrotropin.ti.	2
19 (urine adj3 reducing adj3 substance$).tw.	0
20 ASPARTATE AMINOTRANSFERASES.kw.	2
21 AST.ti.	0
22 ALANINE TRANSAMINASE.kw.	8
23 ALT.ti.	0
24 ALKALINE PHOSPHATASE.kw.	0
25 ALP.ti.	0
26 GAMMA-GLUTAMYLTRANSFERASE.kw.	2
27 GGT.ti.	0
28 HEMOGLOBINS.kw.	14
29 h?emoglobin$.ti.	6
30 HEMATOCRIT.kw.	7
31 h?ematocrit$.ti.	1
32 (peripheral adj3 blood adj3 smear$).tw.	3
33 RETICULOCYTE COUNT.kw.	0
34 (reticulocyte$ adj3 (count$ or number$)).tw.	8
35 BLOOD GAS ANALYSIS.kw.	3
36 (blood adj3 gas$).ti.	0
37 (ABG and arterial).tw.	6
38 SERUM ALBUMIN.kw.	9
39 ((serum or plasma) adj3 albumin).tw.	97
40 (total adj3 serum adj3 bilirubin$).tw.	15
41 (serum adj3 bilirubin$ adj3 level$).tw.	23
42 tsb.tw.	1
43 BILIRUBIN.kw.	4
44 (unconjugated adj3 bilirubin).tw.	5
45 (split adj3 bilirubin).tw.	0
46 URINALYSIS.kw.	10
47 (urine adj3 (test$ or check$ or analys?s or level$)).tw.	143
48 or/14-47	352
49 and/5,13,48	7

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to September Week 1 2008

JAUN_assess_tests_hyperbil_cinahl_050908

#	Searches	Results
1	INFANT, PREMATURE/	6174
2	preterm$.tw.	5276
3	INFANT, NEWBORN/	38718
4	(newborn$ or neonate$).tw.	9765
5	or/1-4	43532
6	HYPERBILIRUBINEMIA/	212
7	hyperbilirubin?emia$.ti.	142
8	bilirubin?emia$.ti.	1
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	26
10	JAUNDICE/	215
11	jaundice$.ti.	301
12	or/6-11	678
13	THYROID FUNCTION TESTS/	387
14	TSH.tw.	195
15	(thyroid adj3 stimulating adj3 hormone$).tw.	226
16	(thyroidstimulating adj3 hormone$).tw.	2
17	thyrotropin.ti.	30
18	(urine adj3 reducing adj3 substance$).tw.	0
19	ASPARATE AMINOTRANSFERASE/	0
20	AST.ti.	99
21	ALANINE AMINOTRANSFERASE/	381
22	ALT.ti.	26
23	ALKALINE PHOSPHATASE/	386
24	ALP.ti.	5
25	GAMMA-GLUTAMYLTRANSFERASE/	105
26	GGT.ti.	8
27	HEMOGLOBINS/ or HEMOGLOBIN A, GLYCOSYLATED/	4835
28	h?emoglobin$.ti.	660
29	Hematocrit/	910
30	h?ematocrit$.ti.	110
31	(peripheral adj3 blood adj3 smear$).tw.	49
32	RETICULOCYTE COUNT/	36
33	(reticulocyte$ adj3 (count$ or number$)).tw.	88
34	BLOOD GAS ANALYSIS/	1598
35	(blood adj3 gas$).ti.	380
36	(ABG and arterial).tw.	64
37	SERUM ALBUMIN/	808
38	((serum or plasma) adj3 albumin).tw.	835

39 (total adj3 serum adj3 bilirubin$).tw.	76
40 (serum adj3 bilirubin$ adj3 level$).tw.	70
41 tsb.tw.	34
42 BILIRUBIN/bl [Blood]	259
43 (unconjugated adj3 bilirubin).tw.	22
44 (split adj3 bilirubin).tw.	1
45 URINALYSIS/	2158
46 (urine adj3 (test$ or check$ or analys?s or level$)).tw.	700
47 or/13-46	12776
48 and/5,12,47	128

CINAHL EBSCO

JAUN_assess_tests_hyperbil_cinahl_050908_4

#	Query	Limiters/Expanders	Last Run Via	Results
S55	S5 and S15 and S54	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S54	S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S53	AB (urine N3 test*) or AB (urine N3 check*) or AB (urine N3 analysis) or AB (urine N3 analyses) or AB (urine N3 level*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S52	TI (urine N3 test*) or TI (urine N3 check*) or TI (urine N3 analysis) or TI (urine N3 analyses) or TI (urine N3 level*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S51	MH URINALYSIS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S50	TI (split bilirubin) or AB (split bilirubin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	Display

			Database - CINAHL with Full Text	
S49	TI (unconjugated N3 bilirubin) or AB (unconjugated N3 bilirubin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S48	MH BILIRUBIN/BL	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S47	TI (tsb) or AB (tsb)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S46	TI (serum albumin level*) or AB (total serum level*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S45	TI (total serum albumin) or AB (total serum albumin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S44	TI (plasma N3 albumin) or AB (plasma N3 albumin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S43	TI (serum N3 albumin) or AB (serum N3 albumin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S42	MH SERUM ALBUMIN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S41	AB (ABG) and AB (arterial)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S40	TI (ABG) and TI (arterial)	Search modes -	Interface - EBSCOhost	Display

		Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S39	TI (blood gas*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S38	MH BLOOD GAS ANALYSIS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S37	TI (reticulocyte* N3 number*) or AB (reticulocyte* N3 number*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S36	TI (reticulocyte* N3 count*) or AB (reticulocyte* N3 count*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S35	MH RETICULOCYTE COUNT	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S34	TI (peripheral blood smear*) or AB (peripheral blood smear*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S33	MH HEMATOCRIT	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S32	TI (haemoglobin* or hemoglobin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S31	MH HEMOGLOBIN A, GLYCOSYLATED	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

			with Full Text	
S30	MH HEMOGLOBINS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S29	TI (GGT)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S28	MH GAMMA-GLUTAMYLTRANSFERASE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S27	TI (ALP)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S26	MH ALKALINE PHOSPHATASE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S25	TI (ALT)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S24	MH ALANINE AMINOTRANSFERASE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S23	TI (AST)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S22	MH ASPARTATE AMINOTRANSFERASE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S21	TI (urine reducing substance*) or AB ((urine reducing substance*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	Display

			Advanced Search Database - CINAHL with Full Text	
S20	TI (thyrotropin) or AB ((thyrotropin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S19	TI (thyroidstimulating N3 hormone*) or AB (thyroidstimulating N3 hormone*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S18	TI (thyroid stimulating hormone*) or AB (thyroid stimulating hormone*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S17	TI (tsb) or AB (tsb)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S16	MH THYROID FUNCTION TESTS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S15	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	(TI jaundice*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S12	(AB "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

S11	(TI "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(AB "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S9	(TI "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI "bilirubinaemia" OR "bilirubinemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S7	(TI "hyperbilirubinemia" or "hyperbilirubinaemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	Display

			Database - CINAHL with Full Text	
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

Question: What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia? Search 2. GDG requested a search on three additional tests G6PD, Coomb's and complete blood count.

Ovid MEDLINE(R) 1950 to October Week 1 2008

JAUN_assess_tests_hyperbil_SEARCH2_medline_091008

#	Searches	Results
1	INFANT, PREMATURE/	33074
2	preterm$.tw.	29486
3	INFANT, NEWBORN/	426267
4	(newborn$ or neonate$).tw.	139364
5	or/1-4	484217
6	HYPERBILIRUBINEMIA/	3433
7	HYPERBILIRUBINEMIA, NEONATAL/	176
8	hyperbilirubin?emia$.ti.	2206
9	bilirubin?emia$.ti.	149
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	286
11	exp JAUNDICE/	10081
12	jaundice$.ti.	9855
13	KERNICTERUS/	896
14	kernicterus$.ti.	363
15	or/6-14	20648
16	Glucosephosphate Dehydrogenase Deficiency/	3783
17	Coombs' Test/	4021
18	BLOOD GROUP INCOMPATIBILITY/	4890
19	G6PD.tw.	2704
20	BLOOD CELL COUNT/	17683
21	complete blood count$.tw.	1926
22	or/16-21	33131
23	and/5,15,22	476
24	limit 23 to (english language and humans)	314

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

JAUN_assess_tests_hyperbil_SEARCH2_cctr_091008

#	Searches	Results
1	INFANT, PREMATURE/	1709
2	preterm$.tw.	3074
3	INFANT, NEWBORN/	8435
4	(newborn$ or neonate$).tw.	4189
5	or/1-4	11391

6	HYPERBILIRUBINEMIA/	58
7	HYPERBILIRUBINEMIA, NEONATAL/	10
8	hyperbilirubin?emia$.ti.	148
9	bilirubin?emia$.ti.	4
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
11	exp JAUNDICE/	251
12	jaundice$.ti.	191
13	KERNICTERUS/	2
14	kernicterus$.ti.	3
15	or/6-14	536
16	Glucosephosphate Dehydrogenase Deficiency/	25
17	Coombs' Test/	18
18	BLOOD GROUP INCOMPATIBILITY/	41
19	G6PD.tw.	26
20	BLOOD CELL COUNT/	542
21	complete blood count$.tw.	157
22	or/16-21	785
23	and/5,15,22	19

DARE, CDSR

JAUN_assess_tests_hyperbil_SEARCH2_cdsrdare_091008

#	Searches	Results
1	INFANT, PREMATURE.kw.	207
2	preterm$.tw,tx.	560
3	INFANT, NEWBORN.kw.	595
4	(newborn$ or neonate$).tw,tx.	954
5	or/1-4	1104
6	HYPERBILIRUBINEMIA.kw.	3
7	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
8	hyperbilirubin?emia$.ti.	2
9	bilirubin?emia$.ti.	0
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw,tx.	5
11	JAUNDICE.kw.	13
12	jaundice$.ti.	10
13	KERNICTERUS.kw.	1
14	kernicterus$.ti.	0
15	or/6-14	18
16	Glucosephosphate Dehydrogenase Deficiency.kw.	0
17	Coombs' Test.kw.	0
18	BLOOD GROUP INCOMPATIBILITY.kw.	1
19	G6PD.tw,tx.	6

20	BLOOD CELL COUNT.kw.	4
21	complete blood count$.tw,tx.	14
22	or/16-21	23
23	and/5,15,22	2

EMBASE 1980 to 2008 Week 40

JAUN_assess_tests_hyperbil_SEARCH2_embase_091008

#	Searches	Results
1	PREMATURITY/	28910
2	preterm$.tw.	26207
3	NEWBORN/	177050
4	(newborn$ or neonate$).tw.	96324
5	or/1-4	237012
6	HYPERBILIRUBINEMIA/	5618
7	hyperbilirubin?emia$.ti.	1053
8	bilirubin?emia$.ti.	15
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	244
10	JAUNDICE/	9651
11	NEWBORN JAUNDICE/	1719
12	jaundice$.ti.	3621
13	KERNICTERUS/	704
14	kernicterus$.ti.	149
15	or/6-14	17878
16	GLUCOSE 6 PHOSPHATE DEHYDROGENASE DEFICIENCY/	1527
17	G6PD.tw.	2020
18	COOMBS TEST/	1620
19	exp BLOOD CELL COUNT/	64937
20	complete blood count$.tw.	1670
21	exp BLOOD GROUP INCOMPATIBILITY/	2599
22	or/16-21	72155
23	and/5,15,22	381

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to October Week 1 2008

JAUN_assess_tests_hyperbil_SEARCH2_cinahl_091008

#	Searches	Results
1	INFANT, PREMATURE/	6268
2	preterm$.tw.	5352
3	INFANT, NEWBORN/	39143

4	(newborn$ or neonate$).tw.	9892
5	or/1-4	44044
6	HYPERBILIRUBINEMIA/	215
7	hyperbilirubin?emia$.ti.	143
8	bilirubin?emia$.ti.	1
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	27
10	JAUNDICE/	221
11	jaundice$.ti.	301
12	Kernicterus/	101
13	kernicterus$.ti.	40
14	or/6-13	727
15	G6PD.tw.	45
16	Glucose-6-phosphate dehydrogenase.tw.	88
17	Coombs' Test/	34
18	exp Blood Group Incompatibility/	580
19	Blood Cell Count/	569
20	complete blood count$.tw.	187
21	or/15-20	1395
22	and/5,14,21	126

CINAHL EBSCO

JAUN_assess_tests_hyperbil_search2_cinahl_091008_2

#	Query	Limiters/Expanders	Last Run Via	Results
S25	S5 and S17 and S24	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S24	S18 or S19 or S20 or S21 or S22 or S23	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S23	TI (complete blood count*) or AB (complete blood count*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S22	MH BLOOD CELL COUNT	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S21	MH BLOOD GROUP	Search modes -	Interface - EBSCOhost	Display

	INCOMPATIBILITY+	Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S20	MH COOMBS' TEST	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S19	TI (glucose 6 phosphate dehydrogenase) or AB (glucose 6 phosphate dehydrogenase)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S18	TI (G6PD) or AB (G6PD)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S17	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S16	(TI "kernicterus*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S15	MH KERNICTERUS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	(TI jaundice*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S12	(AB "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with	Display

			Full Text	
S11	(TI "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(AB "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S9	(TI "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI "bilirubinaemia" OR "bilirubinemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S7	(TI "hyperbilirubinemia" or "hyperbilirubinaemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	Display

			Advanced Search Database - CINAHL with Full Text	
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

Question: What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia? Economic Evaluation

Ovid MEDLINE(R) 1950 to September Week 3 2008

JAUN_assess_tests_hyperbil_economic_medline_240908

#	Searches	Results
1	costs.tw.	77470
2	cost effective$.tw.	44545
3	economic.tw.	66685
4	or/1-3	163873
5	(metabolic adj cost).tw.	486
6	((energy or oxygen) adj cost).tw.	2052
7	4 not (5 or 6)	163640
8	INFANT, PREMATURE/	32893
9	preterm$.tw.	29239
10	INFANT, NEWBORN/	424897
11	(newborn$ or neonate$).tw.	138853
12	or/8-11	482616
13	HYPERBILIRUBINEMIA/	3420
14	HYPERBILIRUBINEMIA, NEONATAL/	173
15	hyperbilirubin?emia$.ti.	2198
16	bilirubin?emia$.ti.	149
17	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	286
18	exp JAUNDICE/	10062
19	jaundice$.ti.	9844
20	or/13-19	20052
21	THYROID FUNCTION TESTS/	11346
22	TSH.tw.	20306
23	(thyroid adj3 stimulating adj3 hormone$).tw.	6104
24	(thyroidstimulating adj3 hormone$).tw.	11
25	thyrotropin.ti.	7581
26	(urine adj3 reducing adj3 substance$).tw.	8
27	ASPARTATE AMINOTRANSFERASES/bl	14626
28	AST.ti.	206
29	ALANINE TRANSAMINASE/bl	15609
30	ALT.ti.	344
31	ALAKALINE PHOSPHATASE/bl	0
32	ALP.ti.	133
33	GAMMA-GLUTAMYLTRANSFERASE/bl	3777
34	GGT.ti.	126
35	HEMOGLOBINS/	51235
36	h?emoglobin$.ti.	30815

37	HEMATOCRIT/	29045
38	h?ematocrit$.ti.	2251
39	(peripheral adj3 blood adj3 smear$).tw.	1233
40	RETICULOCYTE COUNT/	705
41	(reticulocyte$ adj3 (count$ or number$)).tw.	2177
42	BLOOD GAS ANALYSIS/	17355
43	(blood adj3 gas$).ti.	5207
44	(ABG and arterial).tw.	244
45	SERUM ALBUMIN/	35685
46	((serum or plasma) adj3 albumin).tw.	42274
47	(total adj3 serum adj3 bilirubin$).tw.	1281
48	(serum adj3 bilirubin$ adj3 level$).tw.	1850
49	tsb.tw.	512
50	BILIRUBIN/bl [Blood]	11401
51	(unconjugated adj3 bilirubin).tw.	859
52	(split adj3 bilirubin).tw.	3
53	URINALYSIS/	2841
54	(urine adj3 (test$ or check$ or analys?s or level$)).tw.	12386
55	or/21-54	253225
56	and/12,20,55	1576
57	limit 56 to humans	1493
58	limit 57 to english language	1173
59	and/7,12,20,58	14

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

JAUN_assess_tests_hyperbil_economic_cctr_240908

#	Searches	Results
1	costs.tw.	5410
2	cost effective$.tw.	4135
3	economic.tw.	2275
4	or/1-3	8908
5	(metabolic adj cost).tw.	38
6	((energy or oxygen) adj cost).tw.	178
7	4 not (5 or 6)	8898
8	INFANT, PREMATURE/	1709
9	preterm$.tw.	3074
10	INFANT, NEWBORN/	8435
11	(newborn$ or neonate$).tw.	4189
12	or/8-11	11391
13	HYPERBILIRUBINEMIA/	58
14	HYPERBILIRUBINEMIA, NEONATAL/	10

15 hyperbilirubin?emia$.ti.	148
16 bilirubin?emia$.ti.	4
17 ((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
18 exp JAUNDICE/	251
19 jaundice$.ti.	191
20 or/13-19	533
21 THYROID FUNCTION TESTS/	168
22 TSH.tw.	875
23 (thyroid adj3 stimulating adj3 hormone$).tw.	294
24 (thyroidstimulating adj3 hormone$).tw.	1
25 thyrotropin.ti.	231
26 (urine adj3 reducing adj3 substance$).tw.	0
27 ASPARTATE AMINOTRANSFERASES/bl	584
28 AST.ti.	18
29 ALANINE TRANSAMINASE/bl	876
30 ALT.ti.	56
31 ALKALINE PHOSPHATASE/bl	763
32 ALP.ti.	2
33 GAMMA-GLUTAMYLTRANSFERASE/bl	169
34 GGT.ti.	2
35 HEMOGLOBINS/	1869
36 h?emoglobin$.ti.	502
37 HEMATOCRIT/	1204
38 h?ematocrit$.ti.	88
39 (peripheral adj3 blood adj3 smear$).tw.	13
40 RETICULOCYTE COUNT/	94
41 (reticulocyte$ adj3 (count$ or number$)).tw.	227
42 Blood GAS ANALYSIS/	831
43 (blood adj3 gas$).ti.	357
44 (ABG and arterial).tw.	27
45 SERUM ALBUMIN/	742
46 ((serum or plasma) adj3 albumin).tw.	1295
47 (total adj3 serum adj3 bilirubin$).tw.	110
48 (serum adj3 bilirubin$ adj3 level$).tw.	183
49 tsb.tw.	24
50 BILIRUBIN/bl [Blood]	483
51 (unconjugated adj3 bilirubin).tw.	19
52 (split adj3 bilirubin).tw.	0
53 URINALYSIS/	102
54 (urine adj3 (test$ or check$ or analys?s or level$)).tw.	1091
55 or/21-54	10361
56 and/7,12,20,55	3

EBM Reviews - Health Technology Assessment 3rd Quarter 2008

JAUN_assess_tests_hyperbil_economic_hta_240908

#	Searches	Results
1	costs.tw.	1155
2	cost effective$.tw.	915
3	economic.tw.	682
4	or/1-3	1657
5	(metabolic adj cost).tw.	0
6	((energy or oxygen) adj cost).tw.	0
7	4 not (5 or 6)	1657
8	INFANT, PREMATURE/	9
9	preterm$.tw.	22
10	INFANT, NEWBORN/	65
11	(newborn$ or neonate$).tw.	99
12	or/8-11	121
13	HYPERBILIRUBINEMIA/	4
14	HYPERBILIRUBINEMIA, NEONATAL/	1
15	hyperbilirubin?emia$.ti.	3
16	bilirubin?emia$.ti.	0
17	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	1
18	exp JAUNDICE/	1
19	jaundice$.ti.	3
20	or/13-19	8
21	THYROID FUNCTION TESTS/	3
22	TSH.tw.	1
23	(thyroid adj3 stimulating adj3 hormone$).tw.	2
24	(thyroidstimulating adj3 hormone$).tw.	0
25	thyrotropin.ti.	0
26	(urine adj3 reducing adj3 substance$).tw.	0
27	ASPARTATE AMINOTRANSFERASES/bl	0
28	AST.ti.	0
29	ALANINE TRANSAMINASE/bl	0
30	ALT.ti.	0
31	ALAKALINE PHOSPHATASE/bl	0
32	ALP.ti.	0
33	GAMMA-GLUTAMYLTRANSFERASE/bl	0
34	GGT.ti.	0
35	HEMOGLOBINS/	2
36	h?emoglobin$.ti.	9
37	HEMATOCRIT/	1
38	h?ematocrit$.ti.	0

39	(peripheral adj3 blood adj3 smear$).tw.	0
40	RETICULOCYTE COUNT/	0
41	(reticulocyte$ adj3 (count$ or number$)).tw.	0
42	BLOOD GAS ANALYSIS/	3
43	(blood adj3 gas$).ti.	2
44	(ABG and arterial).tw.	0
45	SERUM ALBUMIN/	5
46	((serum or plasma) adj3 albumin).tw.	7
47	(total adj3 serum adj3 bilirubin$).tw.	0
48	(serum adj3 bilirubin$ adj3 level$).tw.	1
49	tsb.tw.	1
50	BILIRUBIN/bl [Blood]	0
51	(unconjugated adj3 bilirubin).tw.	0
52	(split adj3 bilirubin).tw.	0
53	URINALYSIS/	5
54	(urine adj3 (test$ or check$ or analys?s or level$)).tw.	7
55	or/21-54	38
56	and/7,12,20,55	1

EBM Reviews - NHS Economic Evaluation Database 3rd Quarter 2008

JAUN_assess_tests_hyperbil_economic_nhseed_240908

#	Searches	Results
1	costs.tw.	17348
2	cost effective$.tw.	8488
3	economic.tw.	23373
4	or/1-3	23646
5	(metabolic adj cost).tw.	0
6	((energy or oxygen) adj cost).tw.	0
7	4 not (5 or 6)	23646
8	INFANT, PREMATURE/	77
9	preterm$.tw.	79
10	INFANT, NEWBORN/	861
11	(newborn$ or neonate$).tw.	925
12	or/8-11	948
13	HYPERBILIRUBINEMIA/	2
14	HYPERBILIRUBINEMIA, NEONATAL/	1
15	hyperbilirubin?emia$.ti.	1
16	bilirubin?emia$.ti.	0
17	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	0
18	exp JAUNDICE/	5
19	jaundice$.ti.	8

20 or/13-19	14
21 THYROID FUNCTION TESTS/	1
22 TSH.tw.	8
23 (thyroid adj3 stimulating adj3 hormone$).tw.	12
24 (thyroidstimulating adj3 hormone$).tw.	0
25 thyrotropin.ti.	2
26 (urine adj3 reducing adj3 substance$).tw.	0
27 ASPARTATE AMINOTRANSFERASES/bl	1
28 AST.ti.	0
29 ALANINE TRANSAMINASE/bl	10
30 ALT.ti.	0
31 ALAKALINE PHOSPHATASE/bl	0
32 ALP.ti.	0
33 GAMMA-GLUTAMYLTRANSFERASE/bl	0
34 GGT.ti.	0
35 HEMOGLOBINS/	34
36 h?emoglobin$.ti.	14
37 HEMATOCRIT/	17
38 h?ematocrit$.ti.	1
39 (peripheral adj3 blood adj3 smear$).tw.	0
40 RETICULOCYTE COUNT/	3
41 (reticulocyte$ adj3 (count$ or number$)).tw.	7
42 BLOOD GAS ANALYSIS/	9
43 (blood adj3 gas$).ti.	3
44 (ABG and arterial).tw.	3
45 SERUM ALBUMIN/	13
46 ((serum or plasma) adj3 albumin).tw.	29
47 (total adj3 serum adj3 bilirubin$).tw.	5
48 (serum adj3 bilirubin$ adj3 level$).tw.	5
49 tsb.tw.	0
50 BILIRUBIN/bl [Blood]	4
51 (unconjugated adj3 bilirubin).tw.	0
52 (split adj3 bilirubin).tw.	0
53 URINALYSIS/	24
54 (urine adj3 (test$ or check$ or analys?s or level$)).tw.	50
55 or/21-54	209
56 and/7,12,20,55	3

EBM Reviews - NHS Economic Evaluation Database 3rd Quarter 2008

JAUN_assess_tests_hyperbil_economic_nhseed_240908

#	Searches	Results

1	costs.tw.	17348
2	cost effective$.tw.	8488
3	economic.tw.	23373
4	or/1-3	23646
5	(metabolic adj cost).tw.	0
6	((energy or oxygen) adj cost).tw.	0
7	4 not (5 or 6)	23646
8	INFANT, PREMATURE/	77
9	preterm$.tw.	79
10	INFANT, NEWBORN/	861
11	(newborn$ or neonate$).tw.	925
12	or/8-11	948
13	HYPERBILIRUBINEMIA/	2
14	HYPERBILIRUBINEMIA, NEONATAL/	1
15	hyperbilirubin?emia$.ti.	1
16	bilirubin?emia$.ti.	0
17	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	0
18	exp JAUNDICE/	5
19	jaundice$.ti.	8
20	or/13-19	14
21	THYROID FUNCTION TESTS/	1
22	TSH.tw.	8
23	(thyroid adj3 stimulating adj3 hormone$).tw.	12
24	(thyroidstimulating adj3 hormone$).tw.	0
25	thyrotropin.ti.	2
26	(urine adj3 reducing adj3 substance$).tw.	0
27	ASPARTATE AMINOTRANSFERASES/bl	1
28	AST.ti.	0
29	ALANINE TRANSAMINASE/bl	10
30	ALT.ti.	0
31	ALAKALINE PHOSPHATASE/bl	0
32	ALP.ti.	0
33	GAMMA-GLUTAMYLTRANSFERASE/bl	0
34	GGT.ti.	0
35	HEMOGLOBINS/	34
36	h?emoglobin$.ti.	14
37	HEMATOCRIT/	17
38	h?ematocrit$.ti.	1
39	(peripheral adj3 blood adj3 smear$).tw.	0
40	RETICULOCYTE COUNT/	3
41	(reticulocyte$ adj3 (count$ or number$)).tw.	7
42	BLOOD GAS ANALYSIS/	9
43	(blood adj3 gas$).ti.	3

44 (ABG and arterial).tw.	3
45 SERUM ALBUMIN/	13
46 ((serum or plasma) adj3 albumin).tw.	29
47 (total adj3 serum adj3 bilirubin$).tw.	5
48 (serum adj3 bilirubin$ adj3 level$).tw.	5
49 tsb.tw.	0
50 BILIRUBIN/bl [Blood]	4
51 (unconjugated adj3 bilirubin).tw.	0
52 (split adj3 bilirubin).tw.	0
53 URINALYSIS/	24
54 (urine adj3 (test$ or check$ or analys?s or level$)).tw.	50
55 or/21-54	209
56 and/7,12,20,55	3

Question: How effective is phototherapy?Restricted to SRs, meta-analysis and controlled trials

Ovid MEDLINE(R) 1950 to October Week 1 2008

JAUN_phototherapy_medline_131008

#	Searches	Results
1	randomized controlled trial.pt.	266806
2	controlled clinical trial.pt.	80365
3	DOUBLE BLIND METHOD/	100865
4	SINGLE BLIND METHOD/	12612
5	RANDOM ALLOCATION/	63127
6	RANDOMIZED CONTROLLED TRIALS/	57538
7	or/1-6	450144
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	98482
9	clinical trial.pt.	459524
10	exp CLINICAL TRIAL/	567163
11	exp CLINICAL TRIALS AS TOPIC/	213054
12	(clinic$ adj5 trial$).tw,sh.	133527
13	PLACEBOS/	28238
14	placebo$.tw,sh.	127827
15	random$.tw,sh.	565894
16	or/8-15	993442
17	or/7,16	998089
18	META ANALYSIS/	19747
19	META ANALYSIS AS TOPIC/	8778
20	meta analysis.pt.	19747
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	34987
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	18625
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	1956
24	or/18-23	48895
25	review$.pt.	1430230
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	31879
27	((hand or manual$) adj2 search$).tw.	3522
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	5442
29	(pooling or pooled or mantel haenszel).tw,sh.	30059
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1397
31	or/26-30	63968
32	and/25,31	27218
33	or/24,32	64812
34	letter.pt.	650354
35	case report.tw.	138957

