Appendix C Excluded studies

Q1. Which factors affect the relationship between neonatal hyperbilirubinaemia and kernicterus or other adverse outcomes (neurodevelopmental, auditory)?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beutner D, Foerst A, Lang-Roth R et al. Risk factors for auditory neuropathy/auditory synaptopathy. ORL 2007; 69:(4)239-44.</td>
<td>No adjustment for confounding variables</td>
</tr>
<tr>
<td>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.</td>
<td>Outcome not of interest to this guideline</td>
</tr>
</tbody>
</table>
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Background


No adjustment for confounders


Risk factors for jaundice readmission – confounders not controlled for


Synopsis


Effect of early discharge on jaundice readmission rates


No comparison group


Risk factors for re-admission of breastfed babies


Developmental follow-up of babies with bilirubin > 451 micromol/L


Only breastfeeding and genetic risk factors considered


G-6-PD deficiency as a risk factor for jaundice


Overview


Effect of discharge management on readmission rates


Study restricted to African-American males babies


ABO incompatibility as a risk factor for jaundice


hyperbilirubinemia. *Archives of Oto-Rhino-Laryngology* 1986; 243;(2)133.


Young-Lewis LE. Factors contributing to the readmission of previously healthy low-risk neonates for hyperbilirubinemia. *(CASE WESTERN RESERVE UNIVERSITY) **1996; PhD 146.*
Q2. What is the best method of recognizing hyperbilirubinemia?

Q3. When should a baby with hyperbilirubinemia be referred for further testing or formal assessment?

Q5. How useful are the following tests in predicting neonatal hyperbilirubinemia?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhardwaj HP, Narang A, and Bhakoo ON. Evaluation of Minolta jaundicemeter and icterometer for assessment of neonatal jaundice. <em>Indian Pediatrics</em> 1989; 26:(2)161-5.</td>
<td>Poor quality study – EL3</td>
</tr>
<tr>
<td>Bhat V, Srinivasan S, Usha TS et al. Correlation of transcutaneous bilirubinometry with serum bilirubin in south Indian neonates. <em>Indian Journal of Medical Research</em> 1987; 86:49-52.</td>
<td>Reference tests was not a laboratory based test</td>
</tr>
<tr>
<td>Bjerre JV and Ebbesen F. [Incidence of kernicterus in newborn infants in Denmark]. <em>Ugeskift for Laeger</em> 2006; 168:(7)686-91.</td>
<td>Non-English language article</td>
</tr>
<tr>
<td>Bourchier D, Cull AB, and Oettli PE. Transcutaneous bilirubinometry: 22 months experience at Waikato</td>
<td>Unclear of timing of tests</td>
</tr>
</tbody>
</table>
women's Hospital. *New Zealand Medical Journal* 1987; 100;(832)599-600.

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.


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).


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.
Study examined the use of JM-102 in preterm babies

Not all tests carried out with 1-hour

Not a comparative study

Birthweight as a predictor for hyperbilirubinaemia

Poor quality study – EL3

Overview

Poor quality study – EL3

Poor quality study – EL3

Poor quality study – EL3

Poor quality study – EL3

Poor quality study – EL3

Poor quality study – EL3

Data not relevant – overestimation an underestimation of tests

Janjindamai W and Tansantiwong T. Accuracy of transcutaneous bilirubinometer estimates using


Female subjects were included from a retrospective studies

Timing of tests not specified

Review of transcutaneous bilirubinometers

Test timing was 8 hours

Study not relevant – multiple regression used to study different factors

Poor quality study – EL3

Poor quality study – EL3

Deals with progression of bilirubin from plasma to skin

Transcutaneous measurement in pre-term babies

Not all babies tested

Unclear of timing of tests

Coombs’ test only used if phototherapy was indicated

Timing of tests = 4 hours


Minolta JM-101 was used – not a transcutaneous bilirubinometer of interest


Health economic analysis of JM-102


Quality improvement programme not relevant to this guideline


Poor quality study


Unclear if tests were within 1 hour


Incomplete data


Only babies with blood group incompatibility were included


Poor quality study – EL3


Ways to improve algorithm for transcutaneous measurement


Data not extractable


Nidirect comparison of Minolta JM-103 and BiliChek


Retrospective study


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.


