ClinicalEvidence

Neonatal jaundice: phototherapy

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ABSTRACT

INTRODUCTION: About 50% of term and 80% of preterm babies develop jaundice, which usually appears 2 to 4 days after birth, and resolves spontaneously after 1 to 2 weeks. Jaundice is caused by bilirubin deposition in the skin. Most jaundice in newborn infants is a result of increased red cell breakdown and decreased bilirubin excretion. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of different wavelengths of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants? What are the effects of different intensities of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants? What are the effects of different total doses of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants? What are the effects of starting hospital phototherapy at different thresholds in term and preterm infants? We searched Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: Fourteen studies were included. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of different wavelengths, intensities, total doses, and threshold for commencement of the following intervention: hospital phototherapy.

QUESTIONS

What are the effects of different wavelengths of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants? . . . 4

What are the effects of different intensities of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants? . . . 9

What are the effects of different total doses of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants? . . . 12

What are the effects of starting hospital phototherapy at different thresholds in term and preterm infants? . . . 14

INTERVENTIONS

DIFFERENT WAVELENGTHS OF LIGHT IN HOSPITAL PHOTOTHERAPY

Likely to be beneficial

Blue-green fluorescent versus blue fluorescent lamps (blue-green fluorescent light may be more effective at reducing duration of phototherapy than blue fluorescent light) . . . 6

Blue LED versus conventional quartz-halogen (blue LED may reduce hours spent in phototherapy; however, no significant difference in rate of bilirubin decline) . . . 7

Unknown effectiveness

(Daylight) fluorescent versus blue fluorescent lamps . . . 4

Blue fluorescent versus green fluorescent lamps . . . 5

Blue-green LED versus conventional quartz-halogen . . . 8

DIFFERENT INTENSITIES OF LIGHT IN HOSPITAL PHOTOTHERAPY

Likely to be beneficial

Close phototherapy versus distant light-source phototherapy (close phototherapy may reduce duration of treatment and serum bilirubin level) . . . 9

Double phototherapy versus single phototherapy (double phototherapy may reduce duration of treatment and serum bilirubin level) . . . 9

Unknown effectiveness

Triple phototherapy versus double phototherapy . . . 11

DIFFERENT TOTAL DOSES OF LIGHT IN HOSPITAL PHOTOTHERAPY

Unknown effectiveness

Intermittent phototherapy versus continuous phototherapy . . . 12

Increased skin exposure versus standard skin exposure phototherapy . . . 13

STARTING HOSPITAL PHOTOTHERAPY AT DIFFERENT THRESHOLDS

Likely to be beneficial

Low threshold versus high threshold phototherapy (low threshold may reduce neurodevelopmental impairment in extremely low birthweight infants; however, no difference in mortality or need for exchange transfusion) . . . 15

Unknown effectiveness

Prophylactic phototherapy versus threshold phototherapy . . . 14

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Key points

- About 50% of term and 80% of preterm babies develop jaundice, which usually appears 2 to 4 days after birth, and resolves spontaneously after 1 to 2 weeks.

  Jaundice is caused by bilirubin deposition in the skin. Most jaundice in newborn infants is a result of increased red cell breakdown and decreased bilirubin excretion.

  Breastfeeding, haemolysis, and some metabolic and genetic disorders also increase the risk of jaundice.

  Unconjugated bilirubin can be neurotoxic, causing an acute or chronic encephalopathy that may result in cerebral palsy, hearing loss, and seizures.
- Hospital phototherapy is provided by conventional or fibreoptic lights as a treatment to reduce neonatal jaundice.
- We assessed RCTs comparing light with different wavelengths used for hospital phototherapy for unconjugated hyperbilirubinaemia in term and preterm infants. Interventions compared included: conventional phototherapy (using halogen-quartz bulbs), daylight fluorescent lamps, standard blue fluorescent lamps, blue fluorescent lamps with a narrow spectral emission, green fluorescent lamps, blue-green fluorescent lamps, blue LED lamps, and blue-green LED lamps.

  Blue-green fluorescent light may be more effective than blue fluorescent light at reducing the requirement for phototherapy after 24 hours in healthy low birth weight babies with hyperbilirubinaemia in the first 4 days of life.

  Hospital phototherapy using blue LED lamps may be more effective at reducing the number of hours spent under phototherapy compared with conventional phototherapy (using halogen-quartz bulbs) in term and preterm infants.

  Apart from these two comparisons, we found no difference between the other wavelengths of light on the duration of phototherapy required.

  We don't know whether the various wavelengths of light studied differ in their effect on rate of decline in serum bilirubin levels.

  One small RCT found no significant difference in blue LED lamps compared with conventional phototherapy at reducing mortality in preterm infants requiring phototherapy.
- For different intensities of light:

  Close phototherapy compared with distant light-source phototherapy may reduce the duration of phototherapy and mean serum bilirubin level in infants with hyperbilirubinaemia.

  Double conventional phototherapy may be more effective than single conventional phototherapy at reducing the duration of treatment and mean serum bilirubin level in term infants of birth weight 2500 g or above with haemolysis included. However, we don't know if double phototherapy reduces the need for exchange transfusion.

  We don't know whether there is any additional benefit of triple phototherapy compared to double phototherapy.
- We assessed RCTs comparing light with different total doses used for hospital phototherapy for unconjugated hyperbilirubinaemia in term and preterm infants. Interventions included intermittent versus continuous phototherapy and increased skin exposure versus standard skin exposure phototherapy.

  We don’t know whether there is any difference in effectiveness of intermittent phototherapy versus continuous phototherapy or increased skin exposure versus standard skin exposure phototherapy at reducing duration of phototherapy treatment or at improving the rate of decrease of serum bilirubin levels.
- We assessed RCTs comparing different thresholds for commencement of hospital phototherapy. This included comparing prophylactic phototherapy (commencement of phototherapy routinely according to specific criteria other than level of serum bilirubin) with threshold phototherapy (commencement of phototherapy when the serum bilirubin was above a certain predefined level).

  We only found one small RCT comparing prophylactic hospital phototherapy with threshold hospital phototherapy. It is generally accepted that phototherapy should only be applied once serum bilirubin levels reach predefined thresholds.

  Lower thresholds compared with higher thresholds in extremely low birth weight infants may reduce the proportion of infants with neurodevelopmental impairment, profound impairment, and severe hearing loss.

Clinical context

GENERAL BACKGROUND

Neonatal jaundice is a common condition in newborn babies, affecting about 50% of term and 80% of preterm babies. Phototherapy is often used to reduce levels of unconjugated bilirubin that may result in acute or chronic encephalopathy. However, exchange transfusion is still the gold standard of treatment for severe hyperbilirubinaemia.

FOCUS OF THE REVIEW

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The efficacy of phototherapy in the treatment of unconjugated hyperbilirubinaemia may be influenced by the wavelength of the light used, the intensity of the light source, the total dose of light received (time under phototherapy and amount of skin exposed), and/or the threshold at which phototherapy is commenced. In this review we try to determine the most safe and effective method for the delivery of phototherapy to decrease unconjugated bilirubin levels in the neonate.

COMMENTS ON EVIDENCE

Due to a large range of treatment options, the evidence is difficult to interpret. However, it is generally accepted that intensive phototherapy applied to infants with already high serum bilirubin levels or rapidly rising serum bilirubin levels has greatly reduced the need for exchange transfusions in infants with or without haemolysis. If there is a choice of blue-green or blue wavelengths, blue-green appears to be slightly more effective than blue. Using a lower threshold for the commencement of phototherapy in extremely low birth weight (ELBW) infants may improve neurodevelopmental outcome. Overall, there is a lack of RCT evidence on effectiveness of low versus high threshold for the commencement of phototherapy in babies other than those who are ELBW infants.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, February 2010, to January 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. After deduplication and removal of conference abstracts, 75 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 56 studies and the further review of 19 full publications. Of the 19 full articles evaluated, one systematic review and three RCTs were added at this update. One RCT was added to the Comment section.

ADDITIONAL INFORMATION

If treatment is required for neonatal jaundice, phototherapy is generally accepted as first-line clinical management. Exchange transfusion should be reserved for those infants with very high serum bilirubin levels or rapidly rising serum bilirubin levels that are not responding to phototherapy.

DEFINITION

Neonatal jaundice refers to the yellow coloration of the skin and sclera of newborn babies that results from the deposition of bilirubin. This review focuses on phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants; however, exchange transfusion is still the gold standard of treatment for severe hyperbilirubinaemia. Jaundice is usually seen first in the face, and progresses caudally to the trunk and extremities. However, visual estimation of the bilirubin levels can lead to errors, and a low threshold should exist for measuring serum bilirubin. There are devices that measure transcutaneous bilirubin, but these are generally for screening purposes. [1]

INCIDENCE/ PREVALENCE

Jaundice is the most common condition requiring medical attention in newborn babies. About 50% of term and 80% of preterm babies develop jaundice in the first week of life. [2] Jaundice is also a common cause of re-admission to hospital after early discharge of newborn babies. [3] Jaundice usually appears 2 to 4 days after birth and disappears 1 to 2 weeks later, usually without the need for treatment.