36 comment.pt.	372091
37 editorial.pt.	231976
38 historical article.pt.	257421
39 or/34-38	1320137
40 17 not 39	961091
41 33 not 39	61188
42 or/40-41	**992333**
43 INFANT, PREMATURE/	33074
44 preterm$.tw.	29486
45 INFANT, NEWBORN/	426267
46 (newborn$ or neonate$).tw.	139364
47 or/43-46	**484217**
48 exp PHOTOTHERAPY/	20273
49 JAUNDICE, NEONATAL/th [Therapy]	1470
50 LIGHT/th [Therapy]	7
51 (light adj3 therap$).tw.	1488
52 (photoradiation adj3 therap$).tw.	176
53 bilibed.tw.	7
54 biliblanket$.tw.	12
55 (wallaby or wallabies).tw.	918
56 (optic adj2 fibre$).tw.	1075
57 light.ti.	55786
58 (hill?rom adj microlite).tw.	0
59 hill rom microlite.tw.	0
60 (Draeger adj2 phototherap$).tw.	0
61 medestime.tw.	0
62 neoblue$.tw.	2
63 light emitting diode$.tw.	1280
64 (LED and light).tw.	5808
65 (fluorescen$ adj3 light$).tw.	3557
66 (halogen adj3 light$).tw.	342
67 (sunlight or heliotherap$).tw.	5119
68 ohmeda.tw.	382
69 medela.tw.	12
70 or/48-69	**89832**
71 and/42,47,70	276

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

JAUN_phototherapy_cctr_131008

#	Searches	Results
1	randomized controlled trial.pt.	246310

2	controlled clinical trial.pt.	75338
3	DOUBLE BLIND METHOD/	81099
4	SINGLE BLIND METHOD/	7643
5	RANDOM ALLOCATION/	20221
6	RANDOMIZED CONTROLLED TRIALS/	0
7	or/1-6	317038
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	106559
9	clinical trial.pt.	273458
10	exp CLINICAL TRIAL/	0
11	exp CLINICAL TRIALS AS TOPIC/	0
12	(clinic$ adj5 trial$).tw,sh.	35204
13	PLACEBOS/	18244
14	placebo$.tw,sh.	105601
15	random$.tw,sh.	241696
16	or/8-15	386437
17	or/7,16	397360
18	META ANALYSIS/	0
19	META ANALYSIS AS TOPIC/	171
20	meta analysis.pt.	476
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	1056
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	250
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	26
24	or/18-23	1452
25	review$.pt.	2654
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	406
27	((hand or manual$) adj2 search$).tw.	38
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	61
29	(pooling or pooled or mantel haenszel).tw,sh.	2046
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	31
31	or/26-30	2491
32	and/25,31	93
33	or/24,32	1515
34	letter.pt.	4483
35	case report.tw.	149
36	comment.pt.	1562
37	editorial.pt.	280
38	historical article.pt.	58
39	or/34-38	5258
40	17 not 39	392251
41	33 not 39	1481
42	or/40-41	392505

43	INFANT, PREMATURE/	1709
44	preterm$.tw.	3074
45	INFANT, NEWBORN/	8435
46	(newborn$ or neonate$).tw.	4189
47	or/43-46	11391
48	exp PHOTOTHERAPY/	1159
49	JAUNDICE, NEONATAL/th [Therapy]	94
50	LIGHT/th [Therapy]	0
51	(light adj3 therap$).tw.	273
52	(photoradiation adj3 therap$).tw.	0
53	bilibed.tw.	1
54	biliblanket$.tw.	8
55	(wallaby or wallabies).tw.	5
56	(optic adj2 fibre$).tw.	44
57	light.ti.	1135
58	(hill?rom adj microlite).tw.	0
59	hill rom microlite.tw.	0
60	(Draeger adj2 phototherap$).tw.	0
61	medestime.tw.	0
62	neoblue$.tw.	0
63	light emitting diode$.tw.	50
64	(LED and light).tw.	127
65	(fluorescen$ adj3 light$).tw.	80
66	(halogen adj3 light$).tw.	30
67	(sunlight or heliotherap$).tw.	129
68	ohmeda.tw.	58
69	medela.tw.	2
70	or/48-69	2445
71	and/42,47,70	164

DARE, CDSR

JAUN_phototherapy_cdsrdare_131008

#	Searches	Results
1	randomized controlled trial.pt.	0
2	controlled clinical trial.pt.	0
3	DOUBLE BLIND METHOD.kw.	225
4	SINGLE BLIND METHOD.kw.	16
5	RANDOM ALLOCATION.kw.	11
6	RANDOMIZED CONTROLLED TRIALS.kw.	5625
7	or/1-6	5668
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	3814

9	clinical trial.pt.	0
10	CLINICAL TRIAL.kw.	0
11	CLINICAL TRIALS AS TOPIC.kw.	124
12	(clinic$ adj5 trial$).tw,sh.	5952
13	PLACEBOS.kw.	107
14	placebo$.tw,sh.	5335
15	random$.tw,sh.	11318
16	or/8-15	11713
17	or/7,16	11713
18	META ANALYSIS.kw.	159
19	META ANALYSIS AS TOPIC.kw.	26
20	meta analysis.pt.	0
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	7880
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	7752
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	2902
24	or/18-23	11535
25	review$.pt.	0
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	11215
27	((hand or manual$) adj2 search$).tw.	1874
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	2540
29	(pooling or pooled or mantel haenszel).tw,sh.	5741
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	3818
31	or/26-30	11382
32	and/25,31	0
33	or/24,32	11535
34	letter.pt.	0
35	case report.tw.	114
36	comment.pt.	0
37	editorial.pt.	0
38	historical article.pt.	0
39	or/34-38	114
40	17 not 39	11613
41	33 not 39	11439
42	or/40-41	12882
43	INFANT, PREMATURE.kw.	207
44	preterm$.tw,tx.	560
45	INFANT, NEWBORN.kw.	595
46	(newborn$ or neonate$).tw,tx.	954
47	or/43-46	1104
48	PHOTOTHERAPY.kw.	21
49	JAUNDICE, NEONATAL.kw.	7

50 LIGHT.kw.	11
51 (light adj3 therap$).tw,tx.	51
52 (photoradiation adj3 therap$).tw,tx.	0
53 bilibed$.tw,tx.	0
54 biliblanket$.tw,tx.	1
55 (wallaby or wallabies).tw,tx.	1
56 (optic adj2 fibre$).tw,tx.	12
57 light.ti.	15
58 (hill?rom adj microlite).tw,tx.	0
59 hill rom microlite.tw,tx.	0
60 (Draeger adj2 phototherap$).tw,tx.	0
61 medestime.tw,tx.	0
62 neoblue$.tw,tx.	0
63 light emitting diode$.tw,tx.	2
64 (LED and light).tw,tx.	250
65 (fluorescen$ adj3 light$).tw,tx.	5
66 (halogen adj3 light$).tw,tx.	1
67 (sunlight or heliotherap$).tw,tx.	30
68 ohmeda.tw,tx.	2
69 medela.tw.	0
70 or/48-69	352
71 and/42,47,70	42

EMBASE 1980 to 2008 Week 41

JAUN_phototherapy_embase_131008

#	Searches	Results
1	CLINICAL TRIALS/	519099
2	(clinic$ adj5 trial$).ti,ab,sh.	122674
3	SINGLE BLIND PROCEDURE/	7849
4	DOUBLE BLIND PROCEDURE/	70766
5	RANDOM ALLOCATION/	26330
6	CROSSOVER PROCEDURE/	20737
7	PLACEBO/	118995
8	placebo$.ti,ab,sh.	169680
9	random$.ti,ab,sh.	421609
10	RANDOMIZED CONTROLLED TRIALS/	163322
11	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.	91962
12	randomi?ed control$ trial$.tw.	31938
13	or/1-12	850569
14	META ANALYSIS/	34138
15	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.	43611

16	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.	26234
17	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.	1612
18	or/14-17	60164
19	review.pt.	898679
20	(medline or medlars or embase).ab.	22858
21	(scisearch or science citation index).ab.	708
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	8291
23	((hand or manual$) adj2 search$).tw.	2626
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.	4204
25	(pooling or pooled or mantel haenszel).tw.	24298
26	(peto or dersimonian or "der simonian" or fixed effect).tw.	869
27	or/20-26	51485
28	and/19,27	18247
29	or/18,28	70345
30	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.	1703378
31	13 not 30	727892
32	29 not 31	32871
33	or/31-32	760763
34	PREMATURITY/	28948
35	preterm$.tw.	26247
36	NEWBORN/	177181
37	(newborn$ or neonate$).tw.	96416
38	or/34-37	237226
39	exp Phototherapy/	23625
40	(light adj3 therap$).tw.	1258
41	(photoradiati$ adj3 therap$).tw.	129
42	bilibed$.tw.	3
43	biliblanket$.tw.	11
44	(wallaby or wallabies).tw.	635
45	(optic adj2 fibre$).tw.	902
46	exp Light/	52208
47	(hill?rom adj microlite).tw.	0
48	hill rom microlite.tw.	0
49	(Draeger adj2 phototherap$).tw.	0
50	medestime.tw.	0
51	neoblue$.tw.	1
52	light emitting diode$.tw.	1150
53	(LED and light).tw.	4841
54	(fluorescen$ adj3 light$).tw.	2577
55	(halogen adj3 light$).tw.	93
56	(sunlight or heliotherap$).tw.	4612
57	ohmeda.tw.	410

58	medela.tw.	4
59	or/39-58	84117
60	and/33,38,59	217

EMBASE 1980 to 2008 Week 46

JAUN_phototherapy_outcomes_Q6p4_embase_201108

#	Searches	Results
1	PREMATURITY/	29089
2	preterm$.tw.	26428
3	NEWBORN/	177774
4	(newborn$ or neonate$).tw.	96829
5	or/1-4	238203
6	HYPERBILIRUBINEMIA/	5668
7	hyperbilirubin?emia$.ti.	1055
8	bilirubin?emia$.ti.	15
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	247
10	JAUNDICE/	9750
11	NEWBORN JAUNDICE/	1734
12	jaundice$.ti.	3635
13	KERNICTERUS/	708
14	kernicterus$.ti.	149
15	or/6-14	18031
16	exp Phototherapy/	23828
17	(light adj3 therap$).tw.	1262
18	bilibed$.tw.	3
19	biliblanket$.tw.	11
20	(wallaby or wallabies).tw.	638
21	(optic adj2 fibre$).tw.	904
22	exp Light/	52506
23	(hill?rom adj microlite).tw.	0
24	hill rom microlite.tw.	0
25	(Draeger adj2 phototherap$).tw.	0
26	medestime.tw.	0
27	neoblue$.tw.	1
28	light emitting diode$.tw.	1162
29	(LED and light).tw.	4864
30	(fluorescen$ adj3 light$).tw.	2586
31	(halogen adj3 light$).tw.	93
32	(sunlight or heliotherap$).tw.	4637
33	or/16-32	84205
34	mother child relation/	6667

35	object relation/	2475
36	(bonding or bond$).tw.	88835
37	(concern$ or worry or worries).tw.	212424
38	Anxiety/	46655
39	(satisfaction or satisf$).tw.	114088
40	bottle feeding/ or breast feeding/	14406
41	feed$.tw.	126279
42	enteric feeding/ or exp parenteral nutrition/	23201
43	((continu$ or intermitt$) adj3 feed$).tw.	1729
44	or/34-43	601172
45	and/5,15,33,44	115

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to October Week 2 2008

JAUN_phototherapy_cinahl_131008

#	Searches	Results
1	exp CLINICAL TRIALS/	66624
2	clinical trial.pt.	35279
3	(clinic$ adj5 trial$).tw,sh.	16386
4	SINGLE-BLIND STUDIES/	3168
5	DOUBLE-BLIND STUDIES/	12147
6	TRIPLE-BLIND STUDIES/	40
7	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	9029
8	RANDOM ASSIGNMENT/	19554
9	random$.tw.	58620
10	RANDOMIZED CONTROLLED TRIALS/	51717
11	randomi?ed control$ trial$.tw.	12888
12	PLACEBOS/	4737
13	placebo$.tw.	12335
14	or/1-13	107525
15	META ANALYSIS/	7066
16	((meta adj analy$) or metaanalys$ or meta-analy$).tw.	5613
17	SYSTEMATIC REVIEW/	4025
18	systematic review.pt.	12734
19	(systematic$ adj5 (review$ or overview$)).tw.	10107
20	LITERATURE REVIEW/	2606
21	or/15-20	23859
22	("review" or "review studies" or "review academic" or "review tutorial").ti,ab,sh,pt.	118973
23	(medline or medlars or embase or cochrane or scisearch or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation").tw.	10394
24	((hand or manual$) adj2 search$).tw.	1132
25	(electronic database$ or bibliographic database$ or computeri?ed database$ or online	1978

database$).tw.	
26 (pooling or pooled or mantel haenszel).tw.	2938
27 (peto or dersimonian or "der simonian" or fixed effect).tw.	450
28 or/23-27	13738
29 and/22,28	8053
30 or/14,21,29	122343
31 letter.pt.	66262
32 commentary.pt.	87950
33 editorial.pt.	93450
34 or/31-33	199889
35 30 not 34	108809
36 INFANT, PREMATURE/	6269
37 preterm$.tw.	5354
38 INFANT, NEWBORN/	39183
39 (newborn$ or neonate$).tw.	9909
40 or/36-39	44090
41 Phototherapy/	673
42 Light/tu [Therapeutic use]	50
43 (light adj3 therap$).tw.	168
44 (photoradiati$ adj3 therap$).tw.	2
45 bilibed$.tw.	0
46 biliblanket$.tw.	5
47 (wallaby or wallabies).tw.	3
48 (optic adj2 fibre).tw.	32
49 light.tw.	9109
50 (hill?rom adj microlite).tw.	0
51 hill rom microlite.tw.	0
52 (Draeger adj2 phototherap$).tw.	0
53 medestime.tw.	0
54 neoblue$.tw.	1
55 light emitting diode$.tw.	50
56 (LED and light).tw.	182
57 (fluorescen$ adj3 light$).tw.	97
58 (halogen adj3 light$).tw.	23
59 (sunlight or heliotherap$).tw.	248
60 ohmeda.tw.	35
61 medela.tw.	1
62 or/41-61	9911
63 and/35,40,62	59

CINAHL EBSCO

JAUN_phototherapy_cinahl_131008

Tuesday, July 21, 2009 7:46:53 AM

#	Query	Limiters/ Expanders	Last Run Via	Results
S31	S30 and S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S30	S29 or S28 or S27 or S26 or S25 or S24 or S23 or S22 or S21 or S16 or S15 or S14 or S13 or S12 or S11 or S9 or S8 or S7 or S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S29	(TI "medela") or (AB "medela")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S28	(TI "ohmeda") or (AB "ohmeda")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S27	(TI "sunlight" or "heliotherap*") or (AB "sunlight" or "heliotherap*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S26	(TI "halogen" N3 "light*") or (AB "halogen" N3 "light*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S25	(TI "fluorescen*" N3 "light") or (AB "fluorescen*" N3 "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S24	(AB "LED" and "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S23	(TI "LED" and "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

			with Full Text	
S22	(TI "light emitting diode*") or (AB "light emitting diode*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S21	(TI "neoblue*") or (AB "neoblue*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S20	(TI "medestime") or (AB "medestime")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S19	(TI "draeger" N2 "phototherap*") or (AB "draeger" N2 "phototherap*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S18	(TI "hillrom microlite") or (AB "hillrom microlite")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S17	(TI "hillrom" N2 "microlite") or (AB "hillrom" N2 "microlite")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S16	(TI "light") or (AB "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S15	(AB "optic" N2 "fibre*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	TI ("optic" N2 "fibre*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	(AB "wallaby" or "wallabies")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	Display

			Advanced Search Database - CINAHL with Full Text	
S12	(TI "wallaby" or "wallabies")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S11	(TI "biliblanket*") or (AB "biliblanket*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(TI "bilibed*") or (AB "bilibed*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S9	(TI "photoradiati*" N3 "therap*") or (AB "photoradiati*" N3 "therap*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI light N3 therap*) or (AB light N3 therap*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S7	MH "LIGHT/tu"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S6	MH PHOTOTHERAPY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

Question: How effective is phototherapy? Economic evaluation

Ovid MEDLINE(R) 1950 to October Week 1 2008

JAUN_phototherapy_economic_medline_141008

#	Searches	Results
1	costs.tw.	77859
2	cost effective$.tw.	44745
3	economic.tw.	67051
4	or/1-3	164703
5	(metabolic adj cost).tw.	492
6	((energy or oxygen) adj cost).tw.	2055
7	4 not (5 or 6)	164469
8	INFANT, PREMATURE/	33074
9	preterm$.tw.	29486
10	INFANT, NEWBORN/	426267
11	(newborn$ or neonate$).tw.	139364
12	or/8-11	484217
13	exp PHOTOTHERAPY/	20273
14	JAUNDICE, NEONATAL/th [Therapy]	1470
15	LIGHT/th [Therapy]	7
16	(light adj3 therap$).tw.	1488
17	(photoradiation adj3 therap$).tw.	176
18	bilibed.tw.	7
19	biliblanket$.tw.	12
20	(wallaby or wallabies).tw.	918
21	(optic adj2 fibre$).tw.	1075
22	light.ti.	55786
23	(hill?rom adj microlite).tw.	0
24	hill rom microlite.tw.	0
25	(Draeger adj2 phototherap$).tw.	0
26	medestime.tw.	0
27	neoblue$.tw.	2
28	light emitting diode$.tw.	1280
29	(LED and light).tw.	5808
30	(fluorescen$ adj3 light$).tw.	3557
31	(halogen adj3 light$).tw.	342
32	(sunlight or heliotherap$).tw.	5119
33	ohmeda.tw.	382
34	medela.tw.	12
35	or/13-34	89832
36	and/7,12,35	25

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

JAUN_phototherapy_economic_cctr_141008

#	Searches	Results
1	costs.tw.	5410
2	cost effective$.tw.	4135
3	economic.tw.	2275
4	or/1-3	8908
5	(metabolic adj cost).tw.	38
6	((energy or oxygen) adj cost).tw.	178
7	4 not (5 or 6)	8898
8	INFANT, PREMATURE/	1709
9	preterm$.tw.	3074
10	INFANT, NEWBORN/	8435
11	(newborn$ or neonate$).tw.	4189
12	or/8-11	11391
13	exp PHOTOTHERAPY/	1159
14	JAUNDICE, NEONATAL/th [Therapy]	94
15	LIGHT/th [Therapy]	0
16	(light adj3 therap$).tw.	273
17	(photoradiation adj3 therap$).tw.	0
18	bilibed.tw.	1
19	biliblanket$.tw.	8
20	(wallaby or wallabies).tw.	5
21	(optic adj2 fibre$).tw.	44
22	light.ti.	1135
23	(hill?rom adj microlite).tw.	0
24	hill rom microlite.tw.	0
25	(Draeger adj2 phototherap$).tw.	0
26	medestime.tw.	0
27	neoblue$.tw.	0
28	light emitting diode$.tw.	50
29	(LED and light).tw.	127
30	(fluorescen$ adj3 light$).tw.	80
31	(halogen adj3 light$).tw.	30
32	(sunlight or heliotherap$).tw.	129
33	ohmeda.tw.	58
34	medela.tw.	2
35	or/13-34	2445
36	and/7,12,35	2

EBM Reviews - Health Technology Assessment 4th Quarter 2008

JAUN_phototherapy_economic_hta_141008

#	Searches	Results
1	costs.tw.	1172
2	cost effective$.tw.	940
3	economic.tw.	698
4	or/1-3	1688
5	(metabolic adj cost).tw.	0
6	((energy or oxygen) adj cost).tw.	0
7	4 not (5 or 6)	1688
8	INFANT, PREMATURE/	9
9	preterm$.tw.	24
10	INFANT, NEWBORN/	66
11	(newborn$ or neonate$).tw.	102
12	or/8-11	125
13	exp PHOTOTHERAPY/	72
14	JAUNDICE, NEONATAL/th [Therapy]	0
15	LIGHT/th [Therapy]	0
16	(light adj3 therap$).tw.	12
17	(photoradiation adj3 therap$).tw.	0
18	bilibed.tw.	0
19	biliblanket$.tw.	0
20	(wallaby or wallabies).tw.	0
21	(optic adj2 fibre$).tw.	0
22	light.ti.	11
23	(hill?rom adj microlite).tw.	0
24	hill rom microlite.tw.	0
25	(Draeger adj2 phototherap$).tw.	0
26	medestime.tw.	0
27	neoblue$.tw.	0
28	light emitting diode$.tw.	0
29	(LED and light).tw.	0
30	(fluorescen$ adj3 light$).tw.	0
31	(halogen adj3 light$).tw.	0
32	(sunlight or heliotherap$).tw.	2
33	ohmeda.tw.	0
34	medela.tw.	0
35	or/13-34	79
36	and/7,12,35	0

EBM Reviews - NHS Economic Evaluation Database 3rd Quarter 2008

JAUN_phototherapy_economic_nhseed_141008

#	Searches	Results
1	costs.tw.	17348
2	cost effective$.tw.	8488
3	economic.tw.	23373
4	or/1-3	23646
5	(metabolic adj cost).tw.	0
6	((energy or oxygen) adj cost).tw.	0
7	4 not (5 or 6)	23646
8	INFANT, PREMATURE/	77
9	preterm$.tw.	79
10	INFANT, NEWBORN/	861
11	(newborn$ or neonate$).tw.	925
12	or/8-11	948
13	exp PHOTOTHERAPY/	38
14	JAUNDICE, NEONATAL/th [Therapy]	0
15	LIGHT/th [Therapy]	0
16	(light adj3 therap$).tw.	0
17	(photoradiation adj3 therap$).tw.	0
18	bilibed.tw.	0
19	biliblanket$.tw.	0
20	(wallaby or wallabies).tw.	0
21	(optic adj2 fibre$).tw.	8
22	light.ti.	8
23	(hill?rom adj microlite).tw.	0
24	hill rom microlite.tw.	0
25	(Draeger adj2 phototherap$).tw.	0
26	medestime.tw.	0
27	neoblue$.tw.	0
28	light emitting diode$.tw.	0
29	(LED and light).tw.	15
30	(fluorescen$ adj3 light$).tw.	1
31	(halogen adj3 light$).tw.	0
32	(sunlight or heliotherap$).tw.	6
33	ohmeda.tw.	0
34	medela.tw.	0
35	or/13-34	74
36	and/7,12,35	2

EMBASE 1980 to 2008 Week 41

JAUN_phototherapy_economic_embase_141008

#	Searches	Results
1	costs.tw.	64077
2	cost effective$.tw.	40727
3	economic.tw.	53047
4	or/1-3	133824
5	(metabolic adj cost).tw.	378
6	((energy or oxygen) adj cost).tw.	1676
7	4 not (5 or 6)	133650
8	PREMATURITY/	28948
9	preterm$.tw.	26247
10	NEWBORN/	177181
11	(newborn$ or neonate$).tw.	96416
12	or/8-11	237226
13	exp Phototherapy/	23625
14	(light adj3 therap$).tw.	1258
15	(photoradiati$ adj3 therap$).tw.	129
16	bilibed$.tw.	3
17	biliblanket$.tw.	11
18	(wallaby or wallabies).tw.	635
19	(optic adj2 fibre$).tw.	902
20	exp Light/	52208
21	(hill?rom adj microlite).tw.	0
22	hill rom microlite.tw.	0
23	(Draeger adj2 phototherap$).tw.	0
24	medestime.tw.	0
25	neoblue$.tw.	1
26	light emitting diode$.tw.	1150
27	(LED and light).tw.	4841
28	(fluorescen$ adj3 light$).tw.	2577
29	(halogen adj3 light$).tw.	93
30	(sunlight or heliotherap$).tw.	4612
31	ohmeda.tw.	410
32	medela.tw.	4
33	or/13-32	84117
34	and/7,12,33	17

Question: What is the correct procedure of giving phototherapy? Focus on the methods of feeding, types of feeding, maternal-infant bonding etc. Question 6.4.

Ovid MEDLINE(R) 1950 to November Week 2 2008

JAUN_phototherapy_outcomes_Q6p4_medline_201108

#	Searches	Results
1	INFANT, PREMATURE/	33276
2	preterm$.tw.	29760
3	INFANT, NEWBORN/	428448
4	(newborn$ or neonate$).tw.	140387
5	or/1-4	486947
6	HYPERBILIRUBINEMIA/	3447
7	HYPERBILIRUBINEMIA, NEONATAL/	184
8	hyperbilirubin?emia$.ti.	2213
9	bilirubin?emia$.ti.	149
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	289
11	exp JAUNDICE/	10168
12	jaundice$.ti.	9929
13	KERNICTERUS/	904
14	kernicter$.tw.	691
15	or/6-14	20919
16	exp PHOTOTHERAPY/	20437
17	JAUNDICE, NEONATAL/th [Therapy]	1472
18	LIGHT/th [Therapy]	8
19	(light adj3 therap$).tw.	1497
20	(photoradiation adj3 therap$).tw.	177
21	bilibed.tw.	7
22	biliblanket$.tw.	12
23	(wallaby or wallabies).tw.	936
24	(optic adj2 fibre$).tw.	1080
25	light.ti.	56299
26	(hill?rom adj microlite).tw.	0
27	hill rom microlite.tw.	0
28	(Draeger adj2 phototherap$).tw.	0
29	medestime.tw.	0
30	neoblue$.tw.	2
31	light emitting diode$.tw.	1300
32	(LED and light).tw.	5872
33	(fluorescen$ adj3 light$).tw.	3594
34	(halogen adj3 light$).tw.	348
35	(sunlight or heliotherap$).tw.	5169
36	ohmeda.tw.	384

37	medela.tw.	13
38	or/16-37	90649
39	OBJECT ATTACHMENT/ or MOTHER-CHILD RELATIONS/	19598
40	bond$.tw.	104651
41	(concern$ or worry or worries).tw.	261312
42	ANXIETY/	37869
43	(satisfaction or satisf$).tw.	138678
44	BOTTLE FEEDING/ or BREAST FEEDING/	21543
45	feed$.tw.	180003
46	ENTERAL NUTRITION/ or exp PARENTERAL NUTRITION/	29385
47	((continu$ or intermitt$) adj3 feed$).tw.	2212
48	or/39-47	749138
49	and/5,15,38,48	150

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

JAUN_phototherapy_outcomes_Q6p4_cctr_201108

#	Searches	Results
1	INFANT, PREMATURE/	1731
2	preterm$.tw.	3132
3	INFANT, NEWBORN/	8524
4	(newborn$ or neonate$).tw.	4271
5	or/1-4	11554
6	HYPERBILIRUBINEMIA/	58
7	HYPERBILIRUBINEMIA, NEONATAL/	10
8	hyperbilirubin?emia$.ti.	149
9	bilirubin?emia$.ti.	4
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
11	exp JAUNDICE/	51
12	jaundice$.ti.	196
13	KERNICTERUS/	2
14	kernicter$.tw.	7
15	or/6-14	443
16	exp PHOTOTHERAPY/	1173
17	JAUNDICE, NEONATAL/th [Therapy]	94
18	LIGHT/th [Therapy]	0
19	(light adj3 therap$).tw.	278
20	(photoradiation adj3 therap$).tw.	0
21	bilibed.tw.	1
22	biliblanket$.tw.	8
23	(wallaby or wallabies).tw.	5
24	(optic adj2 fibre$).tw.	43

25	light.ti.	1148
26	(hill?rom adj microlite).tw.	0
27	hill rom microlite.tw.	0
28	(Draeger adj2 phototherap$).tw.	0
29	medestime.tw.	0
30	neoblue$.tw.	0
31	light emitting diode$.tw.	52
32	(LED and light).tw.	131
33	(fluorescen$ adj3 light$).tw.	82
34	(halogen adj3 light$).tw.	31
35	(sunlight or heliotherap$).tw.	132
36	ohmeda.tw.	58
37	medela.tw.	2
38	or/16-37	2478
39	OBJECT ATTACHMENT/ or MOTHER-CHILD RELATIONS/	391
40	bond$.tw.	1299
41	(concern$ or worry or worries).tw.	8669
42	ANXIETY/	3210
43	(satisfaction or satisf$).tw.	10962
44	BOTTLE FEEDING/ or BREAST FEEDING/	850
45	feed$.tw.	6812
46	ENTERAL NUTRITION/ or exp PARENTERAL NUTRITION/	1981
47	((continu$ or intermitt$) adj3 feed$).tw.	220
48	or/39-47	31506
49	and/5,15,38,48	12

DARE, CDSR

JAUN_phototherapy_outcomes_Q6p4_cdsrdare_201108

#	Searches	Results
1	INFANT, PREMATURE.kw.	215
2	preterm$.tw,tx.	567
3	INFANT, NEWBORN.kw.	612
4	(newborn$ or neonate$).tw,tx.	975
5	or/1-4	1127
6	HYPERBILIRUBINEMIA.kw.	3
7	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
8	hyperbilirubin?emia$.ti.	2
9	bilirubin?emia$.ti.	0
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw,tx.	5
11	JAUNDICE.kw.	13
12	jaundice$.ti.	10