Device being tested not relevant to this guideline

Correlation of visual inspection and transcutaneous measurement

Not clear if tests were carried out within 2 hour

Poor quality study – EL3

No reference test used

Transcutaneous bilirubin used as the reference test

Unclear of timing of tests

Correspondence

Unclear of timing of tests

Correspondence

Incomplete data

Duplicate publication


Test of different curvettes for Minolta JM


Unclear of time between testing


No possible to extract data
Q4. What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abolghasemi H, Mehrani H, and Amid A. An update on the prevalence of glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Tehran neonates. <em>Clinical Biochemistry</em> 2004; 37:(3)241-4.</td>
<td>Babies were only tested for G-6-PD</td>
</tr>
<tr>
<td>Ahlfors CE and Parker AE. Unbound bilirubin concentration is associated with abnormal automated auditory brainstem response for jaundiced newborns. <em>Pediatrics</em> 2008; 121:(5)976-8.</td>
<td>Test not relevant to this guideline - value of Auditory brainstem response as a predictor of kernicterus</td>
</tr>
<tr>
<td>Ahlfors CE. Bilirubin-albumin binding and free bilirubin. <em>Journal of Perinatology</em> 2001; 21:(SUPPL. 1)S40-S42.</td>
<td>Commentary</td>
</tr>
</tbody>
</table>

Ahmed P and Ahmad KN. Screening of the newborns for glucose-6-phosphate dehydrogenase deficiency. *Indian Pediatrics* 1983; 20:(5)351-5.


Physiological jaundice was excluded

Babies with ABO or Rh incompatibility were excluded

Babies with haemolysis were excluded

No entry level criteria for jaundice were used

Tests not relevant to this guideline

Subjects with physiological jaundice were excluded

Babies were not tested for blood group incompatibility

Unclear if blood group incompatibility was tested for

Data from this study was contained in an included review

Overview

Test for different factors in human breastmilk

Duplicate of Azubuike 1979


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.


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Comparison of different methods of bilirubin analysis


Single test only


Not all babies were jaundiced


Comparison of different methods of measuring bile acids


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


Laboratory analysis of bilirubin toxicity on serum samples


Overview


Overview


Study examine incidence of jaundice in G-6-PD


Results of G-6-PD tests not reported


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.


Babies not tested for G-6-PD


Cases were not tested for G-6-PD deficiency


Jaundice as a predictor of UTI


Test not relevant to this guideline


Incomplete data


Study on the impact of G-6-PD on exchange transfusion levels


Jaundice as a predictor for Urinary Tract Infections


Not all subjects had jaundice


Tests for incidence of infections in babies with jaundice


Animal test


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* Babies were only tested for ABO incompatibility
and Child Health 1990; 26:(3)155-7.


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.


Kaplan M, Beutler E, Vreman HJ *et al.* Neonatal hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient heterozygotes. *Pediatrics* 1999; 104(1 Pt 1):68-


Only babies with G-6-PD deficiency tested

Effect of hyperbilirubinaemia on renal function

Test not relevant to this guideline

Conference abstract

Babies with ABO or Rh incompatibility were excluded

Overview

Babies were not pre-selected for jaundice

Test (cerebro-spinal fluid bilirubin) not relevant to this guideline

Test not relevant to this guideline

Study examining the effect of hyperbilirubinaemic serum on murine astrocytes

Only tested for G-6-PD

Comparison of urinary tract infection rates in conjugated and unconjugated hyperbilirubinaemia


7.


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)1303-11.


Correspondence

Babies were not tested for G-6-PD

Effects of phototherapy on total and unbound bilirubin

Study of auditory brainstem responses

Predictive accuracy of two bilirubin levels for predicting kernicterus

Only 1 in 4 babies were tested for G-6-PD

No tests for G-6-PD

Overview

G-6-PD test not carried out on all babies

Not all babies tested

Case study

Overview

Test not relevant to this guideline


Test not relevant to this guideline


Overview – background information only


Laboratory tests


Link between free bilirubin and bilirubin encephalopathy


Babies with sepsis were excluded


Tests not relevant to this guideline


Study of the saturation index – test not relevant to this guideline


Tests not relevant to this guideline


Overview


Not all subjects were newborn


Only pre-term babies were included

Owa JA and Dawodu AH. Neonatal jaundice among Nigerian preterm infants. *West*


Priolisi A and Zilio 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.