AETIOLOGY/ RISK FACTORS

Jaundice occurs when there is accumulation of bilirubin in the skin and mucous membranes. In most infants with jaundice there is no underlying disease, and the jaundice is termed physiological. Physiological jaundice typically presents on the second or third day of life and results from the increased production of bilirubin (owing to increased circulating red cell mass and a shortened red cell lifespan) and the decreased excretion of bilirubin (owing to low concentrations of the hepatocyte binding protein, low activity of glucuronosyl transferase, and increased enterohepatic circulation) that normally occur in newborn babies. Breastfed infants are more likely to develop jaundice within the first week of life; this is thought to be an exacerbated physiological jaundice caused by a lower calorific intake and increased enterohepatic circulation of bilirubin. Prolonged unconjugated jaundice, persisting beyond the second week, is also seen in breastfed infants. The mechanism for this later 'breast milk jaundice syndrome' is still not completely understood. Non-physiological causes include blood group incompatibility (rhesus or ABO problems), other causes of haemolysis, sepsis, bruising, and metabolic disorders. Gilbert's and Crigler-Najjar syndromes are rare causes of neonatal jaundice.

PROGNOSIS

In the newborn baby, unconjugated bilirubin can penetrate the blood-brain barrier and is potentially neurotoxic. Acute bilirubin encephalopathy consists of initial lethargy and hypotonia, followed by hypertonia (retrocollis and opisthotonus), irritability, apnoea, and seizures. Kernicterus refers to the yellow staining of the deep nuclei of the brain, namely, the basal ganglia (globus pallidus); however, the term is also used to describe the chronic form of bilirubin encephalopathy, which includes symptoms such as athetoid cerebral palsy, hearing loss, failure of upward gaze, and dental enamel dysplasia. The level at which unconjugated bilirubin becomes neurotoxic is unclear, and

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kernicterus at autopsy has been reported in infants in the absence of markedly elevated levels of bilirubin. [4] Reports suggest a resurgence of kernicterus in countries in which this complication had virtually disappeared. [5] This has been attributed mainly to early discharge of newborns from hospital.

AIMS OF INTERVENTION To prevent the development of bilirubin-associated neurodevelopmental sequelae; to reduce serum bilirubin levels, with minimal adverse effects.

OUTCOMES **Mortality**; **neurological/neurodevelopmental outcomes** (including neurodevelopmental delay; incidence of kernicterus and other neurodevelopmental sequelae; hearing loss; blindness; neurological sequlae [e.g., cerebral palsy]); **need for exchange transfusion**; **duration of treatment** (including duration of phototherapy, need for re-treatment with phototherapy, need for phototherapy due to treatment failure); **serum bilirubin levels**; **adverse effects** (including effects on parent-infant bonding). Wherever possible, we have reported on our prespecified clinical outcomes of interest such as neurodevelopmental delay or sequelae. However, many studies did not report on clinical outcomes, but on biochemical measures such as serum bilirubin levels. Hence, we have also reported these non-clinical outcomes.

METHODS *BMJ Clinical Evidence* search and appraisal January 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2014, Embase 1980 to January 2014, and The Cochrane Database of Systematic Reviews 2014, issue 1 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, any level of blinding, and containing at least 20 individuals (at least 10 per arm), of whom at least 80% were followed up. There was no minimum length of follow-up. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 19). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *BMJ Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of different wavelengths of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants?**

OPTION (DAYLIGHT) FLUORESCENT VERSUS BLUE FLUORESCENT LAMPS

Duration of treatment

Fluorescent compared with blue fluorescent lamps We don't know whether daylight fluorescent lamps, standard blue fluorescent lamps, and blue fluorescent lamps with a narrow spectral emission differ in effectiveness at improving the proportion of infants who discontinue phototherapy after 1 to 3 days in infants with hyperbilirubinaemia in the first 72 hours of life (non-haemolytic), as the RCT did not test the significance of differences between groups (low-quality evidence).

Serum bilirubin level

Fluorescent compared with blue fluorescent lamps We don't know whether daylight fluorescent lamps, standard blue fluorescent lamps, and blue fluorescent lamps with a narrow spectral emission differ in effectiveness at improving the mean decrease of serum bilirubin levels at 1 to 3 days in infants with hyperbilirubinaemia in the first 72 hours of life (non-haemolytic), as the RCT did not test the significance of differences between groups (low-quality evidence).

Note

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We found no evidence from RCTs on mortality, neurological/neurodevelopmental outcomes, or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Fluorescent versus blue fluorescent lamps** We found one three-armed RCT (72 infants, hyperbilirubinaemia in first 72 hours of life, serum bilirubin [SBR] >8.6 mg/dL, no sepsis, no respiratory distress, non-haemolytic) comparing daylight fluorescent lamps with standard blue fluorescent lamps and with blue fluorescent lamps with a narrow spectral emission. [6] Phototherapy was discontinued when serum bilirubin concentration had declined steadily for at least 12 hours and had reached a level of at most 8 mg per 100 mL. The RCT found that a smaller proportion of infants discontinued phototherapy after 1 day with daylight fluorescent lamps compared with blue fluorescent lamps (with or without narrow spectral emission) (2/24 [8%] with daylight *v* 6/24 [25%] with standard blue *v* 12/24 [50%] with narrow spectrum blue; P values not reported). [6] However, the RCT found similar rates in the number of infants discontinuing phototherapy on days 2 and 3 (day 2: 6/24 [25%] with daylight *v* 14/24 [58%] with standard blue *v* 8/24 [33%] with narrow spectrum blue; P values not reported; day 3: 7/24 [29%] with daylight *v* 4/24 [17%] with standard blue *v* 4/24 [17%] with narrow spectrum blue; P values not reported). The RCT found that, compared with daylight fluorescent lamps, blue fluorescent lamps (with or without narrow spectral emission) increased mean decreases in serum bilirubin levels after the first 24 hours, the second 24 hours, and the third 24 hours of phototherapy (mean decrease in the first 24 hours: 0.96 mg/dL with daylight *v* 2.17 mg/dL with standard blue *v* 3.52 mg/dL with narrow spectrum blue; P values not reported; mean decrease in the second 24 hours: 0.38 mg/dL with daylight *v* 1.38 mg/dL with standard blue *v* 2.32 mg/dL with narrow spectrum blue; P values not reported; mean decrease in the third 24 hours: 1.46 mg/dL with daylight *v* 1.72 mg/dL with standard blue *v* 1.82 mg/dL with narrow spectrum blue; P values not reported). [6]

Harms: **Fluorescent versus blue fluorescent lamps** The RCT gave no information on adverse effects. [6]

Comment: **Clinical guide**
There appears to be no clear benefit or harm in choosing either a fluorescent or blue fluorescent lamp for the treatment of unconjugated hyperbilirubinaemia.

OPTION BLUE FLUORESCENT VERSUS GREEN FLUORESCENT LAMPS

Duration of treatment
Blue fluorescent compared with green fluorescent lamps Blue fluorescent lamps and green fluorescent lamps seem equally effective at reducing the duration of phototherapy in term and preterm infants with non-haemolytic jaundice (moderate-quality evidence).

Serum bilirubin level
Blue fluorescent compared with green fluorescent lamps We don't know whether blue fluorescent lamps and green fluorescent lamps differ in effectiveness at increasing the rate of fall of serum bilirubin in term and preterm infants with non-haemolytic jaundice or in low birth weight infants with non-haemolytic jaundice stratified by initial serum bilirubin levels (21.0–16.1 mg/dL; 16.0–12.1 mg/dL; 12.0–9.0 mg/dL) (low-quality evidence).