13 KERNICTERUS.kw.	1
14 kernicter$.tw,tx.	14
15 or/6-14	23
16 PHOTOTHERAPY.kw.	21
17 LIGHT.kw.	11
18 (light adj3 therap$).tw,tx.	52
19 (photoradiation adj3 therap$).tw,tx.	0
20 bilibed.tw,tx.	0
21 biliblanket$.tw,tx.	1
22 (wallaby or wallabies).tw,tx.	1
23 (optic adj2 fibre$).tw,tx.	12
24 light.ti.	15
25 (hill?rom adj microlite).tw,tx.	0
26 hill rom microlite.tw,tx.	0
27 (Draeger adj2 phototherap$).tw,tx.	0
28 medestime.tw,tx.	0
29 neoblue$.tw,tx.	0
30 light emitting diode$.tw,tx.	2
31 (LED and light).tw.	250
32 (fluorescen$ adj3 light$).tw,tx.	5
33 (halogen adj3 light$).tw,tx.	1
34 (sunlight or heliotherap$).tw,tx.	30
35 ohmeda.tw,tx.	2
36 medela.tw,tx.	0
37 or/16-36	348
38 (OBJECT ATTACHMENT or MOTHER-CHILD RELATIONS).kw.	20
39 bond$.tw,tx.	156
40 (concern$ or worry or worries).tw,tx.	3076
41 ANXIETY.kw.	192
42 (satisfaction or satisf$).tw,tx.	2376
43 (BOTTLE FEEDING or BREAST FEEDING).kw.	33
44 feed$.tw,tx.	1244
45 (ENTERAL NUTRITION or PARENTERAL NUTRITION).kw.	95
46 ((continu$ or intermitt$) adj3 feed$).tw,tx.	39
47 or/38-46	5034
48 and/5,15,37,47	2

EMBASE 1980 to 2008 Week 47

JAUN_phototherapy_outcomes_Q6p4_embase_201108

#	Searches	Results
1	PREMATURITY/	29115

2	preterm$.tw.	26455
3	NEWBORN/	177875
4	(newborn$ or neonate$).tw.	96908
5	or/1-4	238370
6	HYPERBILIRUBINEMIA/	5678
7	hyperbilirubin?emia$.ti.	1055
8	bilirubin?emia$.ti.	15
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	247
10	JAUNDICE/	9769
11	NEWBORN JAUNDICE/	1734
12	jaundice$.ti.	3639
13	KERNICTERUS/	709
14	kernicterus$.ti.	149
15	or/6-14	18063
16	exp Phototherapy/	23879
17	(light adj3 therap$).tw.	1267
18	bilibed$.tw.	3
19	biliblanket$.tw.	11
20	(wallaby or wallabies).tw.	638
21	(optic adj2 fibre$).tw.	905
22	exp Light/	52569
23	(hill?rom adj microlite).tw.	0
24	hill rom microlite.tw.	0
25	(Draeger adj2 phototherap$).tw.	0
26	medestime.tw.	0
27	neoblue$.tw.	1
28	light emitting diode$.tw.	1162
29	(LED and light).tw.	4873
30	(fluorescen$ adj3 light$).tw.	2590
31	(halogen adj3 light$).tw.	94
32	(sunlight or heliotherap$).tw.	4646
33	or/16-32	84324
34	mother child relation/	6677
35	object relation/	2477
36	(bonding or bond$).tw.	88939
37	(concern$ or worry or worries).tw.	212699
38	Anxiety/	46734
39	(satisfaction or satisf$).tw.	114247
40	bottle feeding/ or breast feeding/	14436
41	feed$.tw.	126456
42	enteric feeding/ or exp parenteral nutrition/	23218
43	((continu$ or intermitt$) adj3 feed$).tw.	1731
44	or/34-43	601976

45 and/5,15,33,44 115

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to November Week 2 2008

JAUN_phototherapy_outcomes_Q6p4_cinahl_201108

#	Searches	Results
1	INFANT, PREMATURE/	6307
2	preterm$.tw.	5404
3	INFANT, NEWBORN/	39507
4	(newborn$ or neonate$).tw.	10009
5	or/1-4	44471
6	HYPERBILIRUBINEMIA/	219
7	hyperbilirubin?emia$.ti.	143
8	bilirubin?emia$.ti.	1
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	27
10	JAUNDICE/	223
11	jaundice$.ti.	304
12	Kernicterus/	102
13	kernicterus$.ti.	41
14	or/6-13	735
15	Phototherapy/	690
16	Light/tu [Therapeutic use]	50
17	(light adj3 therap$).tw.	169
18	(photoradiati$ adj3 therap$).tw.	2
19	bilibed$.tw.	0
20	biliblanket$.tw.	5
21	(wallaby or wallabies).tw.	3
22	(optic adj2 fibre).tw.	32
23	light.tw.	9220
24	(hill?rom adj microlite).tw.	0
25	hill rom microlite.tw.	0
26	(Draeger adj2 phototherap$).tw.	0
27	medestime.tw.	0
28	neoblue$.tw.	1
29	light emitting diode$.tw.	50
30	(LED and light).tw.	185
31	(fluorescen$ adj3 light$).tw.	98
32	(halogen adj3 light$).tw.	24
33	(sunlight or heliotherap$).tw.	252
34	ohmeda.tw.	35
35	medela.tw.	1

36 or/15-35	10041
37 Mother-Child Relations/	1943
38 bond$.tw.	1972
39 (concern$ or worry or worries).tw.	42736
40 anxiety/ or separation anxiety/	7970
41 (satisfaction or satisf$).tw.	25117
42 bottle feeding/ or breast feeding/	7865
43 feed$.tw.	13855
44 enteral nutrition/ or exp parenteral nutrition/	4930
45 ((continu$ or intermitt$) adj3 feed$).tw.	252
46 or/37-45	96923
47 and/5,14,36,46	32

CINAHL EBSCO

JAUN_phototherapy_outcomes_Q6p4_cinahl_201108

Friday, November 21, 2008 9:44:46 AM

#	Query	Limiters /Expanders	Last Run Via	Results
S31	S30 and S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S30	S29 or S28 or S27 or S26 or S25 or S24 or S23 or S22 or S21 or S16 or S15 or S14 or S13 or S12 or S11 or S9 or S8 or S7 or S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S29	(TI "medela") or (AB "medela")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S28	(TI "ohmeda") or (AB "ohmeda")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S27	(TI "sunlight" or "heliotherap*") or (AB "sunlight" or "heliotherap*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

S26	(TI "halogen" N3 "light*") or (AB "halogen" N3 "light*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S25	(TI "fluorescen*" N3 "light") or (AB "fluorescen*" N3 "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S24	(AB "LED" and "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S23	(TI "LED" and "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S22	(TI "light emitting diode*") or (AB "light emitting diode*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S21	(TI "neoblue*") or (AB "neoblue*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S20	(TI "medestime") or (AB "medestime")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S19	(TI "draeger" N2 "phototherap*") or (AB "draeger" N2 "phototherap*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S18	(TI "hillrom microlite") or (AB "hillrom microlite")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S17	(TI "hillrom" N2 "microlite") or (AB "hillrom" N2 "microlite")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	Display

			Database - CINAHL with Full Text	
S16	(TI "light") or (AB "light")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S15	(AB "optic" N2 "fibre*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	TI ("optic" N2 "fibre*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	(AB "wallaby" or "wallabies")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S12	(TI "wallaby" or "wallabies")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S11	(TI "biliblanket*") or (AB "biliblanket*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(TI "bilibed*") or (AB "bilibed*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S9	(TI "photoradiati*" N3 "therap*") or (AB "photoradiati*" N3 "therap*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI light N3 therap*) or (AB light N3 therap*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S7	MH "LIGHT/tu"	Search modes -	Interface - EBSCOhost	Display

		Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S6	MH PHOTOTHERAPY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

Question: **Is it beneficial to give additional fluids during treatment with phototherapy?**

Ovid MEDLINE(R) 1950 to November Week 3 2008

JAUN_fluids2_phototherapy_Q7_medline_081208

#	Searches	Results
1	INFANT, PREMATURE/	33330
2	preterm$.tw.	29802
3	INFANT, NEWBORN/	428896
4	(newborn$ or neonate$).tw.	140553
5	or/1-4	487500
6	HYPERBILIRUBINEMIA/	3451
7	HYPERBILIRUBINEMIA, NEONATAL/	185
8	hyperbilirubin?emia$.ti.	2214
9	bilirubin?emia$.ti.	149
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	290
11	exp JAUNDICE/	10190
12	jaundice$.ti.	9946
13	KERNICTERUS/	905
14	kernicterus.tw.	677
15	or/6-14	20953
16	BOTTLE FEEDING/ or ENTERAL NUTRITION/ or exp PARENTERAL NUTRITION/	32183
17	BREAST FEEDING/	20577
18	feed$.tw.	180353
19	FOOD/	18857
20	food$.tw.	176438
21	((enteral$ or parenteral$ or intravenous$) adj3 (feed$ or food$ or fluid$ or nutrition$)).tw.	23560
22	fluid$.tw.	259556
23	nutritio$.tw.	122433
24	exp GLUCOSE/	198583
25	dextrose.tw.	6037
26	LACTOSE/	8485
27	exp ELECTROLYTES/	368474
28	exp AMINO ACIDS/	609666
29	exp FATS/	66675
30	exp FATTY ACIDS/	300482
31	fatty.tw.	124979
32	exp INFANT FOOD/	9643
33	(formula$ or supplement$).tw.	251163
34	CASEINS/	11762
35	casein hydrolysate.tw.	549
36	rehydrat$.tw.	4978

37	CALCIUM/	214816
38	CALCIUM, DIETARY/	7543
39	exp VITAMINS/	220605
40	MILK/ or MILK, HUMAN/	47660
41	exp ASPARTIC ACID/	25352
42	aspartic$.tw.	12138
43	exp OROTIC ACID/	3149
44	or/16-43	2515888
45	and/5,15,44	852

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

JAUN_fluids2_phototherapy_Q7_cctr_081208

#	Searches	Results
1	INFANT, PREMATURE/	1731
2	preterm$.tw.	3132
3	INFANT, NEWBORN/	8524
4	(newborn$ or neonate$).tw.	4271
5	or/1-4	11554
6	HYPERBILIRUBINEMIA/	58
7	HYPERBILIRUBINEMIA, NEONATAL/	10
8	hyperbilirubin?emia$.ti.	149
9	bilirubin?emia$.ti.	4
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
11	exp JAUNDICE/	51
12	jaundice$.ti.	196
13	KERNICTERUS/	2
14	kernicterus.tw.	7
15	or/6-14	443
16	BOTTLE FEEDING/ or ENTERAL NUTRITION/ or exp PARENTERAL NUTRITION/	2111
17	BREAST FEEDING/	787
18	feed$.tw.	6812
19	FOOD/	839
20	food$.tw.	7227
21	((enteral$ or parenteral$ or intravenous$) adj3 (feed$ or food$ or fluid$ or nutrition$)).tw.	3688
22	fluid$.tw.	7847
23	nutritio$.tw.	7413
24	exp GLUCOSE/	9098
25	dextrose.tw.	805
26	LACTOSE/	221
27	exp ELECTROLYTES/	4961
28	exp AMINO ACIDS/	11618

29	exp FATS/	4051
30	exp FATTY ACIDS/	11708
31	fatty.tw.	5015
32	exp INFANT FOOD/	892
33	(formula$ or supplement$).tw.	26606
34	CASEINS/	166
35	casein hydrolysate.tw.	54
36	rehydrat$.tw.	596
37	CALCIUM/	2282
38	CALCIUM, DIETARY/	492
39	exp VITAMINS/	8044
40	MILK/ or MILK, HUMAN/	1142
41	exp ASPARTIC ACID/	202
42	aspartic$.tw.	71
43	exp OROTIC ACID/	19
44	or/16-43	83981
45	and/5,15,44	41

DARE, CDSR

JAUN_fluids2_phototherapy_Q7_cdsrdare_081208

#	Searches	Results
1	INFANT, PREMATURE.kw.	212
2	preterm$.tw,tx.	574
3	INFANT, NEWBORN.kw.	613
4	(newborn$ or neonate$).tw,tx.	996
5	or/1-4	1149
6	HYPERBILIRUBINEMIA.kw.	3
7	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
8	hyperbilirubin?emia$.ti.	2
9	bilirubin?emia$.ti.	0
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw,tx.	5
11	JAUNDICE.kw.	14
12	jaundice$.ti.	10
13	KERNICTERUS.kw.	1
14	kernicterus.tw,tx.	14
15	or/6-14	23
16	(BOTTLE FEEDING or ENTERAL NUTRITION or PARENTERAL NUTRITION).kw.	95
17	BREAST FEEDING.kw.	31
18	feed$.tw,tx.	1286
19	FOOD.kw.	95
20	food$.tw,tx.	871

21	((enteral$ or parenteral$ or intravenous$) adj3 (feed$ or food$ or fluid$ or nutrition$)).tw,tx.	340
22	fluid$.tw,tx.	1079
23	nutritio$.tw,tx.	966
24	GLUCOSE.kw.	101
25	dextrose.tw,tx.	68
26	LACTOSE.kw.	4
27	ELECTROLYTES.kw.	1
28	AMINO ACIDS.kw.	18
29	FATS.kw.	22
30	FATTY ACIDS.kw.	53
31	fatty.tw,tx.	247
32	INFANT FOOD.kw.	14
33	(formula$ or supplement$).tw,tx.	2751
34	CASEINS.kw.	1
35	casein hydrolysate.tw,tx.	4
36	rehydrat$.tw,tx.	67
37	CALCIUM.kw.	139
38	CALCIUM, DIETARY.kw.	24
39	VITAMINS.kw.	58
40	(MILK or MILK, HUMAN).kw.	33
41	ASPARTIC ACID.kw.	1
42	aspartic$.tw,tx.	8
43	OROTIC ACID.kw.	0
44	or/16-43	4816
45	and/5,15,44	10

EMBASE 1980 to 2008 Week 49

JAUN_fluids2_phototherapy_Q7_embase_101208

#	Searches	Results
1	PREMATURITY/	29195
2	preterm$.tw.	26540
3	NEWBORN/	178121
4	(newborn$ or neonate$).tw.	97095
5	or/1-4	238783
6	HYPERBILIRUBINEMIA/	5702
7	HYPERBILIRUBINEMIA, NEONATAL/	1737
8	hyperbilirubin?emia$.ti.	1057
9	bilirubin?emia$.ti.	16
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	248

11	JAUNDICE/	9796
12	NEWBORN JAUNDICE/	1737
13	jaundice$.ti.	3642
14	KERNICTERUS/	710
15	kernicterus$.ti.	150
16	or/6-15	18115
17	Feeding/ or Infant Feeding/ or Breast Feeding/ or Bottle Feeding/ or Intravenous Feeding/ or Enteric Feeding/	34673
18	Parenteral Nutrition/	10281
19	feed$.tw.	126749
20	((enteral$ or parenteral$ or intravenous$) adj3 (feed$ or food$ or fluid$ or nutrition$)).tw.	19593
21	food/ or exp baby food/ or exp infant nutrition/	37365
22	food.tw.	118597
23	nutritio$.tw.	88341
24	liquid/	11439
25	fluid$.tw.	204075
26	Glucose/	112445
27	dextrose.tw.	4974
28	Lactose/	7837
29	Electrolyte/	10764
30	exp Amino Acid/	546350
31	Fat/	9195
32	exp Fatty Acid/	228119
33	fatty.tw.	94352
34	(formula$ or supplement$).tw.	213906
35	Casein/	5248
36	casein hydrolysate.tw.	294
37	rehydrat$.tw.	3774
38	Calcium Intake/ or Calcium/	103005
39	exp Vitamin/	227676
40	Milk/	13462
41	Aspartic Acid/	15849
42	aspartic$.tw.	9533
43	Orotic Acid/	755
44	or/17-43	1731767
45	and/5,16,44	853

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to December Week 1 2008

JAUN_fluids2_phototherapy_Q7_cinahl_101208

#	Searches	Results

1	INFANT, PREMATURE/	6325
2	preterm$.tw.	5427
3	INFANT, NEWBORN/	39649
4	(newborn$ or neonate$).tw.	10060
5	or/1-4	44637
6	HYPERBILIRUBINEMIA/	221
7	hyperbilirubin?emia$.ti.	144
8	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	28
9	JAUNDICE/	225
10	jaundice$.ti.	304
11	KERNICTERUS/	103
12	kernicterus$.ti.	42
13	or/6-12	739
14	BOTTLE FEEDING/ or exp BREAST FEEDING/ or "ENTERAL FEEDING (SABA CCC)"/	7967
15	exp Parenteral Nutrition/	2257
16	feed$.tw.	13941
17	((enteral$ or parenteral$ or intravenous$) adj3 (feed$ or food$ or fluid$ or nutrition$)).tw.	3458
18	food/ or milk, human/	5097
19	food$.tw.	18854
20	Infant Nutrition/	1511
21	nutritio$.tw.	25614
22	fluid$.tw.	8959
23	GLUCOSE/	1797
24	dextrose.tw.	307
25	Lactose/	101
26	exp Electrolytes/	3369
27	exp Amino Acids/	6582
28	FATS/	382
29	exp Fatty Acids/	7657
30	fatty.tw.	3503
31	exp Infant Food/	1527
32	Infant Feeding/	1583
33	(formula$ or supplement$).tw.	23587
34	Caseins/	34
35	casein hydrolysate.tw.	11
36	rehydrat$.tw.	378
37	CALCIUM, DIETARY/ or CALCIUM/	4494
38	exp Vitamins/	12761
39	Milk/	1083
40	Aspartic Acid/	100
41	aspartic$.tw.	45
42	orotic.tw.	4

43 or/6-42	111537
44 and/5,13,43	446
45 from 44 keep 1-446	446

CINAHL EBSCO

JAUN_fluids2_phototherapy_Q7_cinahl_101208

Tuesday, July 21, 2009 9:01:13 AM

#	Query	Limiters/ Expanders	Last Run Via	Results
S63	S5 and S17 and S62	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S62	S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S61	TI (orotic*) or AB (orotic*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S60	TI (aspartic*) or AB (aspartic*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S59	MH ASPARTIC ACID	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S58	MH MILK	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

S57	MH VITAMINS+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S56	MH CALCIUM	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S55	MH CALCIUM, DIETARY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S54	TI (rehydrat*) or AB (rehydrat*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S53	TI (casein hydrolysate) or AB (casein hydrolysate)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S52	MH CASEINS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S51	TI (formula* or supplement*) or AB (formula* or supplement*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S50	MH INFANT FEEDING	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S49	MH INFANT FOOD+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S48	TI (fatty) or AB (fatty)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	Display

			Database - CINAHL with Full Text	
S47	MH FATTY ACIDS+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S46	MH FATS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S45	MH AMINO ACIDS+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S44	MH ELECTROLYTES+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S43	MH LACTOSE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S42	TI (dextrose) or AB (dextrose)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S41	MH GLUCOSE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S40	TI (fluid*) or AB ((fluid*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S39	TI (nutritio*) or AB (nutritio*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S38	MH INFANT NUTRITION	Search modes -	Interface - EBSCOhost	Display

		Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S37	TI (food*) or AB (food*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S36	MH MILK, HUMAN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S35	MH FOOD	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S34	TI (intravenous N3 nutirtion*) or AB (intravenous N3 nutrition*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S33	TI (intravenous N3 fluid*) or AB (intravenous N3 fluid*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S32	TI (intravenous N3 food*) or AB (intravenous N3 food*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S31	TI (intravenous N3 feed*) or AB (intravenous N3 feed*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S30	TI (parenteral N3 nutrition*) or AB (parenteral N3 nutrition*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S29	TI (parenteral N3 fluid*) or AB (parenteral N3 fluid*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with	Display

			Full Text	
S28	TI (parenteral N3 food*) or AB (parenteral N3 food*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S27	TI (parenteral N3 feed*) or AB (parenteral N3 feed*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S26	TI (enteral N3 nutrition*) or AB (enteral N3 nutrition*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S25	TI (enteral N3 fluid*) or AB (enteral N3 fluid*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S24	TI (enteral N3 food*) or AB (enteral N3 food*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S23	TI (enteral N3 feed*) or AB (enteral N3 feed*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S22	TI (feed*) or AB (feed*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S21	MH PARENTERAL NUTRITION+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S20	(MH "ENTERAL FEEDING (Saba CCC)")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S19	MH BREAST FEEDING+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced	Display

			Search Database - CINAHL with Full Text	
S18	MH BOTTLE FEEDING	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S17	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S16	(TI "kernicterus*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S15	MH KERNICTERUS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	(TI jaundice*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S12	(AB "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S11	(TI "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(AB "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

S9	(TI "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI "bilirubinaemia" OR "bilirubinemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S7	(TI "hyperbilirubinemia" or "hyperbilirubinaemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

Question: How effective is exchange transfusion? Question 8 (restricted to Srs and RCTs)

Ovid MEDLINE(R) 1950 to November Week 3 2008

JAUN_extransfusion_Q8_medline_011208

#	Searches	Results
1	randomized controlled trial.pt.	269354
2	controlled clinical trial.pt.	80768
3	DOUBLE BLIND METHOD/	101524
4	SINGLE BLIND METHOD/	12756
5	RANDOM ALLOCATION/	63696
6	RANDOMIZED CONTROLLED TRIALS/	58451
7	or/1-6	454611
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	99216
9	clinical trial.pt.	460950
10	exp CLINICAL TRIAL/	572520
11	exp CLINICAL TRIALS AS TOPIC/	215006
12	(clinic$ adj5 trial$).tw,sh.	135409
13	PLACEBOS/	28379
14	placebo$.tw,sh.	128819
15	random$.tw,sh.	572739
16	or/8-15	1004679
17	or/7,16	1009351
18	META ANALYSIS/	20239
19	META ANALYSIS AS TOPIC/	8893
20	meta analysis.pt.	20239
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	35744
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	19180
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	1992
24	or/18-23	50031
25	review$.pt.	1443690
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	32625
27	((hand or manual$) adj2 search$).tw.	3596
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	5571
29	(pooling or pooled or mantel haenszel).tw,sh.	30488
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1438
31	or/26-30	65157
32	and/25,31	27889
33	or/24,32	66224
34	letter.pt.	654631

35	case report.tw.	140535
36	comment.pt.	376053
37	editorial.pt.	234808
38	historical article.pt.	258810
39	or/34-38	1331074
40	17 not 39	971945
41	33 not 39	62537
42	or/40-41	1003830
43	INFANT, PREMATURE/	33294
44	preterm$.tw.	29795
45	INFANT, NEWBORN/	428760
46	(newborn$ or neonate$).tw.	140513
47	or/43-46	487320
48	HYPERBILIRUBINEMIA/	3449
49	HYPERBILIRUBINEMIA, NEONATAL/	185
50	hyperbilirubin?emia$.ti.	2214
51	bilirubin?emia$.ti.	149
52	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	290
53	exp JAUNDICE/	10170
54	jaundice$.ti.	9930
55	KERNICTERUS/	904
56	kernicterus.tw.	676
57	or/48-56	20922
58	EXCHANGE TRANSFUSION, WHOLE BLOOD/	4060
59	(exchange adj3 transfusion$).tw.	3519
60	or/58-59	5649
61	and/42,47,57,60	63

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

JAUN_extransfusion_Q8_cctr_011208

#	Searches	Results
1	randomized controlled trial.pt.	249900
2	controlled clinical trial.pt.	75697
3	DOUBLE BLIND METHOD/	82027
4	SINGLE BLIND METHOD/	7788
5	RANDOM ALLOCATION/	20222
6	RANDOMIZED CONTROLLED TRIALS/	0
7	or/1-6	320983
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	107843
9	clinical trial.pt.	273573
10	exp CLINICAL TRIAL/	0

11	exp CLINICAL TRIALS AS TOPIC/	0
12	(clinic$ adj5 trial$).tw,sh.	35968
13	PLACEBOS/	18338
14	placebo$.tw,sh.	106765
15	random$.tw,sh.	246271
16	or/8-15	391449
17	or/7,16	403240
18	META ANALYSIS/	0
19	META ANALYSIS AS TOPIC/	172
20	meta analysis.pt.	478
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	1068
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	265
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	26
24	or/18-23	1478
25	review$.pt.	2652
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	412
27	((hand or manual$) adj2 search$).tw.	40
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	62
29	(pooling or pooled or mantel haenszel).tw,sh.	2075
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	31
31	or/26-30	2530
32	and/25,31	92
33	or/24,32	1540
34	letter.pt.	4515
35	case report.tw.	151
36	comment.pt.	1577
37	editorial.pt.	280
38	historical article.pt.	58
39	or/34-38	5302
40	17 not 39	398088
41	33 not 39	1506
42	or/40-41	398345
43	INFANT, PREMATURE/	1731
44	preterm$.tw.	3132
45	INFANT, NEWBORN/	8524
46	(newborn$ or neonate$).tw.	4271
47	or/43-46	11554
48	HYPERBILIRUBINEMIA/	58
49	HYPERBILIRUBINEMIA, NEONATAL/	10
50	hyperbilirubin?emia$.ti.	149
51	bilirubin?emia$.ti.	4

52	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
53	exp JAUNDICE/	51
54	jaundice$.ti.	196
55	KERNICTERUS/	2
56	kernicterus.tw.	7
57	or/48-56	443
58	EXCHANGE TRANSFUSION, WHOLE BLOOD/	50
59	(exchange adj3 transfusion$).tw.	103
60	or/58-59	123
61	and/42,47,57,60	42

DARE, CDSR

JAUN_extransfusion_Q8_cdsrdare_011208

#	Searches	Results
1	randomized controlled trial.pt.	0
2	controlled clinical trial.pt.	0
3	DOUBLE BLIND METHOD.kw.	233
4	SINGLE BLIND METHOD.kw.	18
5	RANDOM ALLOCATION.kw.	11
6	RANDOMIZED CONTROLLED TRIALS.kw.	6081
7	or/1-6	6124
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	3988
9	clinical trial.pt.	0
10	CLINICAL TRIAL.kw.	0
11	CLINICAL TRIALS AS TOPIC.kw.	826
12	(clinic$ adj5 trial$).tw,sh.	6201
13	PLACEBOS.kw.	112
14	placebo$.tw,sh.	5571
15	random$.tw,sh.	11901
16	or/8-15	12318
17	or/7,16	12318
18	META ANALYSIS.kw.	163
19	META ANALYSIS AS TOPIC.kw.	93
20	meta analysis.pt.	0
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	8308
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	8226
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	2923
24	or/18-23	12169
25	review$.pt.	0
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw,tx.	11759

27	((hand or manual$) adj2 search$).tw,tx.	1940
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	2655
29	(pooling or pooled or mantel haenszel).tw,sh.	6059
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	4041
31	or/26-30	11940
32	and/25,31	0
33	or/24,32	12169
34	letter.pt.	0
35	case report.tw,tx.	122
36	comment.pt.	0
37	editorial.pt.	0
38	historical article.pt.	0
39	or/34-38	122
40	17 not 39	12210
41	33 not 39	12066
42	or/40-41	13589
43	INFANT, PREMATURE.kw.	212
44	preterm$.tw,tx.	574
45	INFANT, NEWBORN.kw.	613
46	(newborn$ or neonate$).tw,tx.	996
47	or/43-46	1149
48	HYPERBILIRUBINEMIA.kw.	3
49	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
50	hyperbilirubin?emia$.ti.	2
51	bilirubin?emia$.ti.	0
52	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw,tx.	5
53	JAUNDICE.kw.	14
54	jaundice$.ti.	10
55	KERNICTERUS.kw.	1
56	kernicterus.tw,tx.	14
57	or/48-56	23
58	EXCHANGE TRANSFUSION, WHOLE BLOOD.kw.	6
59	(exchange adj3 transfusion$).tw,tx.	33
60	or/58-59	33
61	and/42,47,57,60	12

EMBASE 1980 to 2008 Week 48

JAUN_extransfusion_Q8_embase_011208

#	Searches	Results
1	CLINICAL TRIALS/	522052

2	(clinic$ adj5 trial$).ti,ab,sh.	123547
3	SINGLE BLIND PROCEDURE/	7823
4	DOUBLE BLIND PROCEDURE/	70602
5	RANDOM ALLOCATION/	26321
6	CROSSOVER PROCEDURE/	20738
7	PLACEBO/	120388
8	placebo$.ti,ab,sh.	171107
9	random$.ti,ab,sh.	423840
10	RANDOMIZED CONTROLLED TRIALS/	163207
11	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.	91916
12	randomi?ed control$ trial$.tw.	32220
13	or/1-12	856359
14	META ANALYSIS/	34265
15	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.	43974
16	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.	26646
17	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.	1626
18	or/14-17	60821
19	review.pt.	907394
20	(medline or medlars or embase).ab.	23179
21	(scisearch or science citation index).ab.	718
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	8449
23	((hand or manual$) adj2 search$).tw.	2659
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.	4272
25	(pooling or pooled or mantel haenszel).tw.	24530
26	(peto or dersimonian or "der simonian" or fixed effect).tw.	878
27	or/20-26	52106
28	and/19,27	18505
29	or/18,28	71132
30	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.	1717302
31	13 not 30	732458
32	29 not 31	33276
33	or/31-32	765734
34	PREMATURITY/	29136
35	preterm$.tw.	26475
36	NEWBORN/	177971
37	(newborn$ or neonate$).tw.	96976
38	or/34-37	238514
39	HYPERBILIRUBINEMIA/	5686
40	HYPERBILIRUBINEMIA, NEONATAL/	1735
41	hyperbilirubin?emia$.ti.	1055
42	bilirubin?emia$.ti.	15
43	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	247