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Care Nursing Clinics of North America 2004; 16;(2)257-69.


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.


Not all babies who died had an autopsy

Comparison of methods to measure serum bilirubin

Babies with blood group incompatibility were excluded

Three cases studies

Babies with ABO/Rh incompatibility or G-6-PD deficiency were excluded

Babies only tested for G-6-PD deficiency

Babies were not tested for blood group incompatibility

Test not relevant to this guideline – bilirubin binding capacity

Long term outcomes from an included RCT

Comparison of two test to measure bilirubin-albumin binding

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


Test not relevant to guideline


Tests not relevant to this guideline


Babies were not tested for ABO incompatibility


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


Not all subjects newborn


Study for a single syndrome in prolonged jaundice


Test for a single disease


Overview


Test not relevant to this guideline

Turgut M, Basaran O, Cekmen M et al. Oxidant and antioxidant levels in preterm newborns with idiopathic hyperbilirubinemia. *Journal of Paediatrics and Child Health* Babies with ABO or Rh incompatibility were excluded


Effect of prolonged jaundice on serum bile acid profile


No test for G-6-PD


Study compared babies with haemolytic disease of the newborn with controls


Not all babies tested for blood group incompatibility


Test not relevant to this guideline
## Q6. Phototherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliott E, Moncrieff MW, and George WH. Phototherapy for hyperbilirubinaemia in low birthweight infants. <em>Archives of Disease in Childhood</em> 1974; 49;(1)60-2.</td>
<td>Not an RCT</td>
</tr>
</tbody>
</table>
Finlay HVL and Tucker SM. Neonatal plasma bilirubin chart. *Archives of Disease in Childhood* 2009; 53;(1)90.


Kurt A, Aygun AD, Kurt ANC et al. Use of phototherapy for neonatal hyperbilirubinemia affects cytokine

Background information

Home phototherapy not relevant to this guideline

Not an RCT

Comparison of two types of fiberoptic phototherapy

Not an RCT

Non-English language articles

Conference abstract

Not an RCT

Not an RCT

Not an RCT

Effect of G-6-PD deficiency status of phototherapy

Outcome not relevant to this guideline


Pezzati M, Biagiotti R, Vangi V et al. Changes in mesenteric blood flow response to feeding:


Comparison of two combinations of positioning combined with clothing


Executive summary


Not an RCT


Not an RCT


Not an RCT


Not an RCT


Comparison of two types of fluorescent lamps


Follow-up of an included study


Not an RCT


Not an RCT


Incomplete data – 1 case of exchange transfusion but group allocation not given


Not an RCT


**Q7. Is it beneficial to give additional fluids (cup feeds, fluids) during treatment with phototherapy?**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.. <em>Nature</em> 1964; 203:1292-3.</td>
<td>Not an intervention study</td>
</tr>
<tr>
<td>Mowat A. Double-blind trial of effects of aspartic acid, orotic acid and glucose on serum bilirubin concentrations in infants born before term. <em>Archives of Disease in Childhood</em> 1971; 46:(247)397.</td>
<td>Conference abstract</td>
</tr>
</tbody>
</table>


Wharton BA and Bower BD. Immediate or later feeding for premature babies? A controlled trial. *Lancet* 1965; 2:(7420)769-72.


### Q8. Exchange transfusion

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen H, Lee M, and Tsao L. Exchange transfusion using peripheral vessels is safe and effective in newborn infants. <em>Pediatrics</em> 2008; 122;(4)e905-e910.</td>
<td>Conference abstract</td>
</tr>
<tr>
<td>Cser A. Metabolic and hormonal changes during and after exchange transfusion with heparinized or ACD blood. <em>Archives of Disease in Childhood</em> 1974; 49;(12)940-5.</td>
<td>No jaundice related outcomes</td>
</tr>
<tr>
<td>Karamifar H, Pishva N, and Amirhakimi GH. Prevalence of phototherapy-induced hypocalcemia. <em>Iranian Journal of Medical Sciences</em> 2002; 27;(4)166-8.</td>
<td>Outcome not of interest to GDG</td>
</tr>
<tr>
<td>Ozsoylu S. Heparinised whole blood or citrated blood for exchange transfusion. <em>European Journal of Pediatrics</em> 2001; 160;(3).</td>
<td>Correspondence</td>
</tr>
</tbody>
</table>