Note
We found no evidence from RCTs on mortality, neurological/neurodevelopmental outcomes, or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Blue fluorescent versus green fluorescent lamps** We found two RCTs comparing blue fluorescent with green fluorescent light. [7] [8] The first RCT (262 infants, non-haemolytic jaundice) compared treatment with blue fluorescent lamps versus green fluorescent lamps. [7] The RCT also reported a planned subgroup analysis on term (at least 37 weeks' gestation) versus preterm (<37 weeks' gestation) infants. [7] The RCT found no significant difference in the duration of phototherapy in the term infants or preterm infants with blue fluorescent light compared with green fluorescent light (term infants: 49.88 hours with blue light *v* 42.68 hours with green light, P >0.05; preterm infants: 53.29 hours with blue light *v* 53.26 hours with green light, P >0.05). The RCT also found no significant difference in the rate of fall of serum bilirubin in term infants or preterm infants with blue light compared with green light (term infants: 2.86 micromol/hour with blue light *v* 3.27 micromol/hour with green light, P >0.05; preterm infants: 2.50 micromol/hour with blue light *v* 2.91 micromol/hour with green light, P >0.05). [7] The second RCT (84 low birth weight infants, non-haemolytic jaundice, no respiratory distress, no sepsis, no post-phototherapy rebound) compared treatment with blue fluorescent lamps versus green fluorescent lamps. [8] The RCT reported a planned subgroup

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analysis, in which three groups were compared based on initial serum bilirubin levels (group 1: 21.0–16.1 mg/dL; group 2: 16.0–12.1 mg/dL; group 3: 12.0–9.0 mg/dL). [8] The RCT found no significant difference in the percentage decrease in serum bilirubin levels for any of the subgroups with blue light compared with green light at 24 and 48 hours (group 1: 24 hours: 32% decrease with blue light *v* 31% decrease with green light; 48 hours: 36% decrease with blue light *v* 46% decrease with green light; group 2: 24 hours: 22% decrease with blue light *v* 20% decrease with green light: 48 hours: 27% decrease with blue light *v* 22% decrease with green light: group 3: 24 hours: 20% decrease with blue light *v* 19% decrease with green light: 48 hours: 16% decrease with blue light *v* 11% decrease with green light; P >0.5 for all comparisons). [8]

Harms: **Blue fluorescent versus green fluorescent lamps** The RCTs gave no information on adverse effects. [7] [8]

Comment: **Clinical guide**
There appears to be no clear benefit or harm in choosing either a blue fluorescent or a green fluorescent lamp for the treatment of unconjugated hyperbilirubinaemia.

OPTION BLUE-GREEN FLUORESCENT VERSUS BLUE FLUORESCENT LAMPS

Duration of treatment
Blue-green fluorescent compared with blue fluorescent lamps Blue-green fluorescent light may be more effective than blue fluorescent light at reducing the proportion of infants requiring phototherapy after 24 hours in healthy low birth weight infants with hyperbilirubinaemia in the first 4 days of life (low-quality evidence).

Serum bilirubin level
Blue-green fluorescent compared with blue fluorescent lamps We don't know whether blue-green fluorescent and blue fluorescent phototherapy differ in effectiveness at improving serum bilirubin levels. There were conflicting results between trials depending on the population studied, the exact intervention used, and the analysis undertaken (low-quality evidence).

Note
We found no evidence from RCTs on mortality, neurological/neurodevelopmental outcomes, or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Blue-green fluorescent versus blue fluorescent lamps** We found three RCTs comparing blue-green fluorescent light with blue fluorescent light. [9] [10] [11]
The first RCT (85 infants, preterm with a gestational age 196–258 days, postnatal age >24 hours, non-haemolytic hyperbilirubinaemia) compared treatment with six turquoise (blue-green) fluorescent lamps plus two daylight fluorescent lamps versus six blue fluorescent lamps plus two daylight fluorescent lamps. [9] The RCT found no significant difference in total serum bilirubin level decrease after 48 hours of treatment with turquoise light compared with blue light (P = 0.36; absolute data presented graphically).

The second RCT (141 infants, preterm with a gestational age 196–258 days, postnatal age >24 hours, non-haemolytic hyperbilirubinaemia, and no previous phototherapy) compared phototherapy with eight turquoise fluorescent lamps at an average distance of 41 cm versus phototherapy with eight blue fluorescent lamps at an average distance of 32 cm. [10] The RCT found that, compared with blue fluorescent light, turquoise fluorescent light significantly increased the mean decrease in serum bilirubin levels after 24 hours of treatment (mean decrease: 92 micromol/L with turquoise light *v* 78 micromol/L with blue light; mean difference 15 micromol/L; P = 0.008). [10]

The third RCT (40 infants, low birth weight, hyperbilirubinaemia in first 4 days of life, healthy) compared treatment with blue-green fluorescent lights versus treatment with blue fluorescent lights. [11] The RCT found that, compared with blue fluorescent light, blue-green fluorescent light significantly reduced the number of infants still requiring phototherapy after 24 hours of treatment (1/20 [5%] with blue-green light *v* 10/20 [50%] with blue light; P <0.0001). The RCT also found that blue-green fluorescent light significantly increased the mean percentage decrement in serum bilirubin levels after 24 hours of treatment compared with blue fluorescent light (46% with blue-green light v 23% with blue light; P <0.0001). [11]

Harms: **Blue-green fluorescent versus blue fluorescent lamps** The first two RCTs [9] [10] reported that there were no adverse effects apart from 'loose green stools'. However, it is unclear as to the

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number of babies who had this adverse effect and in what treatment allocation group they were. The third RCT gave no information about adverse effects. [11]

Comment: We found one further three-armed RCT (114 jaundiced, but otherwise healthy, term infants), which compared six focused arrays of blue LED phototherapy, six focused arrays of blue-green LED phototherapy, and conventional phototherapy consisting of three halogen-quartz bulbs. [12] We only report the data for the blue LED phototherapy compared with blue-green LED phototherapy arms here (47 infants). [12] The RCT found no significant difference in the mean number of hours spent under phototherapy with blue-green LED phototherapy compared with blue LED phototherapy (39.2 hours with blue-green LED *v* 31.6 hours with blue LED; P value reported as not significant). The RCT also found no significant difference between groups in the mean rate of serum bilirubin level decline (–1.55 micromol/L with blue-green LED *v* –2.82 micromol/L with blue LED; P value reported as not significant). [12] The RCT reported that no adverse effects were noted. [12]

Clinical guide
Blue-green fluorescent light appears to be more effective than blue fluorescent light in reducing the duration of treatment of unconjugated hyperbilirubinaemia.

OPTION BLUE LED VERSUS CONVENTIONAL QUARTZ-HALOGEN

Mortality
Blue LED compared with conventional quartz-halogen We don't know whether blue LED and conventional phototherapy (using halogen-quartz bulbs) differ in effectiveness at reducing mortality in preterm infants as we only found one small RCT (low-quality evidence).

Duration of treatment
Blue LED compared with conventional quartz-halogen Hospital phototherapy using blue LED lamps may be more effective at reducing the number of hours spent under phototherapy compared with conventional phototherapy (using halogen-quartz bulbs) in term and preterm infants (low-quality evidence).

Serum bilirubin level
Blue LED compared with conventional quartz-halogen We don't know whether blue LED and conventional phototherapy (using halogen-quartz bulbs) differ in effectiveness at improving the rate of serum bilirubin decline (low-quality evidence).

Note
We found no evidence from RCTs on neurological/neurodevelopmental outcomes or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Blue LED versus conventional quartz-halogen** We found one systematic review (search date 2010) [13] and two subsequent RCTs. [14] [15] The review (term and preterm neonates) found that phototherapy with blue LED compared with conventional quartz-halogen phototherapy significantly reduced the number of hours spent under phototherapy (4 trials, 292 neonates; MD –5.00, 95% CI –9.03 to –0.98; heterogeneity I^2 = 79%, P = 0.003; absolute results not reported). It also found no significant difference in the rate of serum bilirubin level decline with blue LED compared with conventional phototherapy (2 trials, 173 neonates; MD +0.02, 95% CI –0.03 to +0.07; absolute results not reported). The first RCT (3-armed trial; 45 preterm neonates with neonatal hyperbilirubinemia and indication for phototherapy according to American Academy of Pediatrics [AAP] criteria) compared blue LED, conventional halogen-quartz phototherapy, and conventional fluorescent blue lights. [14] We only report data for blue LED versus conventional halogen-quartz phototherapy here (30 neonates). The RCT found no significant difference in the mean number of hours spent under phototherapy (110.4 hours with blue LED *v* 92.8 hours with conventional halogen-quartz). It also found no significant difference in the mean rate of bilirubin level decline with blue LED versus conventional halogen-quartz phototherapy (0.057 mg/dL/hour with blue LED *v* 0.055 mg/dL/hour with conventional halogen-quartz). The second RCT (58 preterm infants without skin lesions and requiring phototherapy) found no significant difference in mortality rate (5/33 [15%] with blue LED *v* 1/25 [4%] with conventional phototherapy; P = 0.167). [15] It also found no significant difference in mean serum bilirubin after 24 hours (6.2 mg/dL with blue LED *v* 7.5 mg/dL with conventional phototherapy; P = 0.105).

Harms: **Blue LED versus conventional quartz-halogen** The review did not report any adverse effects for this comparison. [13] The first and second RCTs included in the review reported that there were no adverse effects in either group. [12] [16] The third RCT, also included in the review, reported that no one in either group required exchange transfusion, developed rashes, or had temperature instability. [17] It also found no significant difference between groups in weight loss or in the incidence of rebound jaundice (weight loss: 1.89% of weight loss against initial weight with blue LED and

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1.99% of weight loss against initial weight with conventional phototherapy; P = 0.33; rebound jaundice: 27% with blue LED *v* 18% with conventional phototherapy; P = 0.43). [17] The subsequent RCT that reported on adverse effects [15] found no significant difference in the number of skin eruptions (macules; papules or maculopapular; none purpuric or bullous) (11/33 [33%] with blue LED *v* 9/25 [36%] with conventional phototherapy; P = 0.832).