44 JAUNDICE/	9776
45 NEWBORN JAUNDICE/	1735
46 jaundice$.ti.	3639
47 KERNICTERUS/	709
48 kernicterus$.ti.	149
49 or/39-48	18078
50 EXCHANGE BLOOD TRANSFUSION/	1714
51 (exchange adj3 transfusion$).tw.	1856
52 or/50-51	2540
53 and/33,38,49,52	50

CINAHL EBSCO

JAUN_extrafusion_Q8_cinahl_011208

#	Query	Limiters/ Expanders	Last Run Via	Results
S21	S5 and S17 and S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S20	S18 or S19	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S19	TI (exchange N3 transfusion*) or AB (exchange N3 transfusion*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S18	MH EXCHANGE TRANSFUSION, WHOLE BLOOD	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S17	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S16	(TI "kernicterus*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

			with Full Text	
S15	MH KERNICTERUS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	(TI jaundice*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S12	(AB "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S11	(TI "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(AB "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S9	(TI "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI "bilirubinaemia" OR "bilirubinemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S7	(TI "hyperbilirubinemia" or "hyperbilirubinaemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	Display

			Advanced Search Database - CINAHL with Full Text	
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

QUESTION: What are the other ways of treating hyperbilirubinaemia? Question 9 (restricted to Srs and RCTs)

Ovid MEDLINE(R) 1950 to November Week 3 2008

JAUN_other_treatments_hyperbil_medline_041208

#	Searches	Results
1	randomized controlled trial.pt.	269477
2	controlled clinical trial.pt.	80776
3	DOUBLE BLIND METHOD/	101566
4	SINGLE BLIND METHOD/	12762
5	RANDOM ALLOCATION/	63710
6	RANDOMIZED CONTROLLED TRIALS/	58509
7	or/1-6	454816
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	99256
9	clinical trial.pt.	460981
10	exp CLINICAL TRIAL/	572702
11	exp CLINICAL TRIALS AS TOPIC/	215116
12	(clinic$ adj5 trial$).tw,sh.	135508
13	PLACEBOS/	28390
14	placebo$.tw,sh.	128873
15	random$.tw,sh.	573052
16	or/8-15	1005126
17	or/7,16	1009800
18	META ANALYSIS/	20263
19	META ANALYSIS AS TOPIC/	8898
20	meta analysis.pt.	20263
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	35783
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	19221
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	1997
24	or/18-23	50110
25	review$.pt.	1444767
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	32669
27	((hand or manual$) adj2 search$).tw.	3600
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	5576
29	(pooling or pooled or mantel haenszel).tw,sh.	30507
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1441
31	or/26-30	65217
32	and/25,31	27917
33	or/24,32	66312
34	letter.pt.	654713

35 case report.tw.	140604
36 comment.pt.	376142
37 editorial.pt.	234908
38 historical article.pt.	258893
39 or/34-38	1331435
40 17 not 39	972374
41 33 not 39	62622
42 or/40-41	1004300
43 INFANT, PREMATURE/	33330
44 preterm$.tw.	29802
45 INFANT, NEWBORN/	428896
46 (newborn$ or neonate$).tw.	140553
47 or/43-46	487500
48 HYPERBILIRUBINEMIA/	3451
49 HYPERBILIRUBINEMIA, NEONATAL/	185
50 hyperbilirubin?emia$.ti.	2214
51 bilirubin?emia$.ti.	149
52 ((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	290
53 exp JAUNDICE/	10190
54 jaundice$.ti.	9946
55 KERNICTERUS/	905
56 kernicterus.tw.	677
57 or/48-56	20953
58 exp METALLOPORPHYRINS/	27073
59 exp PORPHYRINS/	41919
60 (metalloporphyrin$ or protoporphyrin$ or mesoprophytin$).tw.	6025
61 PORPHOBILINOGEN/	610
62 exp "HEME OXYGENASE (DECYCLIZING)"/	4467
63 SnMP.tw.	87
64 exp GAMMA-GLOBULINS/	19547
65 gammaglobulin$.tw.	1893
66 "gamma globulin$".tw.	8903
67 exp IMMUNOGLOBULINS/	637134
68 immun?globulin$.tw.	101621
69 "immuno globulin$".tw.	109
70 "immune globulin$".tw.	2583
71 phenobarb$.tw.	16064
72 PHENYTOIN/	12136
73 Phenytoin.tw.	8677
74 CLOFIBRATE/	3708
75 CHOLESTYRAMINE/	2484
76 (cholestyramine$ or colestyramine$).tw.	2086
77 AGAR/	7242

78	exp CHARCOAL/	5272
79	SUPPOSITORIES/	3475
80	exp COMPLEMENTARY THERAPIES/	133872
81	MEDICINE, HERBAL/	808
82	((alternative or complementary or traditional or herbal or integrative) adj3 (therap$ or medicine$)).tw.	28175
83	DRUGS, CHINESE HERBAL/	16180
84	"yin chin".tw.	3
85	manna.tw.	33
86	infusion$.tw.	171350
87	exp PENICILLAMINE/	7359
88	"d-penicillamin$".tw.	2965
89	DIAZEPAM/	16365
90	or/58-89	1104119
91	and/42,47,57,90	74

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

JAUN_other_treatments_hyperbil_cctr_041208

#	Searches	Results
1	randomized controlled trial.pt.	249900
2	controlled clinical trial.pt.	75697
3	DOUBLE BLIND METHOD/	82027
4	SINGLE BLIND METHOD/	7788
5	RANDOM ALLOCATION/	20222
6	RANDOMIZED CONTROLLED TRIALS/	0
7	or/1-6	320983
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	107843
9	clinical trial.pt.	273573
10	exp CLINICAL TRIAL/	0
11	exp CLINICAL TRIALS AS TOPIC/	0
12	(clinic$ adj5 trial$).tw,sh.	35968
13	PLACEBOS/	18338
14	placebo$.tw,sh.	106765
15	random$.tw,sh.	246271
16	or/8-15	391449
17	or/7,16	403240
18	META ANALYSIS/	0
19	META ANALYSIS AS TOPIC/	172
20	meta analysis.pt.	478
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	1068
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	265

23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	26
24	or/18-23	1478
25	review$.pt.	2652
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	412
27	((hand or manual$) adj2 search$).tw.	40
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	62
29	(pooling or pooled or mantel haenszel).tw,sh.	2075
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	31
31	or/26-30	2530
32	and/25,31	92
33	or/24,32	1540
34	letter.pt.	4515
35	case report.tw.	151
36	comment.pt.	1577
37	editorial.pt.	280
38	historical article.pt.	58
39	or/34-38	5302
40	17 not 39	398088
41	33 not 39	1506
42	or/40-41	398345
43	INFANT, PREMATURE/	1731
44	preterm$.tw.	3132
45	INFANT, NEWBORN/	8524
46	(newborn$ or neonate$).tw.	4271
47	or/43-46	11554
48	HYPERBILIRUBINEMIA/	58
49	HYPERBILIRUBINEMIA, NEONATAL/	10
50	hyperbilirubin?emia$.ti.	149
51	bilirubin?emia$.ti.	4
52	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	9
53	exp JAUNDICE/	51
54	jaundice$.ti.	196
55	KERNICTERUS/	2
56	kernicterus.tw.	7
57	or/48-56	443
58	exp METALLOPORPHYRINS/	58
59	exp PORPHYRINS/	204
60	(metalloporphyrin$ or protoporphyrin$ or mesoprophytin$).tw.	101
61	PORPHOBILINOGEN/	3
62	exp "HEME OXYGENASE (DECYCLIZING)"/	14
63	SnMP.tw.	4

64	exp GAMMA-GLOBULINS/	151
65	gammaglobulin$.tw.	103
66	"gamma globulin$".tw.	169
67	exp IMMUNOGLOBULINS/	9088
68	immun?globulin$.tw.	2199
69	"immuno globulin$".tw.	5
70	"immune globulin$".tw.	280
71	phenobarb$.tw.	505
72	PHENYTOIN/	451
73	Phenytoin.tw.	624
74	CLOFIBRATE/	186
75	CHOLESTYRAMINE/	234
76	(cholestyramine$ or colestyramine$).tw.	330
77	AGAR/	11
78	exp CHARCOAL/	189
79	SUPPOSITORIES/	470
80	exp COMPLEMENTARY THERAPIES/	7447
81	MEDICINE, HERBAL/	16
82	((alternative or complementary or traditional or herbal or integrative) adj3 (therap$ or medicine$)).tw.	2538
83	DRUGS, CHINESE HERBAL/	1353
84	"yin chin".tw.	0
85	manna.tw.	3
86	infusion$.tw.	21954
87	exp PENICILLAMINE/	159
88	"d-penicillamin$".tw.	172
89	DIAZEPAM/	1755
90	or/58-89	45480
91	and/42,47,57,90	58

DARE, CDSR

JAUN_other_treatments_hyperbil_cdsrdare_041208

#	Searches	Results
1	randomized controlled trial.pt.	0
2	controlled clinical trial.pt.	0
3	DOUBLE BLIND METHOD.kw.	233
4	SINGLE BLIND METHOD.kw.	18
5	RANDOM ALLOCATION.kw.	11
6	RANDOMIZED CONTROLLED TRIALS.kw.	6081
7	or/1-6	6124
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	3988

9	clinical trial.pt.	0
10	CLINICAL TRIAL.kw.	0
11	CLINICAL TRIALS AS TOPIC.kw.	826
12	(clinic$ adj5 trial$).tw,sh.	6201
13	PLACEBOS.kw.	112
14	placebo$.tw,sh.	5571
15	random$.tw,sh.	11901
16	or/8-15	12318
17	or/7,16	12318
18	META ANALYSIS.kw.	163
19	META ANALYSIS AS TOPIC.kw.	93
20	meta analysis.pt.	0
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	8308
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	8226
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	2923
24	or/18-23	12169
25	review$.pt.	0
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	11759
27	((hand or manual$) adj2 search$).tw.	1940
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	2655
29	(pooling or pooled or mantel haenszel).tw,sh.	6059
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	4041
31	or/26-30	11940
32	and/25,31	0
33	or/24,32	12169
34	letter.pt.	0
35	case report.tw.	122
36	comment.pt.	0
37	editorial.pt.	0
38	historical article.pt.	0
39	or/34-38	122
40	17 not 39	12210
41	33 not 39	12066
42	or/40-41	13589
43	INFANT, PREMATURE.kw.	212
44	preterm$.tw,tx.	574
45	INFANT, NEWBORN.kw.	613
46	(newborn$ or neonate$).tw,tx.	996
47	or/43-46	1149
48	HYPERBILIRUBINEMIA.kw.	3
49	HYPERBILIRUBINEMIA, NEONATAL.kw.	1

50	hyperbilirubin?emia$.ti.	2
51	bilirubin?emia$.ti.	0
52	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw,tx.	5
53	JAUNDICE.kw.	14
54	jaundice$.ti.	10
55	KERNICTERUS.kw.	1
56	kernicterus.tw,tx.	14
57	or/48-56	23
58	METALLOPORPHYRINS.kw.	1
59	PORPHYRINS.kw.	3
60	(metalloporphyrin$ or protoporphyrin$ or mesoprophytin$).tw,tx.	7
61	PORPHOBILINOGEN.kw.	0
62	"HEME OXYGENASE (DECYCLIZING)".kw.	0
63	SnMP.tw,tx.	0
64	GAMMA-GLOBULINS.kw.	1
65	gammaglobulin$.tw,tx.	7
66	"gamma globulin$".tw,tx.	14
67	IMMUNOGLOBULINS.kw.	50
68	immun?globulin$.tw,tx.	251
69	"immuno globulin$".tw,tx.	0
70	"immune globulin$".tw,tx.	27
71	phenobarb$.tw,tx.	81
72	PHENYTOIN.kw.	14
73	Phenytoin.tw,tx.	101
74	CLOFIBRATE.kw.	4
75	CHOLESTYRAMINE.kw.	3
76	(cholestyramine$ or colestyramine$).tw,tx.	32
77	AGAR.kw.	0
78	CHARCOAL.kw.	4
79	SUPPOSITORIES.kw.	3
80	COMPLEMENTARY THERAPIES.kw.	84
81	MEDICINE, HERBAL.kw.	4
82	((alternative or complementary or traditional or herbal or integrative) adj3 (therap$ or medicine$)).tw,tx.	964
83	DRUGS, CHINESE HERBAL.kw.	60
84	"yin chin".tw.	0
85	manna.tw,tx.	0
86	infusion$.tw,tx.	729
87	PENICILLAMINE.kw.	6
88	"d-penicillamin$".tw,tx.	23
89	DIAZEPAM.kw.	14
90	or/58-89	2000
91	and/42,47,57,90	9

EMBASE 1980 to 2008 Week 49

JAUN_other_treatments_hyperbil_embase_041208

#	Searches	Results
1	CLINICAL TRIALS/	523012
2	(clinic$ adj5 trial$).ti,ab,sh.	123857
3	SINGLE BLIND PROCEDURE/	7842
4	DOUBLE BLIND PROCEDURE/	70681
5	RANDOM ALLOCATION/	26340
6	CROSSOVER PROCEDURE/	20766
7	PLACEBO/	120719
8	placebo$.ti,ab,sh.	171464
9	random$.ti,ab,sh.	424569
10	RANDOMIZED CONTROLLED TRIALS/	163469
11	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.	92005
12	randomi?ed control$ trial$.tw.	32313
13	or/1-12	857875
14	META ANALYSIS/	34310
15	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.	44066
16	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.	26755
17	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.	1631
18	or/14-17	60986
19	review.pt.	908965
20	(medline or medlars or embase).ab.	23253
21	(scisearch or science citation index).ab.	719
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	8491
23	((hand or manual$) adj2 search$).tw.	2670
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.	4286
25	(pooling or pooled or mantel haenszel).tw.	24587
26	(peto or dersimonian or "der simonian" or fixed effect).tw.	880
27	or/20-26	52240
28	and/19,27	18549
29	or/18,28	71320
30	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.	1719512
31	13 not 30	733767
32	29 not 31	33373
33	or/31-32	767140
34	PREMATURITY/	29195
35	preterm$.tw.	26540
36	NEWBORN/	178121

37	(newborn$ or neonate$).tw.	97095
38	or/34-37	238783
39	HYPERBILIRUBINEMIA/	5702
40	HYPERBILIRUBINEMIA, NEONATAL/	1737
41	hyperbilirubin?emia$.ti.	1057
42	bilirubin?emia$.ti.	16
43	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	248
44	JAUNDICE/	9796
45	NEWBORN JAUNDICE/	1737
46	jaundice$.ti.	3642
47	KERNICTERUS/	710
48	kernicterus$.ti.	150
49	or/39-48	18115
50	exp PORPHYRIN/ or UROPORPHYRIN/ or exp PORPHYRIN DERIVATIVE/	173835
51	(metalloporphyrin$ or protoporphyrin$ or mesoprophytin$).tw.	4773
52	porphobilinogen$.tw.	821
53	HEME OXYGENASE.mp. or HEME OXYGENASE 1/ or HEME OXYGENASE 2/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	5287
54	SnMp.tw.	71
55	exp IMMUNOGLOBULIN/	168343
56	gammaglobulin$.tw.	1482
57	"gamma globulin$".tw.	3801
58	immun?globulin$.tw.	77114
59	"immuno globulin$".tw.	66
60	"immune globulin$".tw.	2079
61	PHENOBARBITAL/	31185
62	phenobarb$.tw.	13026
63	PHENYTOIN/	35076
64	phenytoin.tw.	8259
65	CLOFIBRATE/	5091
66	COLESTYRAMINE/	6654
67	(cholestyramine$ or colestyramine$).tw.	1677
68	AGAR/	4871
69	CHARCOAL/	2304
70	SUPPOSITORY/	2067
71	exp ALTERNATIVE MEDICINE/ or exp TRADITIONAL MEDICINE/	32968
72	((alternative or complementary or traditional or herbal or integrative) adj3 (therap$ or medicine$)).tw.	26693
73	"yin chin".tw.	2
74	MANNAN/	1619
75	infusion$.tw.	147396
76	PENICILLAMINE/	11215

77	"d-penicillamin$".tw.	2317
78	DIAZEPAM/	42601
79	or/50-78	672505
80	and/33,38,49,79	99

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to November Week 4 2008

JAUN_other_treatments_hyperbil_cinahl_041208

#	Searches	Results
1	exp CLINICAL TRIALS/	67451
2	clinical trial.pt.	35791
3	(clinic$ adj5 trial$).tw,sh.	16660
4	SINGLE-BLIND STUDIES/	3223
5	DOUBLE-BLIND STUDIES/	12243
6	TRIPLE-BLIND STUDIES/	44
7	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	9133
8	RANDOM ASSIGNMENT/	19804
9	random$.tw.	59499
10	RANDOMIZED CONTROLLED TRIALS/	52404
11	randomi?ed control$ trial$.tw.	13122
12	PLACEBOS/	4809
13	placebo$.tw.	12467
14	or/1-13	109025
15	META ANALYSIS/	7198
16	((meta adj analy$) or metaanalys$ or meta-analy$).tw.	5719
17	SYSTEMATIC REVIEW/	4138
18	systematic review.pt.	13058
19	(systematic$ adj5 (review$ or overview$)).tw.	10291
20	LITERATURE REVIEW/	2619
21	or/15-20	24384
22	("review" or "review studies" or "review academic" or "review tutorial").ti,ab,sh,pt.	121038
23	(medline or medlars or embase or cochrane or scisearch or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation").tw.	10568
24	((hand or manual$) adj2 search$).tw.	1147
25	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.	2024
26	(pooling or pooled or mantel haenszel).tw.	2984
27	(peto or dersimonian or "der simonian" or fixed effect).tw.	453
28	or/23-27	13988
29	and/22,28	8201
30	or/14,21,29	124217

31 letter.pt.	67553
32 commentary.pt.	89181
33 editorial.pt.	94706
34 or/31-33	202879
35 30 not 34	110523
36 INFANT, PREMATURE/	6317
37 preterm$.tw.	5421
38 INFANT, NEWBORN/	39579
39 (newborn$ or neonate$).tw.	10039
40 or/36-39	44557
41 HYPERBILIRUBINEMIA/	219
42 hyperbilirubin?emia$.ti.	143
43 ((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	27
44 JAUNDICE/	224
45 jaundice$.ti.	304
46 KERNICTERUS/	102
47 kernicterus$.ti.	41
48 or/41-47	735
49 porphyrins/ or metalloporphyrins/	92
50 (metalloporphyrin$ or protoporphyrin$ or mesoprophytin$).tw.	84
51 porphobilinogen.tw.	6
52 heme oxygenase.tw.	92
53 SnMP.tw.	6
54 gamma globulins/ or exp immunoglobulins/	3774
55 gammaglobulin$.tw.	24
56 "gamma globulin$".tw.	51
57 immun?globulin$.tw.	1736
58 "immuno globulin$".tw.	1
59 "immune globulin$".tw.	215
60 Phenobarbital/	162
61 phenobarb$.tw.	157
62 Phenytoin/	388
63 phenytoin.tw.	327
64 clofibrate.tw.	13
65 Cholestyramine/	57
66 (cholestyramine$ or colestyramine$).tw.	34
67 agar.tw.	341
68 Charcoal/	296
69 Suppositories/	135
70 exp Alternative Therapies/	60038
71 exp medicine, herbal/ or exp medicine, traditional/	12079
72 Drugs, Chinese Herbal/	552
73 ((alternative or complementary or traditional or herbal or integrative) adj3 (therap$ or	8267

medicine$)).tw.	
74 "yin chin".tw.	0
75 manna$.tw.	38
76 infusion.tw.	5939
77 Penicillamine/	55
78 "d-penicillamin$".tw.	28
79 Diazepam/	279
80 or/49-79	74802
81 and/35,40,48,80	15

CINAHL EBSCO

JAUN_other_treatments_hyperbil_cinahl_041208

Friday, May 01, 2009 5:22:11 AM

#	Query	Limiters/ Expanders	Last Run Via	Results
S61	S5 and S17 and S60	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	129
S60	S36 or S59	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	80303
S59	S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	74666
S58	immune globulin*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	351
S57	MH DIAZEPAM	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	301
S56	TI (d penicillamin*) or AB (d penicillamin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	32

			Advanced Search Database - CINAHL with Full Text	
S55	MH PENICILLAMINE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	59
S54	TI (infusion) or AB (infusion)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6714
S53	TI (manna*) or AB (manna*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	39
S52	TI (yin chin) or AB (yin chin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	0
S51	TI (integrative N3 medicine*) or AB (integrative N3 medicine*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	294
S50	TI (integrative N3 therap*) or AB (integrative N3 therap*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	126
S49	TI (herbal N3 medicine*) or AB (herbal N3 medicine*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	969
S48	TI (herbal N3 therap*) or AB (herbal N3 therap*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	282
S47	TI (traditional N3 medicine*) or AB (traditional N3 medicine*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1288

S46	TI (traditional N3 therap*) or AB (traditional N3 therap*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	608
S45	TI (alternative N3 medicine*) or AB (alternative N3 medicine*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	2708
S44	TI (alternative N3 therap*) or AB (alternative N3 therap*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	2182
S43	MH DRUGS, CHINESE HERBAL	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	647
S42	MH MEDICINE, TRADITIONAL+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	12848
S41	MH MEDICINE, HERBAL+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	4246
S40	MH ALTERNATIVE THERAPIES+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	63683
S39	MH SUPPOSITORIES	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	149
S38	MH CHARCOAL	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	306
S37	TI (agar*) or AB (agar*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	510

			Database - CINAHL with Full Text	
S36	S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6179
S35	AB (cholestyramine* or colestyramine*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	33
S34	TI (cholestyramine* or colestyramine*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	11
S33	MH CHOLESTYRAMINE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	60
S32	TI (clofibrate) or AB (clofibrate)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	14
S31	TI (phenytoin) or AB (phenytoin)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	363
S30	MH PHENYTOIN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	410
S29	TI (phenobarb*) or AB (phenobarb*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	181
S28	MH PHENOBARBITAL	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	178
S27	TI (immunglobulin* or	Search modes -	Interface - EBSCOhost	1952

	immunoglobulin*) or AB (immunglobulin* or immunoglobulin*)	Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S26	TI (gamma globulin* or gamma globulin*) or AB (gamma globulin* or gamma globulin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	60
S25	TI (heme oxygenase) or AB (heme oxygenase)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	115
S24	MH IMMUNOGLOBULINS+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	4068
S23	MH GAMMA GLOBULINS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	58
S22	TI (SnMP) or AB (SnMP)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6
S21	TI (porphobilinogen*) or AB (porphobilinogen*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	7
S20	TI (metalloporphyrin* or protoporphyrin* or mesoprophytin*) or AB (metalloporphyrin* or protoporphyrin* or mesoprophytin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	90
S19	MH METALLOPORPHYRINS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	34
S18	MH PORPHYRINS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	79

			Database - CINAHL with Full Text	
S17	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	826
S16	(TI "kernicterus*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	49
S15	MH KERNICTERUS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	110
S14	(TI jaundice*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	329
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	248
S12	(AB "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3
S11	(TI "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	0
S10	(AB "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	25
S9	(TI "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	8
S8	(TI "bilirubinaemia" OR	Search modes -	Interface - EBSCOhost	6

	"bilirubinemia")	Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S7	(TI "hyperbilirubinemia" or "hyperbilirubinaemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	196
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	236
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	47455
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	10880
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	41764
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5956
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6737

AMED (Allied and Complementary Medicine) 1985 to March 2009

JAUN_other_treatments_hyperbil_amed_260309

#	Searches	Results
1	exp INFANT NEWBORN/	334
2	(prematur$ adj3 (infant$ or baby or babies)).tw.	150

3	preterm$.tw.	143
4	(newborn$ or neonate$).tw.	493
5	or/1-4	685
6	hyperbilirubin?emi$.tw.	12
7	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	0
8	JAUNDICE/	32
9	jaundice$.tw.	131
10	kernicterus.tw.	3
11	or/6-10	143
12	(metalloporphyrin$ or protoporphyrin$ or mesoprophytin$).tw.	7
13	porphobilinogen.tw.	0
14	heme oxygenase.tw.	11
15	SnMP.tw.	0
16	gamma globulin$.tw.	7
17	exp IMMUNOGLOBULINS/	64
18	immun?globulin$.tw.	125
19	"immuno globulin$".tw.	0
20	"immune globulin$".tw.	1
21	phenobarb$.tw.	42
22	phenytoin.tw.	44
23	clofibrate.tw.	1
24	cholestyramine.tw.	0
25	colestyramine$.tw.	0
26	agar.tw.	166
27	charcoal.tw.	44
28	SUPPOSITORIES/	2
29	exp COMPLEMENTARY THERAPIES/	39578
30	exp HERBAL DRUGS/ or exp DRUGS CHINESE HERBAL/ or exp HERBALISM/	8656
31	((alternative or complementary or traditional or herbal or integrative) adj3 (therap$ or medicine$)).tw.	13567
32	yin chin.tw.	0
33	manna.tw.	0
34	infusion$.tw.	422
35	penicillamine.tw.	3
36	d penicillamine.tw.	1
37	diazepam.tw.	78
38	or/12-37	48662
39	and/5,11,38	5

QUESTION: (i)What are the appropriate criteria for monitoring babies with jaundice who are at lower risk of developing neonatal hyperbilirubinaemia/kernicterus.
(ii) What are the appropriate criteria for monitoring babies diagnosed with neonatal hyperbilirubinaemia who do not require immediate treatment?