Thayyil S and Milligan DWA. Single versus double volume exchange transfusion in jaundiced newborn infants. *Cochrane Database of Systematic Reviews* 2008;(3). Review of a single study – included the original study

**Q9. What are the other ways of treating hyperbilirubinaemia?**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal SS, Misra PK, Upadhyay UK et al. Comparative trials of phototherapy versus photobarb in the management of neonatal hyperbilirubinaemia. <em>Indian Pediatrics</em> 1976; 13:(1)41-5.</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Ashkan MM and Narges P. The effect of low and moderate doses of clofibrate on serum bilirubin level in jaundiced term neonates. <em>Paediatric and Perinatal Drug Therapy</em> 2007; 8:(2)51-4.</td>
<td>Paper withdrawn as it was a duplicate publication</td>
</tr>
<tr>
<td>Blum D and Etienne J. Agar in control of hyperbilirubinemia. <em>Journal of Pediatrics</em> 1973; 83:(2)345.</td>
<td>Correspondence</td>
</tr>
<tr>
<td>Chen H. Artemisia composita for the prevention and treatment of neonatal hemolysis and</td>
<td>Not an RCT</td>
</tr>
</tbody>
</table>


Hosono S, Ohno T, Kimoto H *et al.* Effects of albumin infusion therapy on total and unbound bilirubin values in term infants with intensive phototherapy. *Pediatrics International* 2001; 43:(1)8-11.


Prevention study


Not an RCT


Not an RCT


Not an RCT


Not an RCT


Duplicate publication

Martinez JC, Garcia HO, Otheguy LE et al. Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. Pediatrics 1999; 103:(1)1-5.

Prevention study


Prevention study


Prevention study


Conference abstract

Pawaskar N. Alertness is the key! National Journal of Homoeopathy 2004; 6:(2)109-10.

Not an RCT


Prevention study


Prevention study


Prevention study


Prevention study


Prevention study


Prevention study


Prevention study


Prevention study


Not an RCT


Prevention study
**Q10. How to monitor a baby with jaundice?**

**Q11. When to discharge a baby treated for hyperbilirubinaemia? What follow-up is required?**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhaded SM, Kumar P, and Narang A. Safe bilirubin level for term babies with non-hemolytic jaundice. <em>Indian Pediatrics</em> 1996; 33:(12)1059-60.</td>
<td>Correspondence</td>
</tr>
<tr>
<td>Erdeve O. Rebound bilirubin: On what should the decision to recommence phototherapy be based? <em>Archives of Disease in Childhood</em> 2006; 91:(7)623.</td>
<td>Correspondence</td>
</tr>
<tr>
<td>Managing hyperbilirubinemia and preventing kernicterus. <em>Joint Commission Perspectives on Patient Safety</em> 2006; 6:(6)3.</td>
<td>Overview</td>
</tr>
</tbody>
</table>


Screening reduces the occurrence of hyperbilirubinemia. *Contemporary Pediatrics* 2006; 23;(7)85.


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.
Q13. **What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia?**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Going home with your late preterm infant. <em>Contemporary Pediatrics</em> 2007; 24;(11)59.</td>
<td>Example of a parent information sheet</td>
</tr>
<tr>
<td>Goldenring JM. What to tell parents before they leave the hospital. <em>Contemporary Pediatrics</em> 2007; 24;(4)52.</td>
<td>Example of a parent information sheet</td>
</tr>
<tr>
<td>Information from your family doctor. Jaundice and your baby. <em>American Family Physician</em> 2002; 65;(4)613-4.</td>
<td>Example of a parent information sheet</td>
</tr>
<tr>
<td>Maisels MJ. Jaundice in a newborn: answers to questions about a common clinical problem... first of two parts. <em>Contemporary Pediatrics</em> 2005; 22:(5)34-40.</td>
<td>Overview</td>
</tr>
</tbody>
</table>

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.

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.