Comment: In the meta-analysis, [13] one three-armed RCT combined two arms (blue-green and blue LEDs, n = 47) versus conventional phototherapy (n = 57). In another RCT (n = 31), the control group (n = 14) received phototherapy with a device incorporating a metal vapour discharge blue lamp with two filters, which the systematic review termed as a 'halogen light source'. However, neither of these RCTs was the cause of the heterogeneity.

We found one further RCT (66 healthy infants, at least 35 weeks' gestation) that compared phototherapy using blue LED (overhead neoBLUE LED plus either BiliBlanket or Wallaby system underneath) versus phototherapy with blue fluorescent light (8 overhead blue fluorescent lights plus either BiliBlanket or Wallaby system underneath). [18] The RCT found no significant difference in the mean rate of serum bilirubin level decline with blue LED compared with blue fluorescent phototherapy (0.35 mg/dL/hour with blue LED *v* 0.27 mg/dL/hour with blue fluorescent phototherapy; P = 0.20). [18] The RCT gave no information on adverse effects. [18]

OPTION BLUE-GREEN LED VERSUS CONVENTIONAL QUARTZ-HALOGEN

Duration of treatment
Blue-green LED compared with conventional quartz-halogen We don't know whether six focused arrays of blue-green LED phototherapy and conventional phototherapy consisting of three halogen-quartz bulbs differ in effectiveness at reducing the mean number of hours of phototherapy in jaundiced but otherwise healthy term infants (low-quality evidence).

Serum bilirubin level
Blue-green LED compared with conventional quartz-halogen We don't know whether six focused arrays of blue-green LED phototherapy and conventional phototherapy consisting of three halogen-quartz bulbs differ in effectiveness at improving the mean rate of serum bilirubin decline in jaundiced but otherwise healthy term infants (low-quality evidence).

Note
We found no evidence from RCTs on mortality, neurological/neurodevelopmental outcomes, or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Blue-green LED versus conventional quartz-halogen** We found one systematic review (search date 2010), [13] which identified one three-armed RCT. As the systematic review did not report further information for this comparison, we have reported directly from the RCT. [12] The RCT (114 jaundiced, but otherwise healthy, term infants) compared six focused arrays of blue LED phototherapy, six focused arrays of blue-green LED phototherapy, and conventional phototherapy consisting of three halogen-quartz bulbs. [12] We only report the data for the blue-green LED phototherapy versus conventional phototherapy comparison here (79 infants). The RCT found no significant difference in the mean number of hours spent under phototherapy (39.2 hours with blue-green light *v* 35.4 hours with conventional phototherapy; P value reported as not significant) or in the mean rate of serum bilirubin level decline (–1.55 micromol/hour with blue-green light *v* –2.42 micromol/hour with conventional phototherapy; P value reported as not significant) with blue-green LED phototherapy compared with conventional phototherapy. [12]

Harms: **Blue-green LED versus conventional quartz-halogen** The RCT reported that no adverse effects were found. [12]

Comment: **Clinical guide**
There appears to be no clear benefit or harm in choosing either a blue-green LED or a conventional quartz halogen lamp for the treatment of unconjugated hyperbilirubinaemia. However, other comparisons have found that blue-green LED is more effective than blue LED and blue LED is more effective than conventional quartz-halogen; therefore, in theory, there may be some clinical benefit in choosing blue-green LED over conventional quartz-halogen lights.

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QUESTION **What are the effects of different intensities of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants?**

OPTION CLOSE PHOTOTHERAPY VERSUS DISTANT LIGHT-SOURCE PHOTOTHERAPY

Duration of treatment

Close phototherapy compared with distant light-source phototherapy Close light-source conventional phototherapy from a distance of 20 cm above the neonate seems more effective than more distant light-source phototherapy at 40 cm above the neonate at reducing mean duration of treatment in infants with hyperbilirubinaemia not severe enough to require exchange transfusion and with absence of congenital metabolic disorders (moderate-quality evidence).

Serum bilirubin level

Close phototherapy compared with distant light-source phototherapy Closer phototherapy may be more effective than more distant phototherapy at reducing mean serum bilirubin level in infants with uncomplicated hyperbilirubinaemia (moderate-quality evidence).

Note

We found no evidence from RCTs on mortality, neurological/neurodevelopmental outcomes, or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, **see table, p 19 .**

Benefits:

Close phototherapy versus distant light-source phototherapy We found two RCTs. [19] [20] The first RCT (774 infants, hyperbilirubinaemia not severe enough to require exchange transfusion, absence of history of traditional herbal treatment, absence of treatment with phenobarbitol, absence of septicaemia, absence of hepatomegaly regardless of cause, absence of suspected congenital metabolic disorders) compared conventional phototherapy given from a distance of 20 cm (close light-source) above the neonate versus 40 cm (distant light-source) above the neonate. [19] The RCT found that close light-source phototherapy significantly reduced the mean duration of treatment compared with distant light-source phototherapy (66 hours with close light-source *v* 81.6 hours with distant light-source; P <0.001). [19]

The second four-armed RCT (151 healthy neonates, gestational age at least 33 weeks, uncomplicated hyperbilirubinemia not severe enough to require double phototherapy or exchange transfusion) compared continuous blue LED phototherapy delivered for 24 hours at four distances above the neonates (distances from mattress were 20, 29, 38, and 47 cm). [20] The RCT found that the decreasing distance significantly reduced mean percentage change in serum bilirubin level over 24 hours when considering all four groups (34% with 47-cm distance; 41% with 38-cm distance; 40% with 29-cm distance; 49% with 20-cm distance; P <0.001 among groups). Head-to-head comparisons also showed a significant reduction in serum bilirubin with closer distance except for 38 cm versus 29 cm (47 cm *v* 38 cm: P = 0.004; 38 cm *v* 29 cm: P = 0.98; 29 cm *v* 20 cm: P = 0.001).

Harms:

Close phototherapy versus distant light-source phototherapy The RCT found no significant difference in adverse effects such as troublesome skin rashes, burns, clinical dehydration, or lethargy between close and distant phototherapy (no further data reported). [19]

Comment:

Clinical guide

It is generally accepted that intensive phototherapy applied to reduce the bilirubin levels rapidly (rather than merely to prevent levels rising further) has greatly reduced the need for exchange transfusions in infants with or without haemolysis.

OPTION DOUBLE PHOTOTHERAPY VERSUS SINGLE PHOTOTHERAPY

Need for exchange transfusion

Double compared with single phototherapy We don't know whether fibreoptic plus conventional phototherapy is more effective than conventional phototherapy alone at reducing the rate of exchange transfusion as we found insufficient evidence from one small RCT (low-quality evidence).

Duration of treatment

Double compared with single phototherapy Double conventional phototherapy (using daylight fluorescent lamps) may be more effective than single conventional phototherapy at reducing the duration of treatment in term infants of birth weight 2500 g or above with haemolysis included. Conventional phototherapy plus fibreoptic Wallaby phototherapy may be more effective than Wallaby, BiliBlanket, or conventional phototherapy alone at reducing mean duration of treatment in preterm infants of less than 31 weeks' gestation with haemolytic jaundice excluded. We don't know whether fibreoptic plus conventional phototherapy is more effective than single conventional phototherapy in

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reducing the need for additional phototherapy or repeat phototherapy for rebound jaundice in term and preterm infants. We don't know whether double fibreoptic phototherapy (infants wrapped in 2 BiliBlankets) is more effective than single conventional therapy at reducing duration of treatment or use of repeat phototherapy in term infants with haemolysis excluded (very low-quality evidence).

Serum bilirubin level

Double compared with single phototherapy Double conventional phototherapy (using daylight fluorescent lamps) may be more effective than single conventional phototherapy at increasing the rate of reduction of serum bilirubin in term infants of birth weight 2500 g or above with haemolysis included. Conventional phototherapy plus fibreoptic Wallaby phototherapy may be more effective than Wallaby, BiliBlanket, or conventional phototherapy alone at reducing the increase in bilirubin levels over the first 24 hours in preterm infants of less than 31 weeks' gestation with haemolytic jaundice excluded. We don't know whether fibreoptic plus conventional phototherapy is more effective than single conventional phototherapy at improving the percentage change in serum bilirubin levels after 24 or 48 hours in term and preterm infants. We don't know whether double fibreoptic phototherapy (infants wrapped in 2 Bili-Blankets) is more effective than single conventional therapy at improving the percentage change in serum bilirubin per hour or per day in term infants with haemolysis excluded. Double surface phototherapy may be more effective than single surface phototherapy at increasing the total decline in serum bilirubin levels after 48 hours in term infants of 2500 g or above with non-haemolytic hyperbilirubinaemia who were exclusively breastfed, but we don't know whether it is more effective at 24 to 48 hours (very low-quality evidence).