Ovid MEDLINE(R) 1950 to March Week 2 2009

JAUN_Q10_monitor_medline_200309

#	Searches	Results
1	INFANT, PREMATURE/	32368
2	preterm$.tw.	29467
3	INFANT, NEWBORN/	415422
4	(newborn$ or neonate$).tw.	137510
5	or/1-4	473411
6	HYPERBILIRUBINEMIA/	3391
7	HYPERBILIRUBINEMIA, NEONATAL/	179
8	hyperbilirubin?emia$.ti.	2160
9	bilirubin?emia$.ti.	148
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	288
11	exp JAUNDICE/	9895
12	jaundice$.ti.	9604
13	or/6-12	19658
14	(total adj3 serum adj3 bilirubin$).tw.	1304
15	(serum adj3 bilirubin$ adj3 level$).tw.	1864
16	tsb.tw.	527
17	BILIRUBIN/bl [Blood]	11255
18	(unconjugated adj3 bilirubin).tw.	857
19	RISK ASSESSMENT/	99199
20	(risk$ adj3 (assess$ or index or model$)).tw.	40976
21	RISK FACTORS/	371020
22	risk factor$.tw.	203523
23	or/19-22	552451
24	exp MONITORING, PHYSIOLOGIC/	93688
25	(monitor$ or assess$ or check$ or measure$).tw.	2510349
26	or/14-18,24-25	2555927
27	26 and 23 and 13	279

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2009

JAUN_Q10_monitor_cctr_200309

#	Searches	Results

1	INFANT, PREMATURE/	1763
2	preterm$.tw.	3175
3	INFANT, NEWBORN/	8634
4	(newborn$ or neonate$).tw.	4338
5	or/1-4	11718
6	HYPERBILIRUBINEMIA/	58
7	HYPERBILIRUBINEMIA, NEONATAL/	11
8	hyperbilirubin?emia$.ti.	149
9	bilirubin?emia$.ti.	4
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	10
11	exp JAUNDICE/	54
12	jaundice$.ti.	199
13	or/6-12	445
14	(total adj3 serum adj3 bilirubin$).tw.	119
15	(serum adj3 bilirubin$ adj3 level$).tw.	190
16	tsb.tw.	26
17	BILIRUBIN/bl [Blood]	491
18	(unconjugated adj3 bilirubin).tw.	22
19	RISK ASSESSMENT/	3167
20	(risk$ adj3 (assess$ or index or model$)).tw.	1714
21	RISK FACTORS/	10860
22	risk factor$.tw.	8588
23	or/19-22	18928
24	exp MONITORING, PHYSIOLOGIC/	5952
25	(monitor$ or assess$ or check$ or measure$).tw.	186478
26	or/14-18,24-25	188292
27	and/5,13,23,26	5

DARE, CDSR

JAUN_Q10_monitor_cdsrdare_200309

#	Searches	Results
1	INFANT, PREMATURE.kw.	216
2	preterm$.tw,tx.	586
3	INFANT, NEWBORN.kw.	632
4	(newborn$ or neonate$).tw,tx.	1024
5	or/1-4	1180
6	HYPERBILIRUBINEMIA.kw.	3
7	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
8	hyperbilirubin?emia$.ti.	2
9	bilirubin?emia$.ti.	0
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw,tx.	5

11	JAUNDICE.kw.	15
12	jaundice$.ti.	10
13	or/6-12	19
14	(total adj3 serum adj3 bilirubin$).tw,tx.	15
15	(serum adj3 bilirubin$ adj3 level$).tw,tx.	24
16	tsb.tw,tx.	1
17	BILIRUBIN.kw.	4
18	(unconjugated adj3 bilirubin).tw,tx.	5
19	RISK ASSESSMENT.kw.	297
20	(risk$ adj3 (assess$ or index or model$)).tw,tx.	2532
21	RISK FACTORS.kw.	639
22	risk factor$.tw,tx.	1797
23	or/19-22	3770
24	MONITORING, PHYSIOLOGIC.kw.	24
25	(monitor$ or assess$ or check$ or measure$).tw,tx.	11886
26	or/14-18,24-25	11886
27	and/5,13,23,26	3

EMBASE 1980 to 2009 Week 12

JAUN_Q10_monitor_embase_200309

#	Searches	Results
1	PREMATURITY/	29715
2	preterm$.tw.	27075
3	NEWBORN/	179953
4	(newborn$ or neonate$).tw.	98486
5	or/1-4	241790
6	HYPERBILIRUBINEMIA/	5856
7	hyperbilirubin?emia$.ti.	1072
8	bilirubin?emia$.ti.	16
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	255
10	JAUNDICE/	10024
11	NEWBORN JAUNDICE/	1771
12	jaundice$.ti.	3683
13	or/6-12	18257
14	(total adj3 serum adj3 bilirubin$).tw.	1224
15	(serum adj3 bilirubin$ adj3 level$).tw.	1610
16	tsb.tw.	397
17	exp Bilirubin/	16861
18	bilirubin blood level/	7172
19	(unconjugated adj3 bilirubin).tw.	660

20 or/14-19	19735
21 risk assessment/	178969
22 risk factor/	242752
23 (risk$ adj3 (assess$ or index or model$)).tw.	38687
24 risk factor$.tw.	186438
25 or/21-24	459071
26 BIOLOGICAL MONITORING/	9396
27 (monitor$ or assess$ or check$ or measure$).tw.	2211279
28 or/26-27	2214066
29 or/20,28	2228449
30 and/5,13,25,29	278

CINAHL EBSCO

JAUN_Q10_monitor_cinahl_230309

Tuesday, March 24, 2009 7:53:17 AM

#	Query	Limiters/ Expanders	Last Run Via	Results
S31	S5 and S15 and S23 and S30	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	61
S30	S24 or S25 or S26 or S27 or S28 or S29	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	105500
S29	risk factor*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	92330
S28	MH RISK FACTORS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	35295
S27	risk* N3 model*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1390
S26	risk* N3 index*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced	626

			Search Database - CINAHL with Full Text	
S25	risk* N3 assess*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	21048
S24	MH RISK ASSESSMENT	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	16760
S23	S16 or S17 or S18 or S19 or S20 or S21 or S22	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	363637
S22	monitor* or assess* or check* or measure*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	354439
S21	MH MONITORING, PHYSIOLOGIC+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	26751
S20	unconjugated N3 bilirubin	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	25
S19	MH BILIRUBIN/BL	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	289
S18	tsb	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	41
S17	serum N3 bilirubin* N3 level*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	85

S16	total N3 serum N3 bilirubin*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	90
S15	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	742
S14	TI jaundice*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	328
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	238
S12	hyperbilirubin* N3 encephalopath*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3
S11	bilirubin* N3 encephalopath*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	32
S10	TI bilirubinemia	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1
S9	TI bilirubinaemia	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	0
S8	TI hyperbilirubinaemia	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	17
S7	TI hyperbilirubinemia	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	140

			Database - CINAHL with Full Text	
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	234
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	46957
S4	(newborn* OR neonate*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	43950
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	41224
S2	preterm*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5868
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6597

QUESTION: What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia?

Ovid MEDLINE(R) 1950 to March Week 3 2009

JAUN_Q13_infosupport_medline_010409_2

#	Searches	Results
1	INFANT, PREMATURE/	32387
2	preterm$.tw.	29486
3	INFANT, NEWBORN/	415634
4	(newborn$ or neonate$).tw.	137581
5	or/1-4	473662
6	HYPERBILIRUBINEMIA/	3391
7	HYPERBILIRUBINEMIA, NEONATAL/	179
8	hyperbilirubin?emia$.ti.	2160
9	bilirubin?emia$.ti.	148
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	288
11	exp JAUNDICE/	9897
12	jaundice$.ti.	9604
13	KERNICTERUS/	882
14	kernicterus.tw.	655
15	or/6-14	20332
16	HEALTH EDUCATION/ or PATIENT EDUCATION AS TOPIC/	97466
17	(information$ or education$ or communication$ or advice or advice).ti.	158771
18	PAMPHLETS/	2478
19	(booklet$ or leaflet$ or pamphlet$ or brochure$ or hand?out$).tw.	14834
20	(educat$ adj3 (video$ or literature$)).tw.	1128
21	SELF-HELP GROUPS/	6446
22	((support$ or self-help$) adj3 group$).tw.	9067
23	patient education handout.pt.	2643
24	guideline.pt.	14517
25	practice guideline.pt.	12999
26	HOTLINES/	1698
27	help line$.tw.	64
28	INTERNET/	28890
29	((internet or web) adj based).tw.	7028
30	TELEPHONE/	7139
31	(telephone adj2 support).tw.	230
32	or/16-31	309649
33	and/5,15,32	38

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2009

JAUN_Q13_infosupport_cctr_010409_2

#	Searches	Results
1	INFANT, PREMATURE/	1763
2	preterm$.tw.	3175
3	INFANT, NEWBORN/	8634
4	(newborn$ or neonate$).tw.	4338
5	or/1-4	11718
6	HYPERBILIRUBINEMIA/	58
7	HYPERBILIRUBINEMIA, NEONATAL/	11
8	hyperbilirubin?emia$.ti.	149
9	bilirubin?emia$.ti.	4
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	10
11	exp JAUNDICE/	54
12	jaundice$.ti.	199
13	KERNICTERUS/	2
14	kernicterus.tw.	8
15	or/6-14	450
16	HEALTH EDUCATION/ or PATIENT EDUCATION AS TOPIC/	5434
17	(information$ or education$ or communication$ or advice or advice).ti.	5700
18	PAMPHLETS/	393
19	(booklet$ or leaflet$ or pamphlet$ or brochure$ or hand?out$).tw.	1207
20	(educat$ adj3 (video$ or literature$)).tw.	209
21	SELF-HELP GROUPS/	333
22	((support$ or self-help$) adj3 group$).tw.	1865
23	patient education handout.pt.	6
24	guideline.pt.	24
25	practice guideline.pt.	17
26	HOTLINES/	55
27	help line$.tw.	5
28	INTERNET/	498
29	((internet or web) adj based).tw.	450
30	TELEPHONE/	713
31	(telephone adj2 support).tw.	122
32	or/16-31	12910
33	and/5,15,32	0

DARE, CDSR

JAUN_Q13_infosupport_cdsrdare_010409_2

#	Searches	Results

1	INFANT, PREMATURE.kw.	216
2	preterm$.tw,tx.	586
3	INFANT, NEWBORN.kw.	632
4	(newborn$ or neonate$).tw,tx.	1024
5	or/1-4	1180
6	HYPERBILIRUBINEMIA.kw.	3
7	HYPERBILIRUBINEMIA, NEONATAL.kw.	1
8	hyperbilirubin?emia$.ti.	2
9	bilirubin?emia$.ti.	0
10	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw,tx.	5
11	JAUNDICE.kw.	15
12	jaundice$.ti.	10
13	KERNICTERUS.kw.	1
14	kernicterus.tw,tx.	15
15	or/6-14	24
16	(HEALTH EDUCATION or PATIENT EDUCATION AS TOPIC).kw.	367
17	(information$ or education$ or communication$ or advice or advice).ti.	231
18	PAMPHLETS.kw.	5
19	(booklet$ or leaflet$ or pamphlet$ or brochure$ or hand?out$).tw,tx.	270
20	(educat$ adj3 (video$ or literature$)).tw,tx.	48
21	SELF-HELP GROUPS.kw.	32
22	((support$ or self-help$) adj3 group$).tw,tx.	787
23	patient education handout.pt.	0
24	guideline.pt.	0
25	practice guideline.pt.	0
26	HOTLINES.kw.	2
27	help line$.tw,tx.	13
28	INTERNET.kw.	23
29	((internet or web) adj based).tw,tx.	125
30	TELEPHONE.kw.	22
31	(telephone adj2 support).tw,tx.	45
32	or/16-31	1467
33	and/5,15,32	1

EMBASE 1980 to 2009 Week 13

JAUN_Q13_infosupport_embase_020409_2

#	Searches	Results
1	PREMATURITY/	29758
2	preterm$.tw.	27105
3	NEWBORN/	180064
4	(newborn$ or neonate$).tw.	98572

5	or/1-4	241975
6	HYPERBILIRUBINEMIA/	5862
7	hyperbilirubin?emia$.ti.	1072
8	bilirubin?emia$.ti.	16
9	((bilirubin$ or hyperbilirubin$) adj3 encephalopath$).tw.	255
10	JAUNDICE/	10032
11	NEWBORN JAUNDICE/	1772
12	jaundice$.ti.	3687
13	KERNICTERUS/	729
14	kernicterus$.ti.	154
15	or/6-14	18536
16	PATIENT INFORMATION/	12976
17	(information adj1 (provid$ or provision$ or supply$)).tw.	23297
18	PATIENT EDUCATION/	27311
19	(patient$ adj3 educat$).tw.	11149
20	(booklet$ or leaflet$ or pamphlet$ or brochure$ or hand?out$).tw.	11345
21	(educat$ adj3 (video$ or literature$)).tw.	634
22	SELF HELP/	3169
23	((support$ or self-help$) adj3 group$).tw.	7033
24	CONSUMER HEALTH INFORMATION/ or INFORMATION SERVICE/ or MEDICAL INFORMATION/	35285
25	INTERNET/ or TELEPHONE/	37478
26	(telephone adj2 support).tw.	160
27	((internet or web) adj based).tw.	5104
28	(hotline$ or help line$).tw.	378
29	exp PRACTICE GUIDELINE/	147283
30	or/16-29	286967
31	and/5,15,30	148

CINAHL EBSCO

JAUN_Q13_infosupport_embase_020409_5

Thursday, April 02, 2009 7:31:15 AM

#	Query	Limiters/ Expanders	Last Run Via	Results
S38	S5 and S17 and S37	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	113
S37	S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	432694

	or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36		Database - CINAHL with Full Text	
S36	MH PRACTICE GUIDELINES	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	17274
S35	telephone N2 support	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	202
S34	web based	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	2229
S33	internet based	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	677
S32	MH INTERNET	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	12638
S31	help line*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	225
S30	helpline*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	345
S29	MH TELEPHONE INFORMATION SERVICES	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1589
S28	self-help N3 group*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	458

S27	selfhelp N3 group*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3
S26	support* N3 group*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	7118
S25	MH SUPPORT GROUPS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	4537
S24	educat* N3 literature*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	856
S23	educat* N3 video*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	375
S22	booklet* or leaflet* or pamphlet* or brochure* or handout*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3395
S21	MH PAMPHLETS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1395
S20	information* or education* or communication* or advice or advise	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	410021
S19	MH PATIENT EDUCATION	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	28363
S18	MH HEALTH EDUCATION	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	9160

			Database - CINAHL with Full Text	
S17	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	813
S16	(TI "kernicterus*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S15	MH KERNICTERUS	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S14	(TI jaundice*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S13	MH JAUNDICE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S12	(AB "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S11	(TI "hyperbilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S10	(AB "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S9	(TI "bilirubin*" N3 "encephalopath*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S8	(TI "bilirubinaemia" OR	Search modes -	Interface - EBSCOhost	Display

	"bilirubinemia")	Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL with Full Text	
S7	(TI "hyperbilirubinemia" or "hyperbilirubinaemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S6	MH HYPERBILIRUBINEMIA	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S4	(TI "newborn*" or "neonate*") or (AB "newborn*" or "neonate*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S3	MH INFANT, NEWBORN	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S2	(TI "preterm*") or (AB "preterm*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display
S1	MH INFANT, PREMATURE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	Display

Appendix J

Excluded studies

Which factors affect the relationship between neonatal hyperbilirubinaemia and kernicterus or other adverse outcomes (neurodevelopmental, auditory)?

Reference	Reason for exclusion
Bertini G, Dani C, Tronchin M *et al*. Is breastfeeding really favoring early neonatal jaundice? *Pediatrics* 2001; 107:(3)E41.	No analysis for confounding variables
Beutner D, Foerst A, Lang-Roth R *et al*. Risk factors for auditory neuropathy/auditory synaptopathy. *ORL* 2007; 69:(4)239–44.	No adjustment for confounding variables
Bhutani VK and Johnson LH. Jaundice technologies: prediction of hyperbilirubinemia in term and near-term newborns. *Journal of Perinatology* 2001; 21 Suppl 1:S76-S82.	Overview
Bhutani VK. Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. *Journal of Pediatrics* 2005; 147:(1)123–4.	Synopsis
Blackmon LR, Fanaroff AA, and Raju TNK. Research on prevention of bilirubin-induced brain injury and kernicterus: National Institute of Child Health and Human Development conference executive summary. *Pediatrics* 2004; 114:(1)229–33.	Overview of jaundice research
Brites D, Fernandes A, Falcao AS *et al*. Biological risks for neurological abnormalities associated with hyperbilirubinemia. *J Perinatol* 0 AD; 29:(S1)S8-S13.	Overview - Background
Cronin CM, Brown DR, and hdab-Barmada M. Risk factors associated with kernicterus in the newborn infant: importance of benzyl alcohol exposure. *American Journal of Perinatology* 1991; 8:(2)80–5.	Benzyl alcohol as a risk factor for kernicterus
De Vries LS, Lary S, Whitelaw AG *et al*. Relationship of serum bilirubin levels and hearing impairment in newborn infants. *Early Human Development* 1987; 15:(5)269–77.	Outcome not of interest to this guideline
Ding G, Zhang S, Yao D *et al*. An epidemiological survey on neonatal jaundice in China. *Chinese Medical Journal* 2001; 114:(4)344–7.	No adjustment for confounding variables
Frishberg Y, Zelicovic I, Merlob P *et al*. Hyperbilirubnemia and influencing factors in term infants. *Israel Journal of Medical Sciences* 1989; 25:(1)28–31.	Confounders not controlled for
Gagnon AJ, Waghorn K, Jones MA *et al*. Indicators nurses employ in deciding to test for hyperbilirubinemia. *JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing* 2001; 30:(6)626–33.	Background
Gartner LM and Arias IM. Studies of prolonged neonatal jaundice in the breast-fed infant. *Journal of Pediatrics* 1966; 68:(1)54–66.	No adjustment for confounders
Geiger AM, Petitti DB, and Yao JF. Rehospitalisation for neonatal jaundice: risk factors and outcomes. *Paediatric and Perinatal Epidemiology* 2001; 15:(4)352–8.	Risk factors for jaundice readmission – confounders not controlled for

Reference	Reason for exclusion
Gourley GR. Another risk factor for neonatal hyperbilirubinemia. *Journal of Pediatric Gastroenterology and Nutrition* 2005; 40:(3)388–9.	Synopsis
Grupp-Phelan J, Taylor JA, Liu LL *et al*. Early newborn hospital discharge and readmission for mild and severe jaundice. *Archives of Pediatrics and Adolescent Medicine* 1999; 153:(12)1283–8.	Effect of early discharge on jaundice readmission rates
Guo X, Pu X, An T *et al*. Characteristics of brainstem auditory evoked potential of neonates with mild or moderate hyperbilirubinemia. *Neural Regeneration Research* 2007; 2:(11)660–4.	No comparison group
Hall RT, Simon S, and Smith MT. Readmission of breastfed infants in the first 2 weeks of life. *Journal of Perinatology* 2000; 20:(7)432–7.	Risk factors for readmission of breastfed babies
Harris MC, Bernbaum JC, Polin JR *et al*. Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia. *Pediatrics* 2001; 107:(5)1075–80.	Developmental follow-up of babies with bilirubin > 451 micromol/litre
Huang MJ, Kua KE, Teng HC *et al*. Risk factors for severe hyperbilirubinemia in neonates. *Pediatric Research* 2004; 56:(5)682–9.	Only breastfeeding and genetic risk factors considered
Iranpour R, Akbar MR, and Haghshenas I. Glucose-6-Phosphate Dehydrogenase Deficiency in Neonates. *Indian Journal of Pediatrics* 2003; 70:(11)855–7.	G6PD deficiency as a risk factor for jaundice
Johnson L. Hyperbilirubinemia in the term infant: When to worry, when to treat. *New York State Journal of Medicine* 1991; 91:(11)483–9.	Overview
Kaplan M, Bromiker R, Schimmel MS *et al*. Evaluation of discharge management in the prediction of hyperbilirubinemia: the Jerusalem experience. *Journal of Pediatrics* 2007; 150:(4)412–7.	Effect of discharge management on readmission rates
Kaplan M, Herschel M, Hammerman C *et al*. Neonatal hyperbilirubinemia in African American males: the importance of glucose-6-phosphate dehydrogenase deficiency. *Journal of Pediatrics* 2006; 149:(1)83–8.	Study restricted to African-American males babies
Madlon-Kay DJ. The clinical significance of ABO blood group incompatibility. *Archives of Family Medicine* 1993; 2:(3)285–7.	ABO incompatibility as a risk factor for jaundice
Maisels MJ and Kring E. Length of stay, jaundice, and hospital readmission. *Pediatrics* 1998; 101:(6)995–8.	Risk factors for readmission for jaundice – confounders not controlled for
Nakamura H. Assessing the risk of kernicterus. *Indian Journal of Pediatrics* 1987; 54:(5)625–31.	Unbound bilirubin as a risk factor for kernicterus
Ogun B, Serbetcioglu B, Duman N *et al*. Long-term outcome of neonatal hyperbilirubinaemia: subjective and objective audiological measures. *Clinical Otolaryngology and Allied Sciences* 2003; 28:(6)507–13.	Long-term sequelae of hyperbilirubinaemia
Olusanya BO, Akande AA, Emokpae A *et al*. Infants with severe neonatal jaundice in Lagos, Nigeria: Incidence, correlates and hearing screening outcomes. *Tropical Medicine and International Health* 2009; 14:(3)301–10.	Effect of severe neonatal jaundice on hearing outcomes
Paul IM, Lehman EB, Hollenbeak CS *et al*. Preventable newborn readmissions since passage of the Newborns' and Mothers' Health Protection Act. *Pediatrics* 2006; 118:(6)2349–58.	Predictors of readmission after hospital discharge
Paul IM, Phillips TA, Widome MD *et al*. Cost-effectiveness of postnatal home nursing visits for prevention of hospital care for jaundice and dehydration. *Pediatrics* 2004; 114:(4)1015–22.	Not relevant to this quideline
Phuapradit W, Chaturachinda K, and Auntlamai S. Risk factors for neonatal hyperbilirubinemia. *Journal of the Medical Association of Thailand* 1993; 76:(8)424–8.	No regression analysis
Sales de Almeida F, Pialarissi PR, Monte AA *et al*. Otoacoustic emissions and ABR: Study in hyperbilirubinemic newborns. *Revista Brasileira de Otorrinolaringologia* 2002; 68:(6)851–7.	Outcome not of interest to this guideline

Reference	Reason for exclusion
Sarici SU, Serdar MA, Korkmaz A *et al*. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. *Pediatrics* 2004; 113:(4)775–80.	Not adjustment for confounding variables
Setia S, Villaveces A, Dhillon P *et al*. Neonatal jaundice in Asian, white, and mixed-race infants. *Archives of Pediatrics and Adolescent Medicine* 2002; 156:(3)276–9.	Ethnicity (at least one Asian parent) as a risk factor for jaundice
Shah VA and Cheo LY. Identifying risk of neonatal hyperbilirubinaemia and early discharge for glucose-6-phosphate dehydrogenase deficient newborns in Singapore. *Annals of the Academy of Medicine Singapore* 2007; 36:(12)1003–9.	G6PD deficient babies only
Stiehm ER and Ryan J. Breast-milk jaundice. Report of eight cases and effect of breast feeding on incidence and severity of unexplained hyperbilirubinaemia. *American Journal of Diseases of Children* 1965; 109:212–6.	Case-studies
Thoma J, Gerull G, and Mrowinski D. A long-term study of hearing in children following neonatal hyperbilirubinemia. *Archives of Oto-Rhino-Laryngology* 1986; 243:(2)133.	Non-comparative study
Tudehope D, Bayley G, Munro D *et al*. Breast feeding practices and severe hyperbilirubinaemia. *Journal of Paediatrics and Child Health* 1991; 27:(4)240–4.	Link between breastfeeding and early onset jaundice
van de Bor M, Ens-Dokkum M, Schreuder AM *et al*. Hyperbilirubinemia in low birth weight infants and outcome at 5 years of age. *Pediatrics* 1992; 89:(3)359–64.	Outcome, at 5 year, of low-birthweight babies with hyperbilirubinamia
van de Bor M, van Zeben-van der Aa TM , Verloove-Vanhorick SP *et al*. Hyperbilirubinemia in preterm infants and neurodevelopmental outcome at 2 years of age: Results of a national collaborative survey. *Pediatrics* 1989; 83:(6)915–20.	Long term sequelae of hyperbilirubinaemia in preterm babies
Vohr BR. New approaches to assessing the risks of hyperbilirubinemia. *Clinics in Perinatology* 1990; 17:(2)293–306.	Overview
Watchko JF. Neonatal hyperbilirubinemia -- what are the risks? *New England Journal of Medicine* 2006; 354:(18)1947–9.	Overview
Yaish HM, Niazi GA, Al S *et al*. Increased incidence of hyperbilirubinaemia in 'unchallenged' glucose-6-phosphate dehydrogenase deficiency in term Saudi newborns. *Annals of Tropical Paediatrics* 1991; 11:(3)259–66.	No adjustment for confounding variables
Young-Lewis LE. Factors contributing to the readmission of previously healthy low-risk neonates for hyperbilirubinemia. *(CASE WESTERN RESERVE UNIVERSITY) **1996; PH.D* 146.	PHd thesis

What is the best method of recognising hyperbilirubinaemia?
When should a baby with hyperbilirubinaemia be referred for further testing or formal assessment?
How useful are the following tests in predicting neonatal hyperbilirubinaemia?

Reference	Reason for exclusion
Akman I, Arikan C, Bilgen H *et al*. Transcutaneous measurement of bilirubin by icterometer during phototherapy on a bilibed. *Turkish Journal of Medical Sciences* 2002; 32:(2)165–8.	Transcutaneous measurement undergoing phototherapy
Amato M, Huppi P, and Markus D. Assessment of neonatal jaundice in low birth weight infants comparing transcutaneous, capillary and arterial bilirubin levels. *European Journal of Pediatrics* 1990; 150:(1)59–61.	Poor quality study – EL 3
Awasthi S and Rehman H. Early prediction of neonatal hyperbilirubinemia. *Indian Journal of Pediatrics* 1998; 65:(1)131–9.	Poor quality study – EL 3
Barko HA, Jackson GL, and Engle WD. Evaluation of a point-of-care direct spectrophotometric method for measurement of total serum bilirubin in term and near-term neonates. *Journal of Perinatology* 2006; 26:(2)100–5.	Poor quality study – EL 3
Bhardwaj HP, Narang A, and Bhakoo ON. Evaluation of Minolta jaundicemeter and icterometer for assessment of neonatal jaundice. *Indian Pediatrics* 1989; 26:(2)161–5.	Poor quality study – EL 3
Bhat V, Srinivasan S, Usha TS *et al*. Correlation of transcutaneous bilirubinometry with serum bilirubin in south Indian neonates. *Indian Journal of Medical Research* 1987; 86:49–52.	Reference tests was not a laboratory based test
Bhat YR and Rao A. Transcutaneous bilirubin in predicting hyperbilirubinemia in term neonates. *Indian Journal of Pediatrics* 2008; 75:(2)119–23.	Poor quality study
Bjerre JV and Ebbesen F. [Incidence of kernicterus in newborn infants in Denmark]. *Ugeskrift for Laeger* 2006; 168:(7)686–91.	Non-English language article
Bourchier D, Cull AB, and Oettli PE. Transcutaneous bilirubinometry: 22 months experience at Waikato women's Hospital. *New Zealand Medical Journal* 1987; 100:(832)599–600.	Unclear of timing of tests
Bredemeyer SL, Polverino JM, and Beeby PJ. Assessment of jaundice in the term infant - accuracy of transcutaneous bilirubinometers compared with serum bilirubin levels: part two. *Neonatal, Paediatric and Child Health Nursing* 2007; 10:(1)5–10, 12.	Poor quality study – EL 3
Brouwers HA, Overbeeke MA, van E, I *et al*. What is the best predictor of the severity of ABO-haemolytic disease of the newborn? *Lancet* 1988; 2:641–4.	Study evaluating predictors of the severity of ABO-haemolytic disease of the newborn
Carapella E, Gloria-Bottini F, Tucciarone L *et al*. Annotations on the hyperbilirubinaemia of ABO incompatible infants. *Haematologia* 1982; 15:(1)127–33.	Not relevant to this guideline
Carceller-Blanchard A, Cousineau J, and Delvin EE. Point of care testing: transcutaneous bilirubinometry in neonates. *Clinical Biochemistry* 2009; 42:(3)143–9.	Background information
Centre for Reviews and Dissemination. The value of routine bilirubin screening to detect significant hyperbilirubinemia in Thai healthy term newborns (Brief record). *NHS Economic Evaluation Database (NHSEED)* 2008;(2).	Synopsis
Centre for Reviews and Dissemination. Using Bilicheck for preterm neonates in a sub-intensive unit: diagnostic usefulness and suitability (Brief record). *NHS Economic Evaluation Database (NHSEED)* 2008;(2).	Synopsis
Chuansumrit A, Siripoonya P, Nathalang O *et al*. The benefit of the direct antiglobulin test using gel technique in ABO hemolytic disease of the newborn. *Southeast Asian Journal of Tropical Medicine and Public Health* 1997; 28:(2)428–31.	Comparison of two methods of DAT testing

Reference	Reason for exclusion
Conseil d'Evaluation des Technologies de la Sante. Transcutaneous bilirubinometry in the context of early postnatal discharge (Structured abstract). *Health Technology Assessment Database* 2008;(3).	Overview
Dai J, Krahn J, and Parry DM. Clinical impact of transcutaneous bilirubinometry as an adjunctive screen for hyperbilirubinemia. *Clinical Biochemistry* 1996; 29:(6)581–6.	Effectiveness of Minolta JM-102
De Luca D, Romagnoli C, Tiberi E *et al*. Skin bilirubin nomogram for the first 96 h of life in a European normal healthy newborn population, obtained with multiwavelength transcutaneous bilirubinometry. *Acta Paediatrica, International Journal of Paediatrics* 2008; 97:(2)146–50.	Development of a nomogram based on transcutaneous measurement
De Luca D, Zecca E, Zuppa AA *et al*. The joint use of human and electronic eye: Visual assessment of jaundice and transcutaneous bilirubinometry. *Turkish Journal of Pediatrics* 2008; 50:(5)456–61.	Incomplete data – correlation data or sensitivity/specificity data not reported
Dinesh D. Review of positive direct antiglobulin tests found on cord blood sampling. *Journal of Paediatrics and Child Health* 2005; 41:(9–10)504–10.	Incomplete data – number of true negative snot reported
Donzelli G and Pratesi S. Transcutaneous bilirubinometry in healthy preterm newborns. *Clinical Biochemistry* 2000; 33:(6)505–8.	Study examined the use of JM-102 in preterm babies
Engle WD, Jackson GL, Sendelbach D *et al*. Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinemia in a primarily Hispanic population. *Pediatrics* 2002; 110:(1 I)61–7.	Not all tests carried out with 1-hour
Facchini FP, Mezzacappa MA, Rosa IRM *et al*. Follow-up of neonatal jaundice in term and late premature newborns. [Portuguese, English]. *Jornal de Pediatria* 2007; 83:(4)313–8.	Not a comparative study
Flaherman VJ, Ferrara A, and Newman TB. Predicting significant hyperbilirubinaemia using birth weight. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2008; 93:(4)F307-F309.	Birthweight as a predictor for hyperbilirubinaemia
Goldman SL, Penalver A, and Penaranda R. Jaundice meter: evaluation of new guidelines. *Journal of Pediatrics* 1982; 101:(2)253–6.	Poor quality study – EL 3
Gonzaba G. Research corner. End tidal carbon monoxide: a new method to detect hyperbilirubinemia in newborns. *Newborn and Infant Nursing Reviews* 2007; 7:(2)122–8.	Overview
Grohmann K, Roser M, Rolinski B *et al*. Bilirubin measurement for neonates: comparison of 9 frequently used methods. *Pediatrics* 2006; 117:(4)1174–83.	Poor quality study – EL 3
Gupta PC, Kumari S, Mullick DN *et al*. Icterometer: a useful screening tool for neonatal jaundice. *Indian Pediatrics* 1991; 28:(5)473–6.	Poor quality study – EL 3
Harish R and Sharma DB. Transcutaneous bilirubinometry in neonates: evaluation of Minolta Air shields jaundicemeter. *Indian Pediatrics* 1998; 35:(3)264–7.	Poor quality study – EL 3
Hegyi T, Hiatt IM, and Indyk L. Transcutaneous bilirubinometry. I. Correlations in term infants. *Journal of Pediatrics* 1981; 98:(3)454–7.	Poor quality study – EL 3
Ho EY, Lee SY, Chow CB *et al*. BiliCheck transcutaneous bilirubinometer: a screening tool for neonatal jaundice in the Chinese population. *Hong Kong Medical Journal* 2006; 12:(2)99–102.	Poor quality study – EL 3
Ho HT, Ng TK, Tsui KC *et al*. Evaluation of a new transcutaneous bilirubinometer in Chinese newborns. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2006; 91:(6)F434-F438.	Poor quality study – EL 3
Jangaard KA, Curtis H, and Goldbloom RB. Estimation of bilirubin using BiliChek[trademark], a transcutaneous bilirubin measurement device: Effects of gestational age and use of phototherapy. *Paediatrics and Child Health* 2006; 11:(2)79–83.	Data not relevant – overestimation an underestimation of tests