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits:

Double phototherapy versus single phototherapy We found one systematic review (search date 2000; term and preterm infants; randomised and quasi-randomised trials; see Comment below) [21] and three subsequent RCTs. [22] [23] [24]

The systematic review included one RCT (86 term infants, haemolysis excluded) comparing double fibreoptic phototherapy (infants wrapped in 2 BiliBlankets) versus single conventional phototherapy. [21] The RCT included in the review found no significant difference between groups in duration of treatment, percentage change in serum bilirubin (SBR) per hour, percentage change in serum bilirubin per day, and the use of repeat phototherapy for rebound jaundice (duration of treatment: MD +2.24 hours, 95% CI –10.68 hours to +15.16 hours; percentage change in serum bilirubin per hour: MD –0.04%, 95% CI –0.17% to +0.09%; percentage change in SBR per day: MD +2.82%, 95% CI –1.84% to +7.48%; and the use of repeat phototherapy for rebound jaundice: RR 1.05, 95% CI 0.07 to 16.22). [21] The review also compared double phototherapy using a combination of fibreoptic plus conventional phototherapy versus conventional phototherapy alone. It found no significant difference between fibreoptic plus conventional phototherapy and single conventional phototherapy in exchange transfusion, additional phototherapy, and percentage change in serum bilirubin after 24 or 48 hours, although it noted a trend favouring the fibreoptic plus conventional group (exchange transfusion: 1 trial; 0/19 [0%] with fibreoptic plus conventional *v* 2/23 [8%] with conventional alone; RR 0.24, 95% CI 0.01 to 4.72; additional phototherapy: 1 trial; 0/90 [0%] with fibreoptic plus conventional *v* 4/90 [4%] with conventional; RR 0.11, 95% CI 0.01 to 2.02; percentage change in SBR after 24 hours: 1 trial, 26 infants; MD –3.2%, 95% CI –17.2% to +10.8%; percentage change in SBR after 48 hours: MD –9.2%, 95% CI –25.02% to +6.62%). It found no significant difference between fibreoptic plus conventional phototherapy and single conventional phototherapy in repeat phototherapy for rebound jaundice (6 trials; 36/232 [16%] with fibreoptic plus conventional *v* 30/240 [13%] with conventional; RR 1.29, 95% CI 0.85 to 1.95). [21]

The first subsequent RCT (51 term infants, birth weight 2500 g or more, haemolysis included) compared double conventional phototherapy using daylight fluorescent lamps versus single conventional phototherapy. [22] It found that double conventional phototherapy reduced serum bilirubin at a significantly higher rate during the first 24 hours compared with single conventional phototherapy (3.8 micromol/L/hour with double *v* 2.4 micromol/L/hour with single; P = 0.02). It found a trend for double conventional phototherapy to reduce bilirubin at a higher rate on the second day, but this did not reach significance (P = 0.06). It found that double conventional phototherapy significantly reduced duration of treatment compared with single conventional phototherapy (34.9 hours with double *v* 43.7 hours with single; P = 0.039). It did not report on kernicterus or other long-term outcomes.

The second subsequent RCT (140 preterm infants, gestation <31 weeks, infants with haemolytic jaundice excluded) compared single conventional phototherapy, fibreoptic Wallaby phototherapy, fibreoptic BiliBlanket phototherapy, and combined conventional plus fibreoptic Wallaby phototherapy. [23] It found that the combined phototherapy reduced mean duration of treatment required compared with either of the treatments used alone (Wallaby: 92 hours; BiliBlanket: 95 hours; conventional: 90 hours; combined Wallaby and conventional: 75 hours; P <0.05 for combined Wallaby and conventional *v* either Wallaby or BiliBlanket alone; P <0.01 for combined Wallaby and conventional *v* conventional alone). It also found that the combination of conventional phototherapy plus Wallaby fibreoptic phototherapy produced a smaller increase in bilirubin levels over the first 24

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hours compared with conventional phototherapy alone (16% with conventional plus Wallaby fibre-optic *v* 27% with conventional alone; P <0.01). [23]

The third subsequent RCT (60 term infants 37–42 weeks, birth weight 2500 g or more, exclusively breastfed, 1- and 5-minute Apgar scores >6, total SBR 13.0–19.9 mg/dL, with non-haemolytic hyperbilirubinaemia) compared double surface phototherapy (4 deep blue and 2 daylight fluorescent lamps at least 30 cm above the baby plus 4 deep blue fluorescent lamps 25 cm below the baby) with single surface phototherapy (4 deep blue and 2 daylight fluorescent lamps at least 30 cm above the baby). [24] The RCT found no significant difference in the mean serum bilirubin levels between double surface phototherapy compared with single surface phototherapy at 24 hours (10.3 mg/dL with double surface phototherapy *v* 11.3 mg/dL with single surface phototherapy; P = 0.05). However, the RCT found that, compared with single surface phototherapy, double surface phototherapy significantly increased levels of decline in serum bilirubin after 24 hours (5.4 mg/dL with double surface *v* 3.5 mg/dL with single surface; P <0.001). The RCT found no significant difference between groups in the total declined serum bilirubin levels between 24 and 48 hours (3.1 mg/dL with double surface *v* 3.0 mg/dL with single surface; P = 0.9). The RCT also found that, compared with single surface phototherapy, double surface phototherapy significantly increased total decline in serum bilirubin levels after 48 hours (8.4 mg/dL with double surface *v* 6.5 mg/dL with single surface; P = 0.001). No exchange transfusions were performed in either group. [24]

Harms:

Double phototherapy versus single phototherapy One RCT found no significant difference between double conventional and single conventional phototherapy in weight reduction, frequency of stooling, or fever. [22] Another RCT found a small increase in rates of transient erythema using the combination of Wallaby and conventional phototherapy compared with one type of phototherapy (12/35 [34%] with combined *v* 10/35 [29%] with conventional *v* 9/35 [26%] with Wallaby *v* 8/35 [23%] with BiliBlanket; significance not assessed). [23] The third subsequent RCT found that double surface phototherapy significantly increased body temperature compared with single surface phototherapy after 24 hours of treatment (37.1°C with double surface phototherapy *v* 36.9°C with single surface phototherapy; P = 0.003). [24] The RCT also found that double surface phototherapy significantly lowered the number of stools per day compared with single surface phototherapy (4.3 stools/day with double surface phototherapy *v* 7.2 stools/day with single surface phototherapy; P = 0.001). The RCT found no significant difference between groups in body weight at 24 and 48 hours after phototherapy commenced, percent body weight change at 24 and 48 hours after phototherapy commenced, or temperature after 48 hours of phototherapy (body weight at 24 hours: 3021.7 g with double surface phototherapy *v* 2971.7 g with single surface phototherapy, P = 0.52; body weight at 48 hours: 3043.3 g with double surface phototherapy *v* 3010.7 g with single surface phototherapy, P = 0.69; percent body weight change at 24 hours: 1.0% with double surface phototherapy *v* 1.5% with single surface phototherapy, P = 0.46; percent body weight change at 48 hours: 1.7% with double surface phototherapy *v* 2.3% with single surface phototherapy, P = 0.44; temperature after 48 hours; 36.9°C with double surface phototherapy *v* 36.9°C with single surface phototherapy, P = 0.13). [24]

Comment:

We found one further RCT (160 term infants, birth weight 2300 g or more, with total SBR >300 micromol/L if they were >48 hours of age, and >250 micromol/L if they were <48 hours of age; infants with congenital abnormalities and presence of direct hyperbilirubinaemia >20% excluded) of double conventional phototherapy compared to single phototherapy with reflecting curtains. [25] The RCT found no significant difference in mean serum bilirubin levels at 4 hours (ITT analysis: 22.7 micromol/L with single phototherapy plus reflecting curtains *v* 22.5 micromol/L with double phototherapy). The per-protocol analysis found similar non-significant changes in mean serum bilirubin levels at 4 hours (P = 0.813) and 10 hours (P = 0.678). There was also no significant difference in duration of phototherapy between groups (HR 1.06, 95% CI 0.88 to 1.27). No significant adverse events were reported in either group.

Clinical guide

It is generally accepted that intensive phototherapy applied to infants with already high serum bilirubin levels or rapidly rising serum bilirubin levels has greatly reduced the need for exchange transfusions in infants with or without haemolysis.

OPTION TRIPLE PHOTOTHERAPY VERSUS DOUBLE PHOTOTHERAPY

Serum bilirubin level

Triple phototherapy compared with double phototherapy We don't know whether triple phototherapy (2 single fluorescent lamps 25 cm above bed plus third fluorescent lamp 35 cm from bed) is more effective than double phototherapy (2 single fluorescent lamps 25 cm above bed) at improving mean bilirubin levels at 8, 16, or 24 hours in infants of 2500 g or more and of 37 weeks' gestation or above with non-haemolytic jaundice (low-quality evidence).

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

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Benefits: **Triple phototherapy versus double phototherapy** We found one RCT (40 infants >37 weeks' gestation, >2500 g, with no medical problems and non-haemolytic jaundice) comparing triple phototherapy (2 single fluorescent lamps 25 cm above bed plus third fluorescent lamp 35 cm from bed) with double phototherapy (2 single fluorescent lamps 25 cm above bed). [26] The RCT found no significant difference between triple and double phototherapy in the length of hospital stay (41.5 hours with triple *v* 34.6 hours with double; P = 0.211). The RCT also found no significant difference in mean bilirubin levels between triple and double phototherapy at 8, 16, or 24 hours (8 hours: 14 mg/dL with triple *v* 13.7 mg/dL with double, P = 0.59; 16 hours: 12.4 mg/dL with triple *v* 12.2 mg/dL with double, P = 0.76; 24 hours: 10.9 mg/dL with triple *v* 10.3 mg/dL with double, P = 0.37). [26]

Harms: **Triple phototherapy versus double phototherapy** The RCT gave no information on adverse effects. [26]

Comment: **Clinical guide**
It is generally accepted that intensive phototherapy applied to infants with already high serum bilirubin levels or rapidly rising serum bilirubin levels has greatly reduced the need for exchange transfusions in infants with or without haemolysis.

QUESTION **What are the effects of different total doses of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants?**

OPTION **INTERMITTENT PHOTOTHERAPY VERSUS CONTINUOUS PHOTOTHERAPY**

Duration of treatment
Intermittent phototherapy compared with continuous phototherapy We don't know whether intermittent equal-duration phototherapy (4 hours on, 4 hours off), intermittent short-duration phototherapy (1 hour on, 3 hours off), and continuous phototherapy differ in effectiveness at reducing duration of phototherapy treatment in term infants who are 2500 g or above with physiological jaundice (low-quality evidence).

Serum bilirubin level
Intermittent phototherapy compared with continuous phototherapy We don't know whether intermittent phototherapy (1 hour on, 1 hour off) is more effective than continuous phototherapy (2 hours on, 30 minutes off) at improving mean serum bilirubin levels at 12, 24, 36, and 48 hours in infants above 2000 g with hyperbilirubinaemia not exceeding the range for exchange transfusion nor requiring high-intensity phototherapy. We don't know whether continuous phototherapy and intermittent phototherapy (12 hours on, 12 hours off) differ in effectiveness at reducing the proportion of infants with serum bilirubin levels of more than 12 mg/dL or more than 15 mg/dL in preterm infants with birth weight 1250–2000 g who were Coombs' negative with no haemolytic anaemia, as the trial did not test the significance of differences between groups. We don't know whether intermittent equal-duration phototherapy (4 hours on, 4 hours off), intermittent short-duration phototherapy (1 hour on, 3 hours off), and continuous phototherapy differ in effectiveness at slowing the rate of increase in bilirubin levels or improving the rate of decrease of bilirubin levels in term infants of 2500 g or above with physiological jaundice (low-quality evidence).

Note
We found no evidence from RCTs on mortality, neurological/neurodevelopmental outcomes, or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Intermittent phototherapy versus continuous phototherapy** We found three RCTs comparing intermittent with continuous phototherapy. [27] [28] [29]
The first RCT (114 infants >2000 g, absence of concomitant disease, hyperbilirubinaemia not exceeding the range for exchange transfusion or requiring high-intensity phototherapy) compared intermittent phototherapy (phototherapy on for 1 hour then off for 1 hour) versus continuous phototherapy (2 hours on, 30 minutes off). [28] The RCT found no significant difference between intermittent compared with continuous phototherapy in mean serum bilirubin level at 12, 24, 36, and 48 hours (12 hours: 13.57 mg/dL with intermittent *v* 13.73 mg/dL with continuous, P = 0.6; 24 hours: 10.86 mg/dL with intermittent *v* 11.06 mg/dL with continuous, P = 0.6; 36 hours: 9.02 mg/dL with intermittent *v* 9.17 mg/dL with continuous, P = 0.7; 48 hours: 9.30 mg/dL with intermittent *v* 8.93 mg/dL with continuous, P = 0.7). [28]

The second three-armed RCT (120 preterm infants, birth weight 1250–2000 g, Coombs' negative, no haemolytic anaemia, no gross congenital anomalies, no severe respiratory distress syndrome) compared continuous phototherapy for 5 days versus intermittent phototherapy (12 hours on, 12 hours off) for 5 days or no treatment. [27] We only report the data on continuous and intermittent groups here. The RCT found no difference between groups in the proportion of preterm infants

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who had a serum bilirubin level higher than 12 mg/dL (3/40 [8%] with intermittent phototherapy *v* 2/40 [5%] with continuous phototherapy; P value not reported). However, the RCT found that, compared with intermittent phototherapy, a smaller proportion of preterm infants treated with continuous phototherapy had serum bilirubin levels higher than 15 mg/dL (1/40 [3%] with intermittent phototherapy *v* 0/40 [0%] with continuous phototherapy; P value not reported). [27]

The third RCT (34 term infants >2500 g, physiological jaundice) compared intermittent equal-duration therapy (4 hours on, 4 hours off) versus intermittent short-duration phototherapy (1 hour on, 3 hours off) versus continuous phototherapy. [29] The RCT found no significant difference in the duration of phototherapy required (86.7 hours with intermittent equal *v* 100.0 hours with intermittent short *v* 89.9 hours with continuous, P >0.05), but there was a significant difference in mean total hours of irradiation (43.4 hours with intermittent equal *v* 25.0 hours with intermittent short *v* 89.9 hours with continuous, P <0.001). The RCT also found no significant difference between groups in the rate of increase of serum bilirubin levels or in the rate of decrease in serum bilirubin levels (rate of increase of serum bilirubin levels: 1.25 micromol/L/hour with intermittent equal *v* 0.89 micromol/L/hour with intermittent short *v* 0.82 micromol/L/hour with continuous, P >0.05; rate of decrease in serum bilirubin levels: 1.49 micromol/L/hour with intermittent equal *v* 1.09 micromol/L/hour with intermittent short *v* 1.08 micromol/L/hour with continuous, P >0.05). [29]

Harms: **Intermittent phototherapy versus continuous phototherapy** The RCTs gave no information on adverse effects. [27] [28] [29]

Comment: **Clinical guide**
There appears to be no clear benefit or harm in choosing either continuous or intermittent phototherapy for the treatment of unconjugated hyperbilirubinaemia in infants more than 2000 g or term infants. There is the possibility that preterm infants treated with intermittent phototherapy will have higher serum bilirubin levels.

OPTION INCREASED SKIN EXPOSURE VERSUS STANDARD SKIN EXPOSURE PHOTOTHERAPY

Duration of treatment
Increased skin exposure compared with standard skin exposure phototherapy We don't know whether conventional phototherapy in partially clothed infants (disposable nappy only) and conventional phototherapy in naked infants differ in effectiveness at reducing the proportion of infants still requiring phototherapy at 24 to 48 hours and 48 to 72 hours in preterm infants of 1500 g or more and 36 weeks' gestation or less with non-haemolytic hyperbilirubinaemia with total serum bilirubin in the range for phototherapy (low-quality evidence).

Serum bilirubin level
Increased skin exposure compared with standard skin exposure phototherapy We don't know whether conventional phototherapy in partially clothed infants (disposable nappy only) and conventional phototherapy in naked infants differ in effectiveness at improving the mean percentage decline in serum bilirubin levels or the absolute change in mean serum bilirubin levels in preterm infants of 1500 g or more and of 36 weeks' gestation or less with non-haemolytic hyperbilirubinaemia with total serum bilirubin in the range for phototherapy (low-quality evidence).

Note
We found no evidence from RCTs on mortality, neurological/neurodevelopmental outcomes, or need for exchange transfusion.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Increased skin exposure versus standard skin exposure phototherapy** We found one RCT (59 preterm infants at least 36 weeks' gestation, more than 1500 g birth weight, non-haemolytic hyperbilirubinaemia with total serum bilirubin in range for phototherapy, absence of congenital anomaly, absence of need for respiratory support, absence of co-existing pathology) comparing conventional phototherapy in partially clothed infants (disposable nappy only) versus naked infants. [30] The RCT found no significant difference between groups in the number of infants still requiring phototherapy between 24 and 48 hours (13/30 [43%] with partial clothing *v* 13/29 [45%] with naked infants; P = 0.9). The RCT also found no significant difference between groups in the number of infants still requiring phototherapy between 48 and 72 hours (2/30 [7%] with partial clothing *v* 4/29 [14%] with naked infants; P = 0.4). The RCT found no significant difference between groups in the mean percentage decline in serum bilirubin levels (15.4% with partial clothing *v* 19.0% with naked infants; P = 0.4). There was also no significant difference between groups in the absolute change in mean serum bilirubin levels (37.6 micromol/L with partial clothing *v* 46.4 micromol/L with naked infants; P = 0.4). [30]

Harms: **Increased skin exposure versus standard skin exposure phototherapy** The RCT found no significant difference between phototherapy groups treated partially clothed (disposable nappy

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only) or naked in the incidence of the following Parenting Stress Index scores: 'parental distress', 'parent-child dysfunction' (1/25 [4%] with partial clothing *v* 3/25 [12%] with naked infants; P = 0.3), 'parent-child dysfunction', 'difficult child', or 'total stress score' ('parental distress': 6/25 [24%] with partial clothing *v* 9/25 [36%] with naked infants, P = 0.4; 'difficult child': 4/25 [16%] with partial clothing *v* 3/25 [12%] with naked infants, P = 0.7; 'total stress score': 7/25 [28%] with partial clothing *v* 7/25 [28%] with naked infants, P = 1). [30] The RCT also reported no significant difference between groups in the incidence of rebound jaundice requiring phototherapy (7/30 [23%] with partial clothing *v* 9/29 [31%] with naked infants; P = 0.5). The RCT reported that there were no episodes of patent ductus arteriosus, skin rashes, or dehydration in phototherapy groups treated either partially clothed (disposable nappy only) or naked. [30]

Comment: None.