Reference	Reason for exclusion
Janjindamai W and Tansantiwong T. Accuracy of transcutaneous bilirubinometer estimates using BiliCheck in Thai neonates. *Journal of the Medical Association of Thailand* 2005; 88:(2)187–90.	Poor quality study – EL 3
Kaplan M, Hammerman C, Feldman R *et al*. Predischarge bilirubin screening in glucose-6-phosphate dehydrogenase- deficient neonates. *Pediatrics* 2000; 105:(3)533–7.	Female subjects were included from a retrospective studies
Kaplan M, Shchors I, Algur N *et al*. Visual screening versus transcutaneous bilirubinometry for predischarge jaundice assessment. *Acta Paediatrica* 2008; 97:(6)759–63.	Timing of tests not specified
Kazmierczak S, Bhutani V, Gourley G, Kerr S, Lo S, Robertson A, and Sena SF. Transcutaneous bilirubin testing. Laboratory medicine practice guidelines: evidence-based practice for point-of-care testing. Washington DC: National Academy of Clinical Biochemistry; 2006.	Review of transcutaneous bilirubinometers
Keren, R.; Luan, X.; Tremont, K.; Cnaan, A. Visual Assessment of Jaundice in Term and Late Preterm Infants. *Arch. Dis. Child. Fetal Neonatal Ed.* 2009,	Test timing was 8 hours
Knudsen A and Ebbesen F. Transcutaneous bilirubinometry in neonatal intensive care units. *Archives of Disease in Childhood* 1996; 75:(1 SUPPL.)F53-F56.	Study not relevant – multiple regression used to study different factors
Knudsen A. Predicting the need for phototherapy in healthy mature neonates using transcutaneous bilirubinometry on the first postnatal day. *Biology of the Neonate* 1995; 68:(6)398–403.	Poor quality study – EL 3
Knudsen A. Prediction of the development of neonatal jaundice by increased umbilical cord blood bilirubin. *Acta Paediatrica Scandinavica* 1989; 78:(2)217–21.	Poor quality study – EL 3
Knudsen A. The cephalocaudal progression of jaundice in newborns in relation to the transfer of bilirubin from plasma to skin. *Early Human Development* 1990; 22:(1)23–8.	Deals with progression of bilirubin from plasma to skin
Knupfer M, Pulzer F, Braun L *et al*. Transcutaneous bilirubinometry in preterm infants. *Acta Paediatrica, International Journal of Paediatrics* 2001; 90:(8)899–903.	Transcutaneous measurement in preterm babies
Kolman KB, Mathieson KM, and Frias C. A comparison of transcutaneous and total serum bilirubin in newborn hispanic infants at 35 or more weeks of gestation. *Journal of the American Board of Family Medicine* 2007; #20:(3)266–71.	Not all babies tested
Kumar A, Faridi MM, Singh N *et al*. Transcutaneous bilirubinometry in the management of bilirubinemia in term neonates. *Indian Journal of Medical Research* 1994; 99:227–30.	Unclear of timing of tests
Lim HH, Daniel LM, Lee J *et al*. Predicting significant hyperbilirubinaemia and early discharge for glucose-6-phosphate dehydrogenase deficient newborns. *Annals of the Academy of Medicine Singapore* 2003; 32:(2)257–61.	Coombs' test only used if phototherapy was indicated
Linder N, Regev A, Gazit G *et al*. Noninvasive determination of neonatal hyperbilirubinemia: standardization for variation in skin color. *American Journal of Perinatology* 1994; 11:(3)223–5.	Timing of tests = 4 hours
Mahajan G, Kaushal RK, Sankhyan N *et al*. Transcutaneous bilirubinometer in assessment of neonatal jaundice in northern India. *Indian Pediatrics* 2005; 42:(1)41–5.	Minolta JM-101 was used – not a transcutaneous bilirubinometer of interest
Maisels MJ and Kring E. Transcutaneous bilirubinometry decreases the need for serum bilirubin measurements and saves money. *Pediatrics* 1997; 99:(4)599–601.	Health economic analysis of JM-102
Mercier CE, Barry SE, Paul K *et al*. Improving newborn preventive services at the birth hospitalization: a collaborative, hospital-based quality-improvement project. *Pediatrics* 2007; 120:(3)481–8.	Quality improvement programme not relevant to this guideline
Namba F and Kitajima H. Utility of a new transcutaneous jaundice device with two optical paths in premature infants. *Pediatrics International* 2007; 49:(4)497–501.	Poor quality study

Reference	Reason for exclusion
Narayanan I, Banwalikar J, Mehta R *et al*. A simple method of evaluation of jaundice in the newborn. *Annals of Tropical Paediatrics* 1990; 10:(1)31–4.	Unclear if tests were within 1 hour
Nasser B and de M. Bilirubin dosage in cord blood: Could it predict neonatal hyperbilirubinemia? *Sao Paulo Medical Journal* 2004; 122:(3)99–103.	Incomplete data
Orzalesi M, Gloria-Bottini F, Lucarelli P *et al*. ABO system incompatibility: evaluation of risk of hyperbilirubinaemia at birth by multivariate discriminant analysis. *Experientia* 1983; 39:(1)89–91.	Only babies with blood group incompatibility were included
Prasarnphanich T and Somlaw S. The value of routine bilirubin screening to detect significant hyperbilirubinemia in Thai healthy term newborns. *Journal of the Medical Association of Thailand* 2007; 90:(5)925–30.	Poor quality study – EL 3
Randeberg LL, Roll EB, Nilsen LT *et al*. In vivo spectroscopy of jaundiced newborn skin reveals more than a bilirubin index. *Acta Paediatrica* 2005; 94:(1)65–71.	Ways to improve algorithm for transcutaneous measurement
Robertson A, Kazmierczak S, and Vos P. Improved transcutaneous bilirubinometry: comparison of SpectR(X) BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population. *Journal of Perinatology* 2002; 22:(1)12–4.	Data not extractable
Rodriguez-Capote K, Kim K, Paes B *et al*. Clinical implication of the difference between transcutaneous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinemia. *Clinical Biochemistry* 2009; 42:(3)176–9.	Nidrect comparison of Minolta JM-103 and BiliChek
Rosenfeld J. Umbilical cord bilirubin levels as a predictor of subsequent hyperbilirubinemia. *Journal of Family Practice* 1986; 23:(6)556–8.	Retrospective study
Rubegni P, Cevenini G, Sbano P *et al*. Cutaneous colorimetric evaluation of serum concentrations of bilirubin in healthy term neonates: a new methodological approach. *Skin Research and Technology* 2005; 11:(1)70–5.	Device being tested not relevant to this guideline
Ruchala PL, Seibold L, and Stremsterfer K. Validating assessment of neonatal jaundice with transcutaneous bilirubin measurement. *Neonatal Network: The Journal of Neonatal Nursing* 1996; 15:(4)33–7.	Correlation of visual inspection and transcutaneous measurement
Ruskandi M, Garna H, and Alisjahbana A. The use of icterometer in assessing neonatal jaundice. *Paediatrica Indonesiana* 1978; 18:(5–6)158–63.	Not clear if tests were carried out within 2 hours
Sanpavat S and Nuchprayoon I. Comparison of two transcutaneous bilirubinometers--Minolta AirShields Jaundice Meter JM103 and Spectrx Bilicheck--in Thai neonates. *Southeast Asian Journal of Tropical Medicine and Public Health* 2005; 36:(6)1533–7.	Poor quality study – EL 3
Sanpavat S, Nuchprayoon I, Smathakanee C *et al*. Nomogram for prediction of the risk of neonatal hyperbilirubinemia, using transcutaneous bilirubin. *Journal of the Medical Association of Thailand* 2005; 88:(9)1187–93.	No reference test used
Serrao PA and Modanlou HD. Significance of anti-A and anti-B isohemagglutinins in cord blood of ABO incompatible newborn infants: correlation with hyperbilirubinemia. *Journal of Perinatology* 1989; 9:(2)154–8.	Transcutaneous bilirubin used as the reference test
Sheridan-Pereira M and Gorman W. Transcutaneous bilirubinometry: An evaluation. *Archives of Disease in Childhood* 1982; 57:(9)708–10.	Unclear of timing of tests
Smith DW, Inguillo D, Martin D *et al*. Use of noninvasive tests to predict significant jaundice in full-term infants: preliminary studies. *Pediatrics* 1985; 75:(2)278–80.	Correspondence
Stein H, Wolfsdorf J, and Buchanan N. The use of the icterometer in assessing neonatal jaundice. *Journal of Tropical Pediatrics and Environmental Child Health* 1975; 21:(2)67–8.	Unclear of timing of tests
Stepensky P, Revel-Vilk S, Weintraub M *et al*. Combination of umbilical cord blood with BM from a 2-month-old sibling as lifesaving BMT for very severe aplastic anemia. *Bone Marrow Transplantation* 2008; 42:(8)563–4.	Correspondence

Reference	Reason for exclusion
Surjono A, Triasih R, and Haksari EL. The first 24 hours bilirubin level as a predictor of hyperbilirubinemia in healthy term newborns. *Perinatology* 2003; 5:(4)159–66.	Incomplete data
Taha SA, Karrar ZA, and Dost SM. Transcutaneous bilirubin measurement in evaluating neonatal jaundice among Saudi newborns. *Annals of Tropical Paediatrics* 1984; 4:(4)229–31.	Duplicate publication
Tan KL and Dong F. Transcutaneous bilirubinometry during and after phototherapy. *Acta Paediatrica, International Journal of Paediatrics* 2003; 92:(3)327–31.	Use of transcutaneous bilirubinometer during and after phototherapy
Tan KL, Chia HP, and Koh BC. Transcutaneous bilirubinometry in Chinese, Malay and Indian infants. *Acta Paediatrica, International Journal of Paediatrics* 1996; 85:(8)986–90.	Incomplete data – data not available for 262 babies
Tan KL. Neonatal jaundice in 'healthy' very low birthweight infants. *Australian Paediatric Journal* 1987; 23:(3)185–8.	No comparison goup
Tan KL. Transcutaneous bilirubinometry in Chinese and Malay neonates. *Annals of the Academy of Medicine Singapore* 1985; 14:(4)591–4.	Some babies had been exposed to phototherapy
Venkataseshan S, Murki S, and Kumar P. Non-invasive bilirubinometry in neonates. *Perinatology* 2004; 6:(6)315–9.	Commentary
Wainer S, Bolton KD, Cooper PA *et al.* Transcutaneous bilirubinometry in black infants: Improved reliability after correction for the background signal. *Pediatric Reviews and Communications* 1989; 4:(1–2)93–2.	Importance of background signal in transcutaneous bilirubin measurements
Wainer S, Rabi J, Lyon M *et al.* Coombs' testing and neonatal hyperbilirubinemia... Sgro M, Campbell D, Shah V. Incidence and causes of severe hyperbilirubinemia in Canada. CMAJ 2006;175(6):587–90. *CMAJ: Canadian Medical Association Journal* 2007; 176:(7)972–3, 976.	Correspondence
Webster J, Blyth R, and Nugent F. An appraisal of the use of the Kramer's scale in predicting hyperbilirubinaemia in healthy full term infants. *Birth Issues* 2005; 14:(3)83–9.	Data not extractable
Willems WA, Von D, De W *et al.* Transcutaneous bilirubinometry with the Bilicheck in very premature newborns. *Journal of Maternal-Fetal and Neonatal Medicine* 2004; 16:(4)-Fetal.	Data not relevant
Wong CM, Van Dijk P, and Laing IA. A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2002; 87:(2)F137-F140.	Poor quality study – EL 3
Wong V, Chen WX, and Wong KY. Short- and long-term outcome of severe neonatal nonhemolytic hyperbilirubinemia. *Journal of Child Neurology* 2006; 21:(4)309–15.	Outcomes of severe hyperbilirubinaemia
Yamauchi Y and Yamanouchi I. Clinical application of transcutaneous bilirubin measurement. Early prediction of hyperbilirubinemia. *Acta Paediatrica Scandinavica* 1990; 79:(4)385–90.	Poor quality study – EL 3
Yamauchi Y and Yamanouchi I. Transcutaneous bilirubinometry in normal Japanese infants. *Acta Paediatrica Japonica (Overseas Edition)* 1989; 31:(Overseas Edition)65–72.	Time between compared tests greater than 1 hour
Yamauchi Y and Yamanouchi I. Transcutaneous bilirubinometry: serum bilirubin measurement using transcutaneous bilirubinometer (TcB). A preliminary study. *Biology of the Neonate* 1989; 56:(5)257–62.	Test of different curvettes for Minolta JM
Yap SH, Mohammad I, and Ryan CA. Avoiding painful blood sampling in neonates by transcutaneous bilirubinometry. *Irish Journal of Medical Science* 2002; 171:(4)188–90.	Unclear of time between testing
Yasuda S, Itoh S, Isobe K *et al.* New transcutaneous jaundice device with two optical paths. *Journal of Perinatal Medicine* 2003; 31:(1)81–8.	No possible to extract data

What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia?

Reference	Reason for exclusion
Abolghasemi H, Mehrani H, and Amid A. An update on the prevalence of glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Tehran neonates. *Clinical Biochemistry* 2004; 37:(3)241–4.	Babies were only tested for G6PD
Adachi Y, Katoh H, Fuchi I *et al*. Serum bilirubin fractions in healthy subjects and patients with unconjugated hyperbilirubinemia. *Clinical Biochemistry* 1990; 23:(3)247–51.	Diagnostic criteria not specified
Ahlfors CE and Parker AE. Evaluation of a model for brain bilirubin uptake in jaundiced newborns. *Pediatric Research* 2005; 58:(6)1175–9.	Modelling study
Ahlfors CE and Parker AE. Unbound bilirubin concentration is associated with abnormal automated auditory brainstem response for jaundiced newborns. *Pediatrics* 2008; 121:(5)976–8.	Test not relevant to this guideline - value of Auditory brainstem response as a predictor of kernicterus
Ahlfors CE and Wennberg RP. Bilirubin-albumin binding and neonatal jaundice. *Seminars in Perinatology* 2004; 28:(5)334–9.	Commentary
Ahlfors CE, Amin SB, and Parker AE. Unbound bilirubin predicts abnormal automated auditory brainstem response in a diverse newborn population. *Journal of Perinatology* 2009; 29:(4)305–9.	Test not relevant to this guideline
Ahlfors CE. Bilirubin-albumin binding and free bilirubin. *Journal of Perinatology* 2001; 21:(SUPPL. 1)S40-S42.	Commentary
Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. *Pediatrics* 1994; 93:(3)488–94.	Using the bilirubin/albumin ratio and indicator for exchange transfusion
Ahlfors CE. Measurement of plasma unbound unconjugated bilirubin. *Analytical Biochemistry* 2000; 279:(2)130–5.	Comparison of different methods for measuring conjugated bilirubin
Ahlfors CE. Unbound bilirubin associated with kernicterus: a historical approach. *Journal of Pediatrics* 2000; 137:(4)540–4.	Theoretic analysis of laboratory data
Ahmadi AH and Ghazizadeh Z. Evaluation of glucose-6-phosphate dehydrogenase deficiency without hemolysis in icteric newborns at Mazandaran province, Iran. *Pakistan Journal of Biological Sciences* 2008; 11:(10)1394–7.	Physiological jaundice was excluded
Ahmed P and Ahmad KN. Screening of the newborns for glucose-6-phosphate dehydrogenase deficiency. *Indian Pediatrics* 1983; 20:(5)351–5.	Babies with ABO or Rh incompatibility were excluded
Akman I, Ozek E, Kulekci S *et al*. Auditory neuropathy in hyperbilirubinemia: is there a correlation between serum bilirubin, neuron-specific enolase levels and auditory neuropathy? *International Journal of Audiology* 2004; 43:(9)516–22.	Babies with haemolysis were excluded
Al-Dabbous IA, Owa JA, and Al-Khater NS. Neonatal jaundice in Qatif: The role of glucose-6-phosphate dehydrogenase deficiency in the etiology among outpatient cases. *Annals of Saudi Medicine* 1995; 15:(5)539–41.	No entry level criteria for jaundice were used
Alden ER, Lynch SR, and Wennberg RP. Carboxyhemoglobin determination in evaluating neonatal jaundice. *American Journal of Diseases of Children* 1974; 127:(2)214–7.	Tests not relevant to this guideline
Al-Magamci MSF, Khan A, Bhat BA *et al*. Neonatal jaundice: An etiological survey in the Madinah region. *Annals of Saudi Medicine* 1996; 16:(2)221–3.	Subjects with physiological jaundice were excluded
Al-Naama LM, Al-Sadoon IA, and Al-Naama MM. Neonatal jaundice and glucose-6-phosphate dehydrogenase deficiency in Basrah. *Annals of Tropical Paediatrics* 1987; 7:(2)134–8.	Babies were not tested for blood group incompatibility

Reference	Reason for exclusion
AlOtaibi SF, Blaser S, and MacGregor DL. Neurological complications of kernicterus. *Canadian Journal of Neurological Sciences* 2005; 32:(3)311–5.	Unclear if blood group incompatibility was tested for
Amin SB, Ahlfors C, Orlando MS *et al*. Bilirubin and serial auditory brainstem responses in premature infants. *Pediatrics* 2001; 107:(4)664–70.	Data from this study was contained in an included review
Amin SB. Clinical assessment of bilirubin-induced neurotoxicity in premature infants. *Seminars in Perinatology* 2004; 28:(5)340–7.	Overview
Arias IM, Gartner LM, Seifter S *et al*. Prolonged neonatal unconjugated hyperbilirubinemia associated with breast feeding and a steroid, Pregnane-3(Alpha), 20(beta)-diol, in maternal milk that inhibits glucuronide formation in vitro. *Journal of Clinical Investigation* 1964; 43:2037–47.	Test for different factors in human breast milk
Azubuike JC. Neonatal jaundice in Eastern Nigeria. *Journal of Tropical Pediatrics* 1985; 31:(2)82–4.	Duplicate of Azubuike 1979
Bahl L, Sharma R, and Sharma J. Etiology of neonatal jaundice at Shimla. *Indian Pediatrics* 1994; 31:(10)1275–8.	Uncertainty over criteria for jaundice or hyperbilirubinaemia
Ballowitz L. Bilirubin encephalopathy: changing concepts. *Brain and Development* 1980; 2:(3)219–27.	Overview
Basu K, Das PK, Bhattacharya R *et al*. A new look on neonatal jaundice. *Journal of the Indian Medical Association* 2003; 100:(9)556–60.	Single test only
Beachy JM. Lab values. Investigating jaundice in the newborn. *Neonatal Network: The Journal of Neonatal Nursing* 2007; 26:(5)327-??	Overview
Behjati-Ardakani S, Nikkhah A, and Sedaghat M. The association between G6PD deficiency and total serum bilirubin level in icteric neonates. *Acta Medica Iranica* 2007; 45:(3)233–5.	Only tested for G6PD deficiency
Behjati-Ardakani S, Nikkhah A, Ashrafi MR *et al*. Association between total serum bilirubin level and manifestations of kernicterus. *Acta Medica Iranica* 2006; 44:(6)405–8.	Data on ABO/Rh incompatibility was not reported
Bender GJ, Cashore WJ, and Oh W. Ontogeny of bilirubin-binding capacity and the effect of clinical status in premature infants born at less than 1300 grams. *Pediatrics* 2007; 120:(5)1067–73.	Test not relevant to this guideline
Bernstein J, Braylan R, and Brough AJ. Bile-plug syndrome: a correctable cause of obstructive jaundice in infants. *Pediatrics* 1969; 43:(2)273–6.	Test not relevant to this guideline
Bertini G, Dani C, Pezzati M *et al*. Prevention of bilirubin encephalopathy. *Biology of the Neonate* 2001; 79:(3–4)219–4.	Overview
Bhutia RD, Upadhyay B, and Maneesh M. Association of plasma level of thiobarbituric acid reactive substances with extent of hepatocellular injury in preterm infants with cholestatic jaundice. *Indian Journal of Clinical Biochemistry* 2006; 21:(2)39–41.	Test was for Cholestasis
Bilgen H, Ozek E, Unver T *et al*. Urinary tract infection and hyperbilirubinemia. *Turkish Journal of Pediatrics* 2006; 48:(1)51–5.	Jaundice as a predictor for Urinary Tract Infections
Bilgen H. Urinary tract infection and neonatal hyperbilirubinemia. *Turkish Journal of Pediatrics* 2007; 49:(1)114.	Correspondence
Bonillo-Perales A, Munoz-Hoyos A, Martinez-Morales A *et al*. Changes in erythrocytic deformability and plasma viscosity in neonatal ictericia. *American Journal of Perinatology* 1999; 16:(8)421–7.	Comparison of babies with jaundice and without jaundice
Borgard JP, Szymanowicz A, Pellae I *et al*. Determination of total bilirubin in whole blood from neonates: results from a French multicenter study. *Clinical Chemistry and Laboratory Medicine* 2006; 44:(9)1103–10.	Comparison of different methods of bilirubin analysis
Botha MC, Rees J, Pritchard J *et al*. Glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice among population groups of Cape Town. *South African Medical Journal* 1967; 41:(8)174–80.	Single test only

Reference	Reason for exclusion
Bracci R, Buonocore G, Garosi G *et al*. Epidemiologic study of neonatal jaundice. A survey of contributing factors. *Acta Paediatrica Scandinavica, Supplement* 1989; 78:(360)87–92.	Not all babies were jaundiced
Bratlid D and Winsnes A. Comparison between different methods for determination of bile pigments in icteric serum samples. *Scandinavian Journal of Clinical and Laboratory Investigation* 1973; 31:(2)231–6.	Comparison of different methods of measuring bile acids
Bratlid D. Bilirubin toxicity: Pathophysiology and assessment of risk factors. *New York State Journal of Medicine* 1991; 91:(11)489–92.	Overview
Bratlid D. Reserve albumin binding capacity, salicylate saturation index, and red cell binding of bilirubin in neonatal jaundice. *Archives of Disease in Childhood* 1973; 48:(5)393–7.	Tests not relevant to this guideline
Brito MA, Silva R, Tiribelli C *et al*. Assessment of bilirubin toxicity to erythrocytes. Implication in neonatal jaundice management. *European Journal of Clinical Investigation* 2000; 30:(3)239–47.	Laboratory analysis of bilirubin toxicity on serum samples
Brito MA, Silva RFM, and Brites D. Bilirubin toxicity to human erythrocytes: A review. *Clinica Chimica Acta* 2006; 374:(1–2)46–2.	Overview
Brown AK. Hyperbilirubinemia in black infants. Role of glucose-6-phosphate dehydrogenase deficiency. *Clinical Pediatrics* 1992; 31:(12)712–5.	Overview
Brown WR and Boon WH. Hyperbilirubinemia and kernicterus in glucose-6-phosphate dehydrogenase-deficient infants in Singapore. *Pediatrics* 1968; 41:(6)1055–62.	Study examine incidence of jaundice in G6PD
Buonocore G, Berti D, Cito G *et al*. Moderately increased hemolysis in newborn infants with hyperbilirubinemia of unknown etiology. *Biology of the Neonate* 1983; 44:(4)251–6.	Results of G6PD tests not reported
Casado A, Casado C, Lopez-Fernandez E *et al*. Enzyme deficiencies in neonates with jaundice. *Panminerva Medica* 1995; 37:(4)175–7.	Babies were not tested for blood group incompatibility
Cashore WJ and Oh W. Unbound bilirubin and kernicterus in low-birth-weight infants. *Pediatrics* 1982; 69:(4)481–5.	Autopsy study on link between unbound bilirubin and kernicterus in low-birthweight babies
Cashore WJ, Oh W, Blumberg WE *et al*. Rapid fluorometric assay of bilirubin and bilirubin binding capacity in blood of jaundiced neonates: comparisons with other methods. *Pediatrics* 1980; 66:(3)411–6.	Laboratory evaluation of a new method for measuring bilirubin binding capacity
Chen SH, Chen LY, and Chen JS. Carboxyhemoglobin and serum hepatic enzymes in newborns with hyperbilirubinemia. *Taiwan i Hsueh Hui Tsa Chih - Journal of the Formosan Medical Association* 1986; 85:(2)101–8.	Babies with G6PD deficiency or blood group incompatibility were excluded
Chen SH. Endogenous formation of carbon monoxide in Chinese newborn with hyperbilirubinemia. *Taiwan i Hsueh Hui Tsa Chih - Journal of the Formosan Medical Association* 1981; 80:(1)68–77.	No test for G6PD deficiency
Chen WX, Wong VCN, and Wong KY. Neurodevelopmental outcome of severe neonatal hemolytic hyperbilirubinemia. *Journal of Child Neurology* 2006; 21:(6)474–9.	Babies with sepsis were excluded
Cisowska A, Tichaczek-Goska D, Szozda A *et al*. The bactericidal activity of complement in sera of children with infectious hyperbilirubinemia. *Advances in Clinical and Experimental Medicine* 2007; 16:(5)629–34.	Evaluation of bactericidal activity in blood – not relevant to this guideline
Coban AC, Can G, Kadioglu A *et al*. Adrenal hemorrhage: A rare cause of severe neonatal jaundice. *Pediatric Surgery International* 1994; 9:(1–2)123-??	Case study
Corchia C, Sanna MC, Serra C *et al*. 'Idiopathic' jaundice in Sardinian full-term newborn infants: a multivariate study. *Paediatric and Perinatal Epidemiology* 1993; 7:(1)55–66.	Babies with ABO/Rh incompatibility were excluded

Reference	Reason for exclusion
Dani C, Martelli E, Bertini G *et al*. Plasma bilirubin level and oxidative stress in preterm infants. *Archives of Disease in Childhood Fetal and Neonatal Edition* 2003; 88:(2)F119-F123.	Tests not relevant to this guideline
Deshmukh VV and Sharma KD. Deficiency of erythrocyte G-6-PD as a cause of neonatal jaundice in India. *Indian Pediatrics* 1968; 5:(9)401–5.	Three case studies
Doxiadis SA, Karaklis A, Valaes T *et al*. Risk of severe jaundice in Glucose-6-Phosphate-Dehydrogenase deficiency of the newborn. Differences in population groups. *Lancet* 1964; 2:(7371)1210–2.	Not all babies tested for ABO incompatibility
Ebbesen F, Andersson C, Verder H *et al*. Extreme hyperbilirubinaemia in term and near-term infants in Denmark. *Acta Paediatrica* 2005; 94:(1)59–64.	Babies not tested for G6PD
Ebbesen F. Recurrence of kernicterus in term and near-term infants in Denmark. *Acta Paediatrica, International Journal of Paediatrics* 2000; 89:(10)1213–7.	Cases were not tested for G6PD deficiency
Emamghorashi F, Zendegani N, Rabiee S *et al*. Evaluation of urinary tract infection in newborns with jaundice in south of Iran. *Iranian Journal of Medical Sciences* 2008; 33:(1)17–21.	Jaundice as a predictor of UTI
Esbjorner E, Larsson P, Leissner P *et al*. The serum reserve albumin concentration for monoacetyldiaminodiphenyl sulphone and auditory evoked responses during neonatal hyperbilirubinaemia. *Acta Paediatrica Scandinavica* 1991; 80:(4)406–12.	Test not relevant to this guideline
Esbjorner E. Albumin binding properties in relation to bilirubin and albumin concentrations during the first week of life. *Acta Paediatrica Scandinavica* 1991; 80:(4)400–5.	Incomplete data
Eshaghpour E, Oski FA, and Williams M. The relationship of erythrocyte glucose-6-phosphate dehydrogenase deficiency to byperbilirubinemia in Negro premature infants. *Journal of Pediatrics* 1967; 70:(4)595–601.	Study on the impact of G6PD on exchange transfusion levels
Eslami Z and Sheikhha MH. Investigation of urinary tract infection in neonates with hyperbilirubinemia. *Journal of Medical Sciences* 2007; 7:(5)909–12.	Jaundice as a predictor for Urinary Tract Infections
Etzioni A, Shoshani G, Diamond E *et al*. Unconjugated hyperbilirubinaemia in hypertrophic pyloric stenosis, an enigma. *Zeitschrift fur Kinderchirurgie* 1986; 41:(5)272–4.	Not all subjects had jaundice
Fakhraee SH, Haji-Ebrahim-Tehrani F, Amid MH *et al*. Results of urine and blood cultures in healthy jaundiced newborns: Making the correct choice. *Archives of Iranian Medicine* 2002; 5:(2)88–90.	Tests for incidence of infections in babies with jaundice
Falcao AS, Fernandes A, Brito MA *et al*. Bilirubin-induced inflammatory response, glutamate release, and cell death in rat cortical astrocytes are enhanced in younger cells. *Neurobiology of Disease* 2005; 20:(2)199–206.	Animal test
Feld LG, Langford DJ, and Schwartz GJ. The effect of neonatal hyperbilirubinemia on the measurement of plasma creatinine. *Clinical Pediatrics* 1984; 23:(3)154–6.	Study on effect of jaundice on plasma creatinine
Feng CS, Wan CP, Lau J *et al*. Incidence of ABO haemolytic disease of the newborn in a group of Hong Kong babies with severe neonatal jaundice. *Journal of Paediatrics and Child Health* 1990; 26:(3)155–7.	Babies were only tested for ABO incompatibility
Finni K, Simila S, Koivisto M *et al*. Cholic acid, chenodeoxycholic acid, alpha-1-fetoprotein and alpha-1-antitrypsin serum concentrations in breast-fed infants with prolonged jaundice. *European Journal of Pediatrics* 1982; 138:(1)53–5.	Study for a single syndrome in prolonged jaundice
Finni K, Simila S, Koivisto M *et al*. Serum cholic acid and chenodeoxycholic acid concentrations in neonatal hyperbilirubinemia. *Biology of the Neonate* 1981; 40:(5–6)264–8.	Study for a single syndrome in prolonged jaundice
Fok TF, Lau SP, and Hui CW. Neonatal jaundice: its prevalence in Chinese babies and associating factors. *Australian Paediatric Journal* 1986; 22:(3)215–9.	Babies born by caesarean section were excluded

Reference	Reason for exclusion
Francauai J, Myara A, Benattar C *et al*. Investigation of total and conjugated bilirubin determination during the neonatal period. *European Journal of Clinical Chemistry and Clinical Biochemistry* 1993; 31:(8)499–502.	Not all subjects had jaundice
Fretzayas A, Kitsiou S, Tsezou A *et al*. UGT1A1 promoter polymorphism as a predisposing factor of hyperbilirubinaemia in neonates with acute pyelonephritis. *Scandinavian Journal of Infectious Diseases* 2006; 38:(6–7)537.	Case studies
Funato M, Tamai H, Shimada S *et al*. Vigintiphobia, unbound bilirubin, and auditory brainstem responses. *Pediatrics* 1994; 93:(1)50–3.	Tests not relevant to this guideline
Furuhjelm U, Nevanlinna HR, and Osterlund K. Early neonatal jaundice and hyperbilirubinaemia and their relation to ABO incompatibility. *Acta Paediatrica Scandinavica* 1967; 56:(5)477–84.	Babies with Rh incompatibility were excluded
Garbagnati E and Manitto P. A new class of bilirubin photoderivatives obtained in vitro and their possible formation in jaundiced infants. *Journal of Pediatrics* 1973; 83:(1)109–15.	Study of laboratory processes
Garcia FJ and Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. *Pediatrics* 2002; 109:(5)846–51.	Jaundice as a predictor of UTI
Ghaemi S, Fesharaki RJ, and Kelishadi R. Late onset jaundice and urinary tract infection in neonates. *Indian Journal of Pediatrics* 2007; 74:(2)139–41.	Rates of urinary tract infections in late-onset jaundice
Gibbs WN, Gray R, and Lowry M. Glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Jamaica. *British Journal of Haematology* 1979; 43:(2)263–74.	Babies with biliary obstruction were excluded
Gloria-Bottini F, Orzalesi M, Coccia M *et al*. Neonatal jaundice in ABO incompatible infants. Computer-assisted evaluation of risk of hyperbilirubinaemia and analysis of differences between sexes. *Computers and Biomedical Research* 1981; 14:(1)31–40.	Not tested for G6PD deficiency
Go JMR, Cocjin A, and Dee-Chan R. Jaundice as an early diagnostic sign of urinary tract infection in infants less than 8 weeks of age. *Santo Tomas Journal of Medicine* 2005; 52:(4)131–9.	Jaundice as a predictor of UTI
Goldberg PK, Kozinn PJ, Kodsi B *et al*. Endotoxemia and hyperbilirubinemia in the neonate. *American Journal of Diseases of Children* 1982; 136:(9)845–8.	Test not relevant to this guideline
Gotlieb A, Nir I, and Pesach J. Urinary excretion of free and conjugated glucuronic acid in jaundiced newborn. *Acta Paediatrica Scandinavica* 1971; 60:(4)437–40.	Tests not relevant to this guideline
Haimi-Cohen Y, Merlob P, Davidovitz M *et al*. Renal function in full-term neonates with hyperbilirubinemia. *Journal of Perinatology* 1997; 17:(3)225–7.	Effect of hyperbilirubinaemia on renal function
Hanka¸ E. Unbound bilirubin and risk assessment in the jaundiced newborn: possibilities and limitations. *Pediatrics* 2006; 117:(2)526–7.	Commentary
Hanko E. Unbound bilirubin and risk assessment in the jaundiced newborn: possibilities and limitations. *Pediatrics* 2006; 117:(2)526–7.	Commentary
Hargrove MD, Jr. and Van Sanders C. Extreme elevation in total serum bilirubin: a study of the causes in 32 consecutive cases. *Southern Medical Journal* 1971; 64:(2)213–7.	Subjects were adults with jaundice
Hawkins B. Immuno-serological studies of neonatal jaundice. *Journal of the Singapore Paediatric Society* 1972; 14:(2)101–6.	Babies were not tested for G6PD
Henriksen NT, Drablos PA, and Aagenaes O. Cholestatic jaundice in infancy. The importance of familial and genetic factors in aetiology and prognosis. *Archives of Disease in Childhood* 1981; 56:(8)622–7.	Examination of cholestatic jaundice
Herschel M, Karrison T, Wen M *et al*. Isoimmunization is unlikely to be the cause of hemolysis in ABO-incompatible but direct antiglobulin test-negative neonates. *Pediatrics* 2002; 110:(1 I)127–30.	Not all babies were not jaundiced

Reference	Reason for exclusion
Hitch DC, Leonard JC, Pysher TJ *et al*. Differentiation of cholestatic jaundice in infants. Utility of diethyl-IDA. *American Journal of Surgery* 1981; 142:(6)671–7.	Diagnosis of biliary atresia
Hon AT, Balakrishnan S, and Ahmad Z. Hyperbilirubinaemia and erythrocytic glucose 6 phosphate dehydrogenase deficiency in Malaysian children. *Medical Journal of Malaysia* 1989; 44:(1)30–4.	Only babies with G6PD deficiency tested
Howorth PJ. Determination of serum albumin in neonatal jaundice. The albumin saturation index. *Clinica Chimica Acta* 1971; 32:(2)271–8.	Comparison of two methods to measure serum albumin
Huang A, Tai BC, Wong LY *et al*. Differential risk for early breastfeeding jaundice in a multi-ethnic asian cohort. *Annals of the Academy of Medicine Singapore* 2009; 38:(3)217–24.	Babies less than 2500 g were excluded
Husain S and Pohowalla JN. Serum iron levels in jaundice in infancy and childhood. *Journal of the Indian Medical Association* 1969; 53:(5)237–40.	Test not relevant to this guideline
Hwang KC, Hsieh KH, and Chen JH. Immunological studies of newborn infants with hyperbilirubinemia. *Chinese Journal of Microbiology and Immunology* 1981; 14:(2)1–7.	Tests not relevant to this guideline
Jalloh S, Van RH, Yusoff NM *et al*. Poor correlation between hemolysis and jaundice in glucose 6-phosphate dehydrogenase-deficient babies. *Pediatrics International* 2005; 47:(3)258–61.	Incomplete data – number with blood group incompatibility were not reported
Jangaard KA, Fell DB, Dodds L *et al*. Outcomes in a population of healthy term and near-term infants with serum bilirubin levels of >or=325 micromol/L (>or=19 mg/dL) who were born in Nova Scotia, Canada, between 1994 and 2000. *Pediatrics* 2008; 122:(1)119–24.	Adverse effects of severe hyperbilirubinaemia
Javitt NB. Hyperbilirubinemic and cholestatic syndromes. New concepts aiding recognition and management. *Postgraduate Medicine* 1979; 65:(1)120–4.	Overview
Kaapa P. Immunoreactive thromboxane B2 and 6-keto-prostaglandin F1 alpha in neonatal hyperbilirubinemia. *Prostaglandins Leukotrienes and Medicine* 1985; 17:(1)97–105.	Only babies with idiopathic jaundice were included
Kaini NR, Chaudhary D, Adhikary V *et al*. Overview of cases and prevalence of jaundice in neonatal intensive care unit. *Nepal Medical College Journal: NMCJ* 2006; 8:(2)133–5.	Not test for G6PD deficiency
Kaplan M and Hammerman C. Understanding severe hyperbilirubinemia and preventing kernicterus: adjuncts in the interpretation of neonatal serum bilirubin. *Clinica Chimica Acta* 2005; 356:(1–2)9–21.	Overview
Kaplan M, Algur N, and Hammerman C. Onset of jaundice in glucose-6-phosphate dehydrogenase-deficient neonates. *Pediatrics* 2001; 108:(4)956–9.	Babies with blood group incompatibility were excluded
Kaplan M, Beutler E, Vreman HJ *et al*. Neonatal hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient heterozygotes. *Pediatrics* 1999; 104:(1 Pt 1)68–74.	Babies with a positive Coombs' text were excluded
Kaplan M, Rubaltelli FF, Hammerman C *et al*. Conjugated bilirubin in neonates with glucose-6-phosphate dehydrogenase deficiency. *Journal of Pediatrics* 1996; 128:(5 I)695–7.	Only babies with G6PD deficiency tested
Kavukcu S, Turkmen M, Polat M *et al*. Urinary enzyme changes in newborns with unconjugated hyperbilirubinemia. *Acta Paediatrica Japonica* 1997; 39:(Overseas Edition)-204.	Effect of hyperbilirubinaemia on renal function
Kedar PS, Warang P, Colah RB *et al*. Red cell pyruvate kinase deficiency in neonatal jaundice cases in India. *Indian Journal of Pediatrics* 2006; 73:(11)985–8.	Test not relevant to this guideline
Keenan WJ, Arnold JE, and Sutherland JM. Serum bilirubin binding determined by sephadex column chromatography. *Journal of Pediatrics* 1969; 74:(5)813.	Conference abstract

Reference	Reason for exclusion
Kilic M, Turgut M, Taskin E *et al*. Nitric oxide levels and antioxidant enzyme activities in jaundices of premature infants. *Cell Biochemistry and Function* 2004; 22:(5)339–42.	Babies with ABO or Rh incompatibility were excluded
Kirk JM. Neonatal jaundice: a critical review of the role and practice of bilirubin analysis. *Annals of Clinical Biochemistry* 2008; 45:(Pt 5)452–62.	Overview
Knudsen A. The influence of the reserve albumin concentration and pH on the cephalocaudal progression of jaundice in newborns. *Early Human Development* 1991; 25:(1)37–41.	Babies were not pre-selected for jaundice
Kulkarni SV, Merchant RH, Gupte SC *et al*. Clinical significance of serum and cerebro spinal fluid bilirubin indices in neonatal jaundice. *Indian Pediatrics* 1989; 26:(12)1202–8.	Test (cerebro-spinal fluid bilirubin) not relevant to this guideline
Kumar A, Pant P, Basu S *et al*. Oxidative stress in neonatal hyperbilirubinemia. *Journal of Tropical Pediatrics* 2007; 53:(1)69–71.	Test not relevant to this guideline
Kumral A, Genc S, Genc K *et al*. Hyperbilirubinemic serum is cytotoxic and induces apoptosis in murine astrocytes. *Biology of the Neonate* 2005; 87:(2)99–104.	Study examining the effect of hyperbilirubinaemic serum on murine astrocytees
Lai HC, Lai MP, and Leung KS. Glucose-6-phosphate dehydrogenase deficiency in Chinese. *Journal of Clinical Pathology* 1968; 21:(1)44–7.	Only tested for G6PD
Lee HC, Fang SB, Yeung CY *et al*. Urinary tract infections in infants: comparison between those with conjugated vs unconjugated hyperbilirubinaemia. *Annals of Tropical Paediatrics* 2005; 25:(4)277–82.	Comparison of urinary tract infection rates in conjugated and unconjugated hyperbilirubinaemia
Lee KS and Gartner LM. Management of unconjugated hyperbilirubinemia in the newborn. *Seminars in Liver Disease* 1983; 3:(1)52–64.	Overview
Lee WS, McKiernan PJ, Beath SV *et al*. Bile bilirubin pigment analysis in disorders of bilirubin metabolism in early infancy. *Archives of Disease in Childhood* 2001; 85:(1)38–42.	Study for a single syndrome in prolonged jaundice
Leung AK. Screening of jaundiced neonates for glucose-6-phosphate dehydrogenase deficiency. *Southern Medical Journal* 1987; 80:(2)217–8.	Babies were not tested for blood group incompatibility
Lie-Injo LE, Virik HK, Lim PW *et al*. Red cell metabolism and severe neonatal jaundice in West Malaysia. *Acta Haematologica* 1977; 58:(3)152–60.	Babies with isoimmunisation were excluded
Lin M, Shieh SH, Hwang FY *et al*. The Le(a) antigen and neonatal hyperbilirubinemia in Taiwan. *Vox Sanguinis* 1995; 69:(2)131–4.	Babies with blood group incompatibility or G6PD were excluded
Linder N, Yatsiv I, Tsur M *et al*. Unexplained neonatal jaundice as an early diagnostic sign of septicemia in the newborn. *Journal of Perinatology* 1988; 8:(4)325–7.	Test not relevant to guideline
MacKinlay GA. Jaundice persisting beyond 14 days after birth. *British Medical Journal* 1993; 306:(6890)1426–7.	Overview
Madan N and Sood SK. Role of G6PD, ABO incompatibility, low birth weight and infection in neonatal hyperbilirubinaemia. *Tropical and Geographical Medicine* 1987; 39:(2)163–8.	Babies with Rh incompatibility were excluded
Madan N, Sundaram KR, Bhargava SK *et al*. Glucose-6-phosphate dehydrogenase deficiency and neonatal hyperbilirubinaemia. *Indian Journal of Medical Research* 1989; 90:306–13.	Babies were not tested for blood group incompatibility
Maisels MJ and Kring E. Risk of sepsis in newborns with severe hyperbilirubinemia. *Pediatrics* 1992; 90:(5)741–3.	Babies were not tested for G6PD deficiency
Maisels MJ, Newman TB, Garcia FJ *et al*. Neonatal Jaundice and Urinary Tract Infections. *Pediatrics* 2003; 112:(5)1213–4.	Correspondence

Reference	Reason for exclusion
Martin TC, Shea M, Alexander D *et al*. Did exclusive breast-feeding and early discharge lead to excessive bilirubin levels in newborns in Antigua and Barbuda? *West Indian Medical Journal* 2002; 51:(2)84–8.	Babies were not tested for G6PD
Maruo Y, Nishizawa K, Sato H *et al*. Association of neonatal hyperbilirubinemia with bilirubin UDP- glucuronosyltransferase polymorphism. *Pediatrics* 1999; 103:(6 I)1224–7.	Genetic test not relevant to this guideline
Maruo Y, Nishizawa K, Sato H *et al*. Prolonged unconjugated hyperbilirubinemia associated with breast milk and mutations of the bilirubin uridine diphosphate- glucuronosyltransferase gene. *Pediatrics* 2000; 106:(5)E59.	A single genetic test
Marwaha N, Sarode R, Marwaha RK *et al*. Bilirubin crystals in peripheral blood smears from neonates with unconjugated hyperbilirubinaemia. *Medical Laboratory Sciences* 1990; 47:(4)278–81.	Test already routinely done
McClean P. Recognizing liver disease in jaundiced infants. *British Journal of Midwifery* 2008; 16:(2)106–9.	Overview
McCulloch JC. Red cell potassium levels in neonatal jaundice –a preliminary study. *Medical Laboratory Sciences* 1977; 34:(2)115–22.	Not tested for blood group incompatibility
McDonagh AF. Ex uno plures: The concealed complexity of bilirubin species in neonatal blood samples. *Pediatrics* 2006; 118:(3)1185–7.	Review
McKiernan PJ. Neonatal cholestasis. *Seminars in Neonatology* 2002; 7:(2)153–65.	Overview
McKiernan PJ. The infant with prolonged jaundice: Investigation and management. *Current Paediatrics* 2001; 11:(2)83–9.	Overview
Meisel P, Jahrig D, Beyersdorff E *et al*. Bilirubin binding and acid-base equilibrium in newborn infants with low birthweight. *Acta Paediatrica Scandinavica* 1988; 77:(4)496–501.	Effect of acid-base on bilirubin-albumin binding
Meyers RL, Book LS, O'Gorman MA *et al*. Percutaneous Cholecysto-Cholangiography in the Diagnosis of Obstructive Jaundice in Infants. *Journal of Pediatric Surgery* 2004; 39:(1)16–8.	Tests not relevant to this quideline
Monaghan G, McLellan A, McGeehan A *et al*. Gilbert's syndrome is a contributory factor in prolonged unconjugated hyperbilirubinemia of the newborn. *Journal of Pediatrics* 1999; 134:(4)441–6.	Test for a single syndrome in prolonged jaundice
Moyer V, Freese DK, Whitington PF *et al*. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2004; 39:(2)115–28.	Guideline for Cholestatic jaundice
Muslu N, Dogruer ZN, Eskandari G *et al*. Are glutathione S-transferase gene polymorphisms linked to neonatal jaundice? *European Journal of Pediatrics* 2008; 167:(1)57–61.	Tests not relevant to this guideline
Muslu N, Turhan AB, Eskandari G *et al*. The frequency of UDP-glucuronosyltransferase 1 A1 promoter region (TA)7 polymorphism in newborns and it's relation with jaundice. *Journal of Tropical Pediatrics* 2007; 53:(1)64–8.	Correspondence
Nair RR, Murty JS, Rao MN *et al*. ABO incompatibility and neonatal jaundice. *Indian Journal of Medical Research* 1980; 71:567–75.	Babies were not tested for G6PD
Nakamura H, Lee Y, and Takemoto H. Effects of photo-irradiation on bilirubin binding affinity of icteric sera. *Kobe Journal of Medical Sciences* 1981; 27:(2)59–69.	Effects of phototherapy on total and unbound bilirubin
Nakamura H, Takada S, Shimabuku R *et al*. Auditory nerve and brainstem responses in newborn infants with hyperbilirubinemia. *Pediatrics* 1985; 75:(4)703–8.	Study of auditory brainstem responses
Nakamura H, Yonetani M, Uetani Y *et al*. Determination of serum unbound bilirubin for prediction of kernicterus in low birthweight infants. *Acta Paediatrica Japonica* 1992; 34:(6)642–7.	Predictive accuracy of two bilirubin levels for predicting kernicterus

Reference	Reason for exclusion
Nelson BT. Jaundice survey: Grenada, West Indies. *International Pediatrics* 1998; 13:(3)150–4.	Only 1 in 4 babies were tested for G6PD
Newman TB and Easterling MJ. Yield of reticulocyte counts and blood smears in term infants. *Clinical Pediatrics* 1994; 33:(2)71–6.	No tests for G6PD
Newman TB and Maisels MJ. Evaluation and treatment of jaundice in the term newborn: a kinder, gentler approach. *Pediatrics* 1992; 89:(5 Pt 1)809–18.	Overview
Newman TB, Liljestrand P, and Escobar GJ. Infants with bilirubin levels of 30 mg/dL or more in a large managed care organization. *Pediatrics* 2003; 111:(6 I)1303–11.	G6PD test not carried out on all babies
Newman TB, Liljestrand P, Jeremy RJ *et al*. Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more. *New England Journal of Medicine* 2006; 354:(18)1889–900.	Not all babies tested
Nong SH, Xie YM, Chan KW *et al*. Severe hyperbilirubinaemia in a Chinese girl with type I Crigler-Najjar syndrome: First case ever reported in Mainland China. *Journal of Paediatrics and Child Health* 2005; 41:(5–6)300–6.	Case study
Nowicki MJ and Poley JR. The hereditary hyperbilirubinaemias. *Bailliere's Clinical Gastroenterology* 1998; 12:(2)355–67.	Overview
Odell GB, Cohen SN, and Kelly PC. Studies in kernicterus. II. The determination of the saturation of serum albumin with bilirubin. *Journal of Pediatrics* 1969; 74:(2)214–30.	Test not relevant to this guideline
Odell GB, Storey GN, and Rosenberg LA. Studies in kernicterus. 3. The saturation of serum proteins with bilirubin during neonatal life and its relationship to brain damage at five years. *Journal of Pediatrics* 1970; 76:(1)12–21.	Test not relevant to this guideline
Odell GB. Neonatal jaundice. *Progress in Liver Diseases* 1976; 5:457–75.	Overview – background information only
Ogita S, Shimamoto T, Ohnishi M *et al*. Hemolytic pattern of erythrocytes in the newborn measured by the coil planet centrifuge system and its relationship to neonatal jaundice. *European Journal of Pediatrics* 1978; 127:(2)67–73.	Laboratory tests
Oktay R, Satar M, and Atici A. The risk of bilirubin encephalopathy in neonatal hyperbilirubinemia. *Turkish Journal of Pediatrics* 1996; 38:(2)199–204.	Link between free bilirubin and bilirubin encephalopathy
Okumus N, Turkyilmaz C, Onal EE *et al*. Tau and S100B proteins as biochemical markers of bilirubin-induced neurotoxicity in term neonates. *Pediatric Neurology* 2008; 39:(4)245–52.	Babies with sepsis were excluded
Olah VA, Csathy L, and Karmazsin L. Erythrocyte damage in newborn babies caused by hyperbilirubinaemia and hypoxia. *Acta Paediatrica Hungarica* 1991; 31:(3)357–64.	Tests not relevant to this guideline
Ostrea EM, Jr., Bassel M, Fleury CA *et al*. Influence of free fatty acids and glucose infusion on serum bilirubin and bilirubin binding to albumin: clinical implications. *Journal of Pediatrics* 1983; 102:(3)426–32.	Study of the saturation index – test not relevant to this guideline
Ostrea EM, Jr., Ongtengco EA, Tolia VA *et al*. The occurrence and significance of the bilirubin species, including delta bilirubin, in jaundiced infants. *Journal of Pediatric Gastroenterology and Nutrition* 1988; 7:(4)511–6.	Tests not relevant to this guideline
Ostrow JD. Photochemical and biochemical basis of the treatment of neonatal jaundice. *Progress in Liver Diseases* 1972; 4:447–62.	Overview
Ou CN, Buffone GJ, Herr-Calomeni PJ *et al*. Unconjugated hyperbilirubinemia is overestimated in neonates with cholestasis. A more reliable method is proposed. *American Journal of Clinical Pathology* 1985; 84:(6)752–6.	Not all subjects were newborn
Owa JA and Dawodu AH. Neonatal jaundice among Nigerian preterm infants. *East African Medical Journal* 1988; 65:(8)552–6.	Only preterm babies were included
Owa JA and Dawodu AH. Neonatal jaundice among Nigerian preterm infants. *West African Journal of Medicine* 1990; 9:(4)252–7.	Only preterm babies were included

Reference	Reason for exclusion
Owa JA, Durosinmi MA, and Alabi AO. Determinants of severity of neonatal hyperbilirubinaemia in ABO incompatibility in Nigeria. *Tropical Doctor* 1991; 21:(1)19–22.	Study only included babies with ABO incompatibility
Palmer DC and Drew JH. Jaundice: a 10 year review of 41,000 live born infants. *Australian Paediatric Journal* 1983; 19:(2)86–9.	Study was superseded by a 15 year analysis of this data
Pashapour N, Nikibahksh AA, and Golmohammadlou S. Urinary tract infection in term neonates with prolonged jaundice. *Urology Journal* 2007; 4:(2)91–4.	Babies were only tested for urinary tract infections
Pays M and Beljean M. Microdetermination of unbound bilirubin. Application to the prevention of kernicterus by estimation of the serum bilirubin binding capacity in neonatal hyperbilirubinemia. *Zeitschrift fur Klinische Chemie und Klinische Biochemie* 1974; 12:(5)250–1.	Conference abstract
Penberthy L, St JA, and Blake G. Bilirubin analyses in neonatal jaundice. *Medical Journal of Australia* 1978; 1:(12)659.	Correspondence
Polacek K. Risk of kernicterus in newborn infants with a high level of conjugated bilirubin. *Acta Paediatrica Scandinavica* 1966; 55:(4)401–4.	Only babies with conjugated hyperbilirubinaemia were included
Priolisi A and Ziino L. Comparative analysis between the reserve albumin-binding capacity (HBABA method) and the saturation index of hyperbilirubinemic sera. *Biology of the Neonate* 1971; 19:(4)258–71.	Tests not relevant to guideline
Priolisi A. Clinical experience with Sephadex gel filtration for the estimation of non-albumin bound bilirubin in sera of jaundiced infants. *Birth Defects: Original Article Series* 1976; 12:(2)245–54.	No test for G6PD
Rastogi D and Rastogi S. Neonatal hyperbilirubinemia in healthy breast-fed newborn: Assessment at discharge. *Emergency and Office Pediatrics* 1999; 12:(3)100–2.	Case study
Ratnavel N and Ives NK. Investigation of prolonged neonatal jaundice. *Current Paediatrics* 2005; 15:(2)85–91.	Overview
Rehman H, Khan MA, Hameed A *et al*. Erythrocyte glucose 6 phosphate dehydrogenase deficiency and neonatal jaundice. *JPMA - Journal of the Pakistan Medical Association* 1995; 45:(10)259–60.	Incomplete data – numbers with blood group incompatibility not given
Reiser DJ. Neonatal jaundice: physiologic variation or pathologic process. *Critical Care Nursing Clinics of North America* 2004; 16:(2)257–69.	Overview
Ritter DA, Kenny JD, Norton HJ *et al*. A prospective study of free bilirubin and other risk factors in the development of kernicterus in premature infants. *Pediatrics* 1982; 69:(3)260–6.	Not all babies who died had an autopsy
Rolinski B, Kuster H, Ugele B *et al*. Total bilirubin measurement by photometry on a blood gas analyzer: potential for use in neonatal testing at the point of care. *Clinical Chemistry* 2001; 47:(10)1845–7.	Comparison of methods to measure serum bilirubin
Roux P, Karabus CD, and Hartley PS. The effect of glucose-6-phosphate dehydrogenase deficiency on the severity of neonatal jaundice in Cape Town. *South African Medical Journal* 1982; 61:(21)781–2.	Babies with blood group incompatibility were excluded
Sansone G, Perroni L, and Yoshida A. Glucose-6-phosphate dehydrogenase variants from Italian subjects associated with severe neonatal jaundice. *British Journal of Haematology* 1975; 31:(2)159–65.	Three cases studies
Sarici SU, Serdar MA, Erdem G *et al*. Evaluation of plasma ionized magnesium levels in neonatal hyperbilirubinemia. *Pediatric Research* 2004; 55:(2)243–7.	Babies with ABO/Rh incompatibility or G6PD deficiency were excluded
Sarma DK, Shukla R, Lodha A *et al*. Neonatal screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency: Experience in a private hospital. *Emirates Medical Journal* 2006; 24:(3)211–4.	Babies only tested for G6PD deficiency