QUESTION **What are the effects of starting hospital phototherapy at different thresholds in term and preterm infants?**

OPTION **PROPHYLACTIC PHOTOTHERAPY VERSUS THRESHOLD PHOTOTHERAPY**

Neurological/neurodevelopmental outcomes
Prophylactic phototherapy compared with threshold phototherapy We don't know whether prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) is more effective than threshold phototherapy (commencement once SBR > predetermined level; in this case >150 micromol/L) at reducing the proportion of infants with cerebral palsy, with the composite outcome of cerebral palsy or death, or with an abnormal developmental index score at 18 months, in infants of birth weight less than 1500 g within 12 hours of birth without isoimmunisation or major life-threatening anomaly (very low-quality evidence).

Duration of treatment
Prophylactic phototherapy compared with threshold phototherapy We don't know whether prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) is more effective than threshold phototherapy (commencement once SBR > predetermined level; in this case >150 micromol/L) at reducing the mean number of hours of phototherapy in infants of birth weight less than 1500 g within 12 hours of birth without isoimmunisation or major life-threatening anomaly (low-quality evidence).

Serum bilirubin level
Prophylactic phototherapy compared with threshold phototherapy We don't know whether prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) is more effective than threshold phototherapy (commencement once SBR > predetermined level; in this case >150 micromol/L) at reducing peak unconjugated serum bilirubin levels in infants of birth weight less than 1500 g within 12 hours of birth without isoimmunisation or major life-threatening anomaly. Subgroup analysis suggests that prophylactic phototherapy may be more effective than threshold phototherapy at reducing peak unconjugated serum bilirubin levels in infants with a birth weight less than 1000 g, but not in infants with a birth weight of 1000 g to 1499 g (low-quality evidence).

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits: **Prophylactic phototherapy versus threshold phototherapy** We found one RCT (95 infants, birth weight <1500 g, within 12 hours of birth, without isoimmunisation or major life-threatening anomaly) that compared prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) with threshold phototherapy (commencement once serum bilirubin [SBR] >150 micromol/L). [31] The RCT found no significant difference between groups in the combined outcome of death and cerebral palsy at 18 months (5/40 [13%] with prophylactic phototherapy *v* 10/43 [23%] with threshold phototherapy; OR 1.86, 95% CI 0.58 to 5.92; P = 0.4). The RCT also found no significance between groups in the incidence of cerebral palsy or in the incidence of abnormal developmental index score at 18 months (cerebral palsy: 2/37 [5%] with prophylactic phototherapy *v* 5/38 [12%] with threshold phototherapy; OR 2.43, 95% CI 0.44 to 13.34; P = 0.44; abnormal developmental index score <84: 9/37 [24%] with prophylactic phototherapy *v* 8/38 [21%] with threshold phototherapy; OR 0.87, 95% CI 0.30 to 2.48; P = 0.78). The RCT found no significant difference in the mean number of hours of phototherapy or in the mean total of days in neonatal intensive care unit with prophylactic compared with threshold phototherapy (mean number of hours of phototherapy: 85 hours with prophylactic phototherapy *v* 68.5 hours with threshold phototherapy; P >0.05; mean total of days in neonatal intensive care unit: 82.3 days with prophylactic phototherapy *v* 82.7 days with threshold phototherapy; P >0.05). [31]
The RCT found no significant difference in the peak unconjugated serum bilirubin levels between groups (170 micromol/L with prophylactic phototherapy *v* 183.5 micromol/L with threshold phototherapy; P >0.05); however, a subgroup analysis of infants with a birth weight <1000 g found that, compared with threshold phototherapy, prophylactic phototherapy significantly reduced peak unconjugated serum bilirubin levels (139.2 micromol/L with prophylactic phototherapy *v* 171.2 micro-

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mol/L with threshold phototherapy; P <0.02). [31] A further subgroup analysis of infants with a birth weight of 1000 g to 1499 g found no significant difference between groups in peak unconjugated serum bilirubin level (190.6 micromol/L with prophylactic phototherapy *v* 191.9 micromol/L with threshold phototherapy; P >0.05). The RCT found that, compared with threshold phototherapy, prophylactic phototherapy significantly reduced the number of infants whose peak serum bilirubin level was reached before 48 hours of age (1/45 [2%] with prophylactic phototherapy *v* 14/47 [30%] with threshold phototherapy; P <0.001). [31]

Harms: **Prophylactic phototherapy versus threshold phototherapy** The RCT found no significant difference between groups in the incidence of percentage weight loss, mean days to regain birth weight, incidence of intraventricular haemorrhage, incidence of periventricular leukomalacia, incidence of retinopathy of prematurity greater than stage 2, or rebound phototherapy (weight loss: 12% with prophylactic phototherapy *v* 11% with threshold phototherapy, P >0.05; mean days to regain birth weight: 11.8 days with prophylactic phototherapy *v* 11 days with threshold phototherapy, P >0.05; intraventricular haemorrhage: 15/43 [35%] with prophylactic phototherapy *v* 14/44 [32%] with threshold phototherapy, P >0.05; periventricular leukomalacia: 2/43 [4.7%] with prophylactic phototherapy *v* 2/44 [4.5%] with threshold phototherapy, P >0.05; retinopathy of prematurity >stage 2: 7/43 [16%] with prophylactic phototherapy *v* 11/44 [25%] with threshold phototherapy, P >0.05; rebound phototherapy (18/45 [40%] with prophylactic phototherapy *v* 12/47 [26%] with threshold phototherapy, P >0.05). [31]

Comment: **Clinical guide**
It is generally accepted that phototherapy should only be applied once serum bilirubin levels reach predefined thresholds.

OPTION LOW THRESHOLD VERSUS HIGH THRESHOLD PHOTOTHERAPY

Mortality
Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, serum bilirubin [SBR] expected to be 85 micromol/L, and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) and high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) seem equally effective at improving mortality before day 15, mortality before discharge, and mortality or the composite outcome of mortality and neurodevelopmental impairment at 18 to 22 months in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality (moderate-quality evidence).

Neurological/neurodevelopmental outcomes
Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L, and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) seems more effective than high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) at reducing the proportion of infants with neurodevelopmental impairment, profound impairment, and severe hearing loss at 18 to 22 months in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality, but we don't know about cerebral palsy or blindness (moderate-quality evidence).

Need for exchange transfusion
Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L, and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) and high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) seem equally effective at preventing the need for exchange transfusions in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality (moderate-quality evidence).

Duration of treatment
Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L, and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) seems less effective than high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) at reducing the duration of phototherapy in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality. We don't know whether commencing phototherapy once SBR is more than 13 mg/dL, commencing phototherapy once SBR is 10 mg/dL or above and treating for 12 hours, and commencing phototherapy once SBR is 10 mg/dL or above and treating for 24 hours differ in effectiveness at reducing the proportion of infants who receive phototherapy at less than 72 hours or more than 72 hours in infants of birth weight under 2500 g (moderate-quality evidence).

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Serum bilirubin level

Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L, and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) seems more effective than high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) at decreasing the level of serum bilirubin at day 5 in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality (moderate-quality evidence).

For GRADE evaluation of interventions for neonatal jaundice, see table, p 19 .

Benefits:

Low threshold versus high threshold phototherapy We found two RCTs comparing low threshold with high threshold phototherapy. [32] [33] We also found one subsequent report of the first RCT, [32] which did not add any further information to our outcomes of interest. [34]
The first RCT (1974 infants, extremely low birth weight, 12–36 hours old, absence of terminal condition, absence of previous phototherapy, absence of major congenital anomaly, non-severe haemolytic disease, absence of congenital non-bacterial infection) compared low threshold phototherapy (initiation of phototherapy at enrolment, serum bilirubin [SBR] expected to be 85 micromol/L and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) versus high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life). [32]

The RCT found no significant difference between groups in mortality before day 15 or mortality before discharge (mortality before day 15: 96/990 [9.7%] with low threshold *v* 95/984 [9.7%] with high threshold; RR 1.00, 95% CI 0.88 to 1.30; mortality before discharge: 209/990 [21%] with low threshold *v* 201/984 [20%] with high threshold; RR 1.03, 95% CI 0.88 to 1.21). [32] The RCT also found no significant difference between groups in mortality or mortality and neurodevelopmental impairment at 18 to 22 months (mortality: 230/946 [24%] with low threshold *v* 218/944 [23%] with high threshold; RR 1.05, 95% CI 0.90 to 1.22; mortality and neurodevelopmental impairment: 465/902 [52%] with low threshold *v* 493/902 [55%] with high threshold; RR 0.94, 95% CI 0.87 to 1.02).