Reference	Reason for exclusion
Sasanakul W, Hathirat P, Jeraporn K *et al*. Neonatal jaundice and glucose-6-phosphate dehydrogenase deficiency. *Journal of the Medical Association of Thailand* 1989; 72 Suppl 1:130–2.	Babies were not tested for blood group incompatibility
Satar M, Atici A, and Oktay R. The influence of clinical status on total bilirubin binding capacity in newborn infants. *Journal of Tropical Pediatrics* 1996; 42:(1)43–5.	Test not relevant to this guideline – bilirubin binding capacity
Scheidt PC, Graubard BI, Nelson KB *et al*. Intelligence at six years in relation to neonatal bilirubin levels: follow-up of the National Institute of Child Health and Human Development Clinical Trial of Phototherapy. *Pediatrics* 1991; 87:(6)797–805.	Long term outcomes from an included RCT
Schiff D, Chan G, and Stern L. Proceedings: Clinical implications of bilirubin-albumin binding in the newborn. *Revue Canadienne de Biologie* 1973; 32:(Suppl)-8.	Comparison of two test to measure bilirubin-albumin binding
Settin A, Al-Haggar M, Al-Baz R *et al*. Screening for G6PD Mediterranean mutation among Egyptian neonates with high or prolonged jaundice. *HAEMA* 2006; 9:(1)81–8.	Single test only
Shenoi UD and Nandi GK. Bilirubin crystals in neutrophils in neonatal hyperbilirubinaemia. *Indian Journal of Pediatrics* 1997; 64:(1)93–6.	Tests not relevant to this guideline
Siklar Z, Tezer H, Dallar Y *et al*. Borderline congenital hypothyroidism in the neonatal period. *Journal of Pediatric Endocrinology* 2002; 15:(6)817–21.	Test not relevant to guideline
Singh B, Ezhilarasan R, Kumar P *et al*. Neonatal hyperbilirubinemia and its association with thyroid hormone levels and urinary iodine excretion. *Indian Journal of Pediatrics* 2003; 70:(4)311–5.	Tests not relevant to this guideline
Slusher TM, Vreman HJ, McLaren DW *et al*. Glucose-6-phosphate dehydrogenase deficiency and carboxyhemoglobin concentrations associated with bilirubin-related morbidity and death in Nigerian infants. *Journal of Pediatrics* 1995; 126:(1)102–8.	Babies were not tested for ABO incompatibility
Spear ML, Stahl GE, Hamosh M *et al*. Effect of heparin dose and infusion rate on lipid clearance and bilirubin binding in premature infants receiving intravenous fat emulsions. *Journal of Pediatrics* 1988; 112:(1)94–8.	Not all babies were jaundiced
Tateno M. Relationship between the serum transaminase activities and the serum bilirubin concentration in the icterus neonatorum. *Acta Obstetrica et Gynaecologica Japonica* 1970; 17:(4)239–44.	Tests not relevant to this guideline
Tazawa Y and Konno T. Urinary monohydroxy bile acids in young infants with obstructive jaundice. *Acta Paediatrica Scandinavica* 1982; 71:(1)91–5.	Not all subjects newborn
Tazawa Y, Abukawa D, Watabe M *et al*. Abnormal results of biochemical liver function tests in breast-fed infants with prolonged indirect hyperbilirubinaemia. *European Journal of Pediatrics* 1991; 150:(5)310–3.	Study for a single syndrome in prolonged jaundice
Tazawa Y, Yamada M, Nakagawa M *et al*. Serum bile acids and their conjugates in breast-fed infants with prolonged jaundice. *European Journal of Pediatrics* 1985; 144:(1)37–40.	Test for a single disease
Thaler MM. Jaundice in the newborn. Algorithmic diagnosis of conjugated and unconjugated hyperbilirubinemia. *JAMA: the journal of the American Medical Association* 1977; 237:(1)58–62.	Overview
Tiker F, Gurakan B, and Tarcan A. Relationship between serum bilirubin and coagulation test results in 1-month-old infants. *Indian Journal of Pediatrics* 2005; 72:(3)205–7.	Test not relevant to this guideline
Turgut M, Basaran O, Cekmen M *et al*. Oxidant and antioxidant levels in preterm newborns with idiopathic hyperbilirubinaemia. *Journal of Paediatrics and Child Health* 2004; 40:(11)633–7.	Babies with ABO or Rh incompatibility were excluded
Uetani Y, Nakamura H, Okamoto O *et al*. Carboxyhemoglobin measurements in the diagnosis of ABO hemolytic disease. *Acta Paediatrica Japonica* 1989; 31:171–6.	Test not relevant to this guideline

Reference	Reason for exclusion
Ullrich D, Fevery J, Sieg A *et al*. The influence of gestational age on bilirubin conjugation in newborns. *European Journal of Clinical Investigation* 1991; 21:(1)83–9.	Babies with hepatic diseases were excluded
Vaca G, Ibarra B, Hernandez A *et al*. Glucose-6-phosphate dehydrogenase deficiency and abnormal hemoglobins in mexican newborns with jaundice. *Revista de Investigacion Clinica* 1981; 33:(3)259–61.	Unclear if all babies were tested for blood group incompatibility
Vos GH, Adhikari M, and Coovadia HM. A study of ABO incompatibility and neonatal jaundice in Black South African newborn infants. *Transfusion* 1981; 21:(6)744–9.	Babies were not tested for G6PD
Voutetakis A, Maniati-Christidi M, Kanaka-Gantenbein C *et al*. Prolonged jaundice and hypothyroidism as the presenting symptoms in a neonate with a novel Prop1 gene mutation (Q83X). *European Journal of Endocrinology* 2004; 150:(3)257–64.	Case study
Weiss JS, Gautam A, Lauff JJ *et al*. The clinical importance of a protein-bound fraction of serum bilirubin in patients with hyperbilirubinemia. *New England Journal of Medicine* 1983; 309:(3)147–50.	Not all subjects had jaundice
Wennberg R. Unbound bilirubin: a better predictor of kernicterus? *Clinical Chemistry* 2008; 54:(1)207–8.	Opinion piece
Wolf MJ, Beunen G, Casaer P *et al*. Extreme hyperbilirubinaemia in Zimbabwean neonates: neurodevelopmental outcome at 4 months. *European Journal of Pediatrics* 1997; 156:(10)803–7.	Babies were not tested for G6PD
Wolf MJ, Beunen G, Casaer P *et al*. Neurological status in severely jaundiced Zimbabwean neonates. *Journal of Tropical Pediatrics* 1998; 44:(3)161–4.	Babies were not tested for G6PD
Wolf MJ, Wolf B, Beunen G *et al*. Neurodevelopmental outcome at 1 year in Zimbabwean neonates with extreme hyperbilirubinaemia. *European Journal of Pediatrics* 1999; 158:(2)111–4.	Babies were not tested for G6PD
Wolff JA, Grossman BH, and Paya K. Neonatal serum bilirubin and glucose-6-phosphate dehydrogenase. Relationship of various perinatal factors to hyperbilirubinemia. *American Journal of Diseases of Children* 1967; 113:(2)251–4.	Babies were not tested for blood group incompatibility
Woodfield DG and Biddulph J. Neonatal jaundice and glucose-6-phosphate dehydrogenase deficiency in Papua New Guinea. *Medical Journal of Australia* 1975; 1:(14)443–6.	Follow-up of an included study
Yamada M, Tazawa Y, Nakagawa M *et al*. Alterations of serum bile acid profile in breast-fed infants with prolonged jaundice. *Journal of Pediatric Gastroenterology and Nutrition* 1985; 4:(5)741–5.	Effect of prolonged jaundice on serum bile acid profile
Yamauchi Y and Yamanouchi I. Transcutaneous bilirubinometry: Bilirubin kinetics of the skin and serum during and after phototherapy. *Biology of the Neonate* 1989; 56:(5)263–9.	No test for G6PD
Yen HJ, Chen SJ, Soong WJ *et al*. Analysis of test of hemolytic disease in newborn with neonatal hyperbilirubinemia. *Clinical Neonatology* 2005; 12:(1)1–5.	Study compared babies with haemolytic disease of the newborn with controls
Yu MW, Hsiao KJ, Wuu KD *et al*. Association between glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice: interaction with multiple risk factors. *International Journal of Epidemiology* 1992; 21:(5)947–52.	Not all babies tested for blood group incompatibility
Yurdakok M and Yilmazoglu G. Gamma-glutamyl transferase in neonatal non-hemolytic indirect hyperbilirubinemia. *Turkish Journal of Pediatrics* 1990; 32:(1)21–3.	Test not relevant to this guideline

Phototherapy

Reference	Reason for exclusion
Amato M, Howald H, and von MG. Interruption of breast-feeding versus phototherapy as treatment of hyperbilirubinemia in full-term infants. *Helvetica Paediatrica Acta* 1985; 40:(2–3)127–31.	Not all babies received phototherapy
Boo NY and Chew EL. A randomised control trial of clingfilm for prevention of hypothermia in term infants during phototherapy. *Singapore Medical Journal* 2006; 47:(9)757–62.	Intervention to prevent hypothermia
Boo NY, Chee SC, and Rohana J. Randomized controlled study of the effects of different durations of light exposure on weight gain by preterm infants in a neonatal intensive care unit. *Acta Paediatrica* 2002; 91:(6)674–9.	No jaundice-related outcomes
Brown AK, Kim MH, Wu PY *et al*. Efficacy of phototherapy in prevention and management of neonatal hyperbilirubinemia. *Pediatrics* 1985; 75:(2 Pt 2)393–400.	Secondary publication of NICHHD study
Bryla DA. Randomized, controlled trial of phototherapy for neonatal hyperbilirubinemia. Development, design, and sample composition. *Pediatrics* 1985; 75:(2 Pt 2)387–92.	Secondary publication of NICHHD study
Costarino AT, Ennever JF, Baumgart S *et al*. Bilirubin photoisomerization in premature neonates under low- and high-dose phototherapy. *Pediatrics* 1985; 75:(3)519–22.	Not an RCT
Costarino AT, Jr., Ennever JF, Baumgart S *et al*. Effect of spectral distribution on isomerization of bilirubin in vivo. *Journal of Pediatrics* 1985; 107:(1)125–8.	Not an RCT
Donzelli GP, Moroni M, Pratesi S *et al*. Fibreoptic phototherapy in the management of jaundice in low birthweight neonates. *Acta Paediatrica* 1996; 85:(3)366–70.	Not an RCT
Eggert LD, Pollary RA, Folland DS *et al*. Home phototherapy treatment of neonatal jaundice. *Pediatrics* 1985; 76:(4)579–84.	Home phototherapy not relevant to this guideline
Elliott E, Moncrieff MW, and George WH. Phototherapy for hyperbilirubinaemia in low birthweight infants. *Archives of Disease in Childhood* 1974; 49:(1)60–2.	Not an RCT
Ennever JF, Knox I, and Speck WT. Differences in bilirubin isomer composition in infants treated with green and white light phototherapy. *Journal of Pediatrics* 1986; 109:(1)119–22.	Not an RCT
Fiberoptic phototherapy systems. *Health Devices* 1995; 24:(4)132–53.	Not an RCT
Finlay HVL and Tucker SM. Neonatal plasma bilirubin chart. *Archives of Disease in Childhood* 2009; 53:(1)90.	Background information
Fuller J. Home phototherapy. *Caring* 1990; 9:(12)8–11.	Home phototherapy not relevant to this guideline
Garg AK, Prasad RS, and Hifzi IA. A controlled trial of high-intensity double-surface phototherapy on a fluid bed versus conventional phototherapy in neonatal jaundice. *Pediatrics* 1995; 95:(6)914–6.	Not an RCT
George P and Lynch M. Ohmeda Biliblanket vs Wallaby Phototherapy System for the reduction of bilirubin levels in the home-care setting. *Clinical Pediatrics* 1994; 33:(3)178–80.	Comparison of two types of fibreoptic phototherapy
Giunta F and Rath J. Effect of environmental illumination in prevention of hyperbilirubinemia of prematurity. *Pediatrics* 1969; 44:(2)162–7.	Not an RCT

Reference	Reason for exclusion
Hammerman C and Kaplan M. Comparative effects of two phototherapy delivery systems on cerebral blood flow velocity in term neonates. *Biology of the Neonate* 2004; 86:(4)254–8.	Not an RCT
Hohenauer L, Haschke F, and Gerstl JW. [Fototherapy of neonatal hyperbilirubinemia. Results of its clinical application (author's transl)]. [German]. *Klinische Padiatrie* 1976; 188:(4)314–9.	Non-English language articles
Ittmann PE and Schumacher PI. Blue light special: randomized trial of fiberoptic phototherapy in preterm infants. *Pediatric Research* 1992; 31:205A.	Conference abstract
Jackson CL, Tudehope D, Willis L *et al*. Home phototherapy for neonatal jaundice--technology and teamwork meeting consumer and service need. *Australian Health Review* 2000; 23:(2)162–8.	Not an RCT
Jaldo-Alba F, Munoz-Hoyos A, Molina-Carballo A *et al*. Light deprivation increases plasma levels of melatonin during the first 72 h of life in human infants. *Acta Endocrinologica* 1993; 129:(5)442–5.	Not an RCT
Kang JH and Shankaran S. Double phototherapy with high irradiance compared with single phototherapy in neonates with hyperbilirubinemia. *American Journal of Perinatology* 1995; 12:(3)178–80.	Not an RCT
Kaplan E, Herz F, Scheye E *et al*. Phototherapy in ABO hemolytic disease of the newborn infant. *Journal of Pediatrics* 1971; 79:(6)911–4.	Not an RCT
Kaplan M and Abramov A. Neonatal hyperbilirubinemia associated with glucose-6-phosphate dehydrogenase deficiency in Sephardic-Jewish neonates: Incidence, severity, and the effect of phototherapy. *Pediatrics* 1992; 90:(3 I)401–5.	Effect of G6PD deficiency status of phototherapy
Kurt A, Aygun AD, Kurt ANC *et al*. Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. *Neonatology* 2009; 95:(3)262–6.	Outcome not relevant to this guideline
Landry RJ, Scheidt PC, and Hammond RW. Ambient light and phototherapy conditions of eight neonatal care units: A summary report. *Pediatrics* 1985; 75:(2 II SUPPL.)434–6.	Not an RCT
Lemaitre BJ, Toubas PL, Dreux C *et al*. Increased gonadotropin levels in newborn premature females treated by phototherapy. *Journal of Steroid Biochemistry* 1979; 10:(3)335–7.	Outcome was not relevant to this guideline
Lucey J, Ferriero M, and Hewitt J. Prevention of hyperbilirubinemia of prematurity by phototherapy. *Pediatrics* 1968; 41:(6)1047–54.	Not an RCT
Ludington-Hoe SM and Swinth JY. Kangaroo mother care during phototherapy: effect on bilirubin profile. *Neonatal Network - Journal of Neonatal Nursing* 2001; 20:(5)41–8.	Comparison of three methods of giving 24 hour phototherapy
Maisels MJ and Gifford K. Normal serum bilirubin levels in the newborn and the effect of breast-feeding. *Pediatrics* 1986; 78:(5)837–43.	Not an RCT
Maisels MJ, Kring EA, and DeRidder J. Randomized controlled trial of light-emitting diode phototherapy. *Journal of Perinatology* 2007; 27:(9)565–7.	Comparison of two methods of applying multiple phototherapy
Maurer, H. M.; Fratkin, M.; McWilliams, N. B.; Kirkpatrick, B.; Draper, D.; Haggins, J. C.; Hunter, C. R. Effects of Phototherapy on Platelet Counts in Low-Birthweight Infants and on Platelet Production and Life Span in Rabbits. *Pediatrics* **1976,** *57,* 506–512.	No jaundice related outcomes
Mohapatra SS, Menon PS, Bhan MK *et al*. Cockington nomogram as a guide to phototherapy in the management of neonatal hyperbilirubinemia: evaluation in Indian neonates. *Indian Pediatrics* 1984; 21:(3)229–33.	Comparison of two criteria for managing hyperbilirubinaemia
Newman T, Kuzniewicz M, Liljestrand P *et al*. Numbers Needed to Treat with Phototherapy According to American Academy of Pediatrics Guidelines. *Pediatrics* . 2009.	Background information

Reference	Reason for exclusion
Niknafs P, Mortazavi AA, Torabinejad MH *et al*. Intermittent versus continuous phototherapy for reducing neonatal hyperbilirubinemia. *Iranian Journal of Pediatrics* 2008; 18:(3)251–6.	Comparison of two forms of intermittent phototherapy
Ozkan H, Olgun N, Oren H *et al*. The effect of phototherapy on total phospholipid levels of red cell membrane in jaundiced neonates. *Indian Journal of Pediatrics* 1993; 60:(4)600–2.	Not an RCT
Ozmert E, Erdem G, Topcu M *et al*. Long-term follow-up of indirect hyperbilirubinemia in full-term Turkish infants. *Acta Paediatrica* 1996; 85:(12)1440–4.	Not an RCT
Pezzati M, Biagiotti R, Vangi V *et al*. Changes in mesenteric blood flow response to feeding: Conventional versus fiber-optic phototherapy. *Pediatrics* 2000; 105:(2)350–3.	Not an RCT
Pritchard MA, Beller EM, and Norton B. Skin exposure during conventional phototherapy in preterm infants: A randomized controlled trial. *Journal of Paediatrics and Child Health* 2004; 40:(5–6)270–4.	Comparison of two combinations of positioning combined with clothing
Randomized, controlled trial of phototherapy for neonatal hyperbilirubinemia. Executive summary. *Pediatrics* 1985; 75:(2 Pt 2)385–6.	Executive summary
Reid MM, Marks E, McClure G *et al*. Phototherapy in rhesus haemolytic disease. *Lancet* 1972; 1:(7756)879–80.	Not an RCT
Rosenfeld W, Twist P, and Concepcion L. A new device for phototherapy treatment of jaundiced infants. *Journal of Perinatology* 1990; 10:(3)243–8.	Not an RCT
Sarici SU, Alpay F, Unay B *et al*. Comparison of the efficacy of conventional special blue light phototherapy and fiberoptic phototherapy in the management of neonatal hyperbilirubinaemia. *Acta Paediatrica* 1999; 88:(11)1249–53.	Not an RCT
Sarici SU, Alpay F, Unay B *et al*. Double versus single phototherapy in term newborns with significant hyperbilirubinemia. *Journal of Tropical Pediatrics* 2000; 46:(1)36–9.	Not an RCT
Sarin M, Dutta S, and Narang A. Randomized controlled trial of compact fluorescent lamp versus standard phototherapy for the treatment of neonatal hyperbilirubinemia. *Indian Pediatrics* 2006; 43:(7)583–90.	Comparison of two types of fluorescent lamps
Scheidt PC, Bryla DA, Nelson KB *et al*. Phototherapy for neonatal hyperbilirubinemia: six-year follow-up of the National Institute of Child Health and Human Development clinical trial. *Pediatrics* 1990; 85:(4)455–63.	Follow-up of an included study
Sharma SK, Sood SC, Sharma A *et al*. Double versus single surface phototherapy in neonatal hyperbilirubinemia. *Indian Pediatrics* 1985; 22:(3)235–9.	Not an RCT
Srivastava KL, Misra PK, Kaul R *et al*. Double surface phototherapy versus single surface phototherapy in neonatal jaundice. *Indian Journal of Medical Research* 1980; 71:746–50.	Not an RCT
Tabb PA, Savage DC, Inglis J *et al*. Controlled trial of phototherapy of limited duration in the treatment of physiological hyperbilirubinaemia in low-birth-weight infants. *Lancet* 1972; 2:(7789)1211–2.	Incomplete data – 1 case of exchange transfusion but group allocation not given
Tan KL, Chirino-Barcelo Y, Aw TC *et al*. Effect of phototherapy on thyroid stimulatory hormone and free thyroxine levels. *Journal of Paediatrics and Child Health* 1996; 32:(6)508–11.	Not an RCT
Tan KL. Comparison of the efficacy of fiberoptic and conventional phototherapy for neonatal hyperbilirubinemia. *Journal of Pediatrics* 1994; 125:(4)607–12.	Not an RCT
Tan KL. Decreased response to phototherapy for neonatal jaundice in breast-fed infants. *Archives of Pediatrics and Adolescent Medicine* 1998; 152:(12)1187–90.	Not an RCT

Reference	Reason for exclusion
Thaithumyanon P and Visutiratmanee C. Double phototherapy in jaundiced term infants with hemolysis. *Journal of the Medical Association of Thailand* 2002; 85:(11)1176–81.	Not an RCT
Yaseen H, Khalaf M, Rashid N *et al*. Does prophylactic phototherapy prevent hyperbilirubinemia in neonates with ABO incompatibility and positive Coombs' test? *Journal of Perinatology* 2005; 25:(9)590–4.	Not an RCT
Zainab K and Adlina S. Effectiveness of home versus hospital phototherapy for term infants with uncomplicated hyperbilirubinemia: a pilot study in Pahang, Malaysia. *Medical Journal of Malaysia* 2004; 59:(3)395–401.	Conference abstract

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

Reference	Reason for exclusion
Amato M, Berthet G, and von MG. Influence of fatty diet on neonatal jaundice in breast-fed infants. *Acta Paediatrica Japonica* 1988; 30:(4)492–6.	Not an intervention study
Arias IM and Gartner LM. Production of unconjugated hyperbilirubinaemia in full-term in new-born infants following administration of pregnane-3(Alpha),20(Beta)-diol.. *Nature* 1964; 203:1292–3.	Not an intervention study
Capps FP, Gilles HM, Jolly H *et al*. Glucose-6-Phosphate Dehydrogenase deficiency and neonatal jaundice in Nigeria: Their relation to the use of prophylactic vitamin-K. *Lancet* 1963; 2:(7304)379–83.	Prevention study
De Carvalho M, Hall M, and Harvey D. Effects of water supplementation on physiological jaundice in breast-fed babies. *Archives of Disease in Childhood* 1981; 56:(7)568–9.	Prevention study
Elander G and Lindberg T. Hospital routines in infants with hyperbilirubinemia influence the duration of breast feeding. *Acta Paediatrica Scandinavica* 1986; 75:(5)708–12.	Not an RCT
Gourley GR, Li Z, Kreamer BL *et al*. A controlled, randomized, double-blind trial of prophylaxis against jaundice among breastfed newborns. *Pediatrics* 2005; 116:(2)385–91.	Prevention study
Gulcan H, Tiker F, and Kilicdag H. Effect of feeding type on the efficacy of phototherapy. *Indian Pediatrics* 2007; 44:(1)32–6.	Not an RCT
Lucas A and Baker BA. Breast milk jaundice in premature infants. *Archives of Disease in Childhood* 1986; 61:(11)1063–7.	Prevention study
Lucas A, Gore SM, Cole TJ *et al*. Multicentre trial on feeding low birthweight infants: effects of diet on early growth. *Archives of Disease in Childhood* 1984; 59:(8)722–30.	Prevention study
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Zhuo A, Luo L, Chen C *et al*. Clinical observation of Chinese drugs in prevention of neonatal hyperbilirubinemia. *Journal of Traditional Chinese Medicine* 1997; 17:(3)174–7.	Prevention study

Q9. How to monitor a baby with jaundice?
Q101. When to discharge a baby treated for hyperbilirubinaemia? What follow-up is required?

Reference	Reason for exclusion
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Managing hyperbilirubinemia and preventing kernicterus. *Joint Commission Perspectives on Patient Safety* 2006; 6:(6)3.	Overview
Managing jaundice in full-term infants. *Nurse Practitioner* 2005; 30:(1)6–7.	Synopsis of AAP 2004
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Zanjani SE, Safavi M, Jalali S *et al*. Incidence and associated factors of neonatal hyperbilirubinemia at Hedayat Hospital [Farsi]. *SBMU Faculty of Nursing & Midwifery Quarterly* 2007; 16:(59)-1p.	Non-English language article

Q11. What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia?

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Balaguer A, Quiroga-Gonzalez R, Camprubi M *et al*. Reducing errors in the management of hyperbilirubinaemia: validating a software application. Archives of Disease in Childhood - Fetal and Neonatal Edition 2009; 94:(1)F45-F47.	Evaluation of a software package
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Christakis DA and Rivara FP. Pediatricians' awareness of and attitudes about four clinical practice guidelines. Pediatrics 1998; 101:(5)825–30.	Awareness of guidelines
Davanzo R, Brondello C, and Cerchio R. Hospital discharge of healthy newborns. [Italian]. Medico e Bambino 2006; 25:(9)562–9.	Non-=English language article
Going home with your late preterm infant. Contemporary Pediatrics 2007; 24:(11)59.	Example of a parent information sheet
Goldenring JM. What to tell parents before they leave the hospital. Contemporary Pediatrics 2007; 24:(4)52.	Example of a parent information sheet
Information from your family doctor. Jaundice and your baby. American Family Physician 2002; 65:(4)613–4.	Example of a parent information sheet
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Khalesi N and Rakhshani F. Knowledge, attitude and behaviour of mothers on neonatal jaundice. JPMA - Journal of the Pakistan Medical Association 2008; 58:(12)671–4.	Maternal knowledge of jaundice
Madlon-Kay DJ. Maternal assessment of neonatal jaundice after hospital discharge. Journal of Family Practice 2002; 51:(5)445–8.	Training parents to assess jaundice
Maisels MJ. Jaundice in a newborn: answers to questions about a common clinical problem... first of two parts. Contemporary Pediatrics 2005; 22:(5)34–40.	Overview
Maisels MJ. Jaundice in a newborn: how to head off an urgent situation... second of two parts. Contemporary Pediatrics 2005; 22:(5)41.	Overview
Mannel R. Initiating breastfeeding and special considerations for the infant with hyperbilirubinemia: what the childbirth educator needs to know. International Journal of Childbirth Education 2006; 21:(1)11–3.	Education on breastfeeding – not specific to jaundice
McMillan DD, Lockyer JM, Magnan L *et al*. Effect of educational program and interview on adoption of guidelines for the management of neonatal hyperbilirubinemia.[see comment]. CMAJ Canadian Medical Association Journal 1991; 144:(6)707–12.	Eduction was for clinicians
Ogunfowora OB, Adefuye PO, and Fetuga MB. What do expectant mothers know about neonatal jaundice? International Electronic Journal of Health Education 2006; 9:134–40.	Maternal knowledge of jaundice
Patient education. How to care for your baby with jaundice. Nurse Practitioner 1999; 24:(4)29.	Example of a parent information sheet
Petrova A, Mehta R, Birchwood G *et al*. Management of neonatal hyperbilirubinemia: Pediatricians' practices and educational needs. BMC Pediatrics 2006; 6,;#2006. Article Number.	Education for clinicians
Sater KJ. Color me yellow: caring for the infant with hyperbilirubinemia. Journal of Intravenous Nursing 1995; 18:(6)317–25.	Overview – background information only
Stokowski LA. Family teaching toolbox. Newborn jaundice. Advances in Neonatal Care 2002; 2:(2)115–6.	Example of a parent information sheet

Abbreviations, Glossary and References

Abbreviations

AAP	American Academy of Pediatrics
ABR	auditory brainstem response
AROC	area under the ROC curve
B/A ratio	bilirubin/albumin ratio
BW	birthweight
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
CPD	citrate phosphate dextrose
DAT	direct antiglobulin test, also known as 'Coombs' test'
DVET	double-volume exchange transfusion
ETCOc	corrected end-tidal carbon monoxide concentration (the concentration at the end of an expired breath)
GA	gestational age
GDG	Guideline Development Group
G6PD	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.
HPLC	high-performance liquid chromatography
IVIG	intravenous immunoglobulin
LED	light-emitting diode
MD	mean difference
NICU	neonatal intensive care unit
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
QALY	quality-adjusted life year
RMSSD	root mean square of successive differences
ROC	receiver operating characteristic
RR	risk ratio
TCB	transcutaneous bilirubin
SD	standard deviation
SD1	width of Poincaré plot images
SD2	Length of Poincaré plot images
SVET	single-volume exchange transfusion
TEWL	trans-epidermal water loss
TSB	total serum bilirubin
UCB	umbilical cord blood 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. Some mothers have naturally occurring anti-A and anti-B antibodies present in the circulation, which can pass across the placenta and bind to antigenic sites on fetal red cell. Some mothers are sensitised by feto-maternal transfusion of ABO incompatible blood..
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 healthcare 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	Phototherapy given using a single light source (not fibreoptic) that is positioned above the baby
Coombs' test	See Direct Antibody Test (DAT)
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare 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 healthcare 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 Antiglobulin Test (DAT)	Also known as the direct Coombs' test; this 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.
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	Phototherapy given using a single light source that comprises a light generator, a fibre-optic cable through which the light is carried and a flexible 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 (G6PD deficiency) is associated with a tendency to haemolysis. 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 maternal antibodies which pass into the fetus and trigger haemolysis of 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 healthcare 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	An elevation of serum bilirubin to a level requiring treatment (see key terms 1.1
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
Jaundice, visible	Jaundice detected by visual inspection
Jaundice, prolonged	Jaundice lasting more than 14 days in term babies and more than 21 days in preterm babies (see 1.1)
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 ioften refers to the clinical syndrome and sequelae of bilirubin encephalopathy
LED (light emitting diode) phototherapy	A phototherapy unit that comprises light-emitting diodes rather than fluorescent or halogen tubes that is positioned above the baby..
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	Phototherapy that is given using more than one light source simultaneously; for example two or more conventional units, or a combination of conventional and fibreoptic units.
Near-term	35 to 36 weeks gestational age (see key terms 1.1)
Necrotising enterocolitis	A gastrointestinal condition that mostly affects preterm 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 common, generally harmless, jaundice seen in babies in 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 dummy 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	Less than 37 weeks gestational age (see key terms 1.1)
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare 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.
Single phototherapy	Phototherapy given using a single light source.
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

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