The RCT found that, compared with high threshold phototherapy, low threshold phototherapy significantly reduced the risk of neurodevelopmental impairment and profound impairment at 18 to 22 months (neurodevelopmental impairment: 235/902 [26%] with low threshold *v* 275/902 [30%] with high threshold; RR 0.86, 95% CI 0.74 to 0.99; profound impairment: 80/895 [9%] with low threshold *v* 119/896 [13%] with high threshold; RR 0.68, 95% CI 0.52 to 0.89). [32] However, the RCT found no significant difference between groups in cerebral palsy at 18 to 22 months (mild/moderate or severe: 81/929 [9%] with low threshold *v* 91/924 [10%] with high threshold; RR 0.89, 95% CI 0.67 to 1.18).

The RCT found that low threshold phototherapy significantly reduced the risk of severe hearing loss compared with high threshold phototherapy at 18 to 22 months (9/925 [1%] with low threshold *v* 28/922 [3%] with high threshold; RR 0.32, 95% CI 0.15 to 0.98). It found no significant difference in blindness compared with high threshold phototherapy at 18 to 22 months (2/928 [0.2%] with low threshold *v* 7/924 [0.8%] with high threshold; RR 0.28, 95% CI 0.06 to 1.37). [32]

The RCT found that low threshold phototherapy significantly increased the duration of phototherapy compared with high threshold phototherapy (88 hours with low threshold *v* 35 hours with high threshold; P <0.001). However, it found no significant difference between groups in the number of exchange transfusions or length of hospital stay (exchange transfusions: 2 with low threshold *v* 3 with high threshold, P = 0.69; length of hospital stay: 97 days with low threshold *v* 100 days with high threshold, P = 0.11). [32] The RCT found that low threshold phototherapy significantly decreased the serum bilirubin level at day 5 compared with high threshold phototherapy (0.33 mg/dL with low threshold *v* 0.48 mg/dL with high threshold; P <0.001). [32]

The second RCT (78 infants, birth weight <2500 g) compared starting phototherapy once serum bilirubin levels were above 13 mg/dL versus starting phototherapy once serum bilirubin levels were 10 mg/dL or more and treating for 12 hours, versus starting phototherapy once serum bilirubin levels were 10 mg/dL or more and treating for 24 hours. [33]

The RCT found no difference in the number of infants requiring phototherapy at less than 72 hours of age (14/26 [54%] with higher threshold *v* 17/29 [59%] with lower threshold and 12 hours of phototherapy *v* 9/23 [39%] with lower threshold and 24 hours of phototherapy; P values not reported). [33]

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The RCT also found no difference in the number of infants who received phototherapy in the first 72 hours of life and then required additional phototherapy (8/14 [57%] with higher threshold *v* 6/17 [35%] with lower threshold and 12 hours of phototherapy *v* 2/9 [22%] with lower threshold and 24 hours of phototherapy; P values not reported). [33]

The RCT found no difference in the number of infants requiring phototherapy at 72 hours of age or more (12/26 [46%] with higher threshold *v* 12/29 [41%] with lower threshold and 12 hours of phototherapy *v* 14/23 [61%] with lower threshold and 24 hours of phototherapy; P values not reported). [33]

The RCT found no difference in the number of infants who received phototherapy after 72 hours of age and required additional phototherapy (3/12 [25%] with higher threshold *v* 1/12 [8%] with lower threshold and 12 hours of phototherapy *v* 2/14 [8%] with lower threshold and 24 hours of phototherapy; P values not reported). [33]

Harms: **Low threshold versus high threshold phototherapy** The first RCT found no significant difference between groups in patent ductus arteriosus (556/990 [56%] with low threshold *v* 582/984 [59%] with high threshold; RR 0.95, 95% CI 0.88 to 1.02), or necrotising enterocolitis (105/990 [11%] with low threshold *v* 117/984 [12%] with high threshold; RR 0.90, 95% CI 0.79 to 1.14). [32] The second RCT gave no information on adverse effects. [33]

Comment: **Clinical guide**
Using a lower threshold (SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) for the commencement of phototherapy in extremely low birth weight infants decreases the risk of long term complications such as neurodevelopmental impairment and severe hearing loss.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

(Daylight) fluorescent versus blue fluorescent lamps Condition restructured. No new evidence. Categorised as 'unknown effectiveness'.

Blue LED versus conventional quartz-halogen Condition restructured. One systematic review [13] and two RCTs [14] [15] added. Categorised as 'likely to be beneficial'.

Blue fluorescent versus green fluorescent lamps Condition restructured. No new evidence. Categorised as 'unknown effectiveness'.

Blue-green LED versus conventional quartz-halogen Condition restructured. One systematic review added. [13] Categorised as 'unknown effectiveness'.

Blue-green fluorescent versus blue fluorescent lamps Condition restructured. No new evidence. Categorised as 'likely to be beneficial'.

Close phototherapy versus distant light-source phototherapy Condition restructured. One RCT added. [20] Categorised as 'likely to be beneficial'.

Double phototherapy versus single phototherapy Condition restructured. One RCT added to the Comment section. [25] Categorised as 'likely to be beneficial'.

Increased skin exposure versus standard skin exposure phototherapy Condition restructured. No new evidence. Categorised as 'unknown effectiveness'.

Intermittent phototherapy versus continuous phototherapy Condition restructured. No new evidence. Categorised as 'unknown effectiveness'.

Low threshold versus high threshold phototherapy Condition restructured. One subsequent report of a previously included RCT added. [34] Categorised as 'likely to be beneficial'.

Prophylactic phototherapy versus threshold phototherapy Condition restructured. No new evidence. Categorised as 'unknown effectiveness'.

Triple phototherapy versus double phototherapy Condition restructured. No new evidence. Categorised as 'unknown effectiveness'.

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REFERENCES

1. Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. *Pediatrics* 2004;114:e130–e153.[PubMed]
2. Kumar RK. Neonatal jaundice. An update for family physicians. *Aust Fam Physician* 1999;28:679–682.[PubMed]
3. Gale R, Seidman DS, Stevenson DK. Hyperbilirubinemia and early discharge. *J Perinatol* 2001;21:40–43.[PubMed]
4. Turkel SB, Guttenberg ME, Moynes DR, et al. Lack of identifiable risk factors for kernicterus. *Pediatrics* 1980;66:502–506.[PubMed]
5. Hansen TW. Kernicterus in term and near-term infants – the specter walks again. *Acta Paediatr* 2000;89:1155–1157.[PubMed]
6. Sisson TR, Kendall N, Shaw E, et al. Phototherapy of jaundice in the newborn infant. II. Effect of various light intensities. *J Pediatr* 1972;81:35–38.[PubMed]
7. Ayyash H, Hadjigeorgiou E, Sofatzis I, et al. Green or blue light phototherapy for neonates with hyperbilirubinaemia. *Arch Dis Child* 1987;62:843–845.[PubMed]
8. Vecchi C, Donzelli GP, Sbrana G, et al. Phototherapy for neonatal jaundice: clinical equivalence of fluorescent green and "special" blue lamps. *J Pediatr* 1986;108:452–456.[PubMed]
9. Ebbesen F, Agati G, Pratesi R, et al. Phototherapy with turquoise versus blue light. *Arch Dis Child Fetal Neonat Ed* 2003;88:F430–F431.[PubMed]
10. Ebbesen F, Madsen P, Stovring S, et al. Therapeutic effect of turquoise versus blue light with equal irradiance in preterm infants with jaundice. *Acta Paediatr* 2007;96:837–841.[PubMed]
11. Donzelli GP, Pratesi S, Rapisardi G, et al. 1-Day phototherapy of neonatal jaundice with blue-green lamp. *Lancet* 1995;346:184–185.[PubMed]
12. Seidman DS, Moise J, Ergaz Z, et al. A prospective randomized controlled study of phototherapy using blue and blue-green light-emitting devices, and conventional halogen-quartz phototherapy. *J Perinatol* 2003;23:123–127.[PubMed]
13. Kumar P, Chawla D, Deorari A. Light-emitting diode phototherapy for unconjugated hyperbilirubinaemia in neonates. In: The Cochrane Library, Issue 1, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2010.
14. Viau Colindres J, Rountree C, Destarac MA, et al. Prospective randomized controlled study comparing low-cost LED and conventional phototherapy for treatment of neonatal hyperbilirubinemia. *J Trop Pediatr* 2012;58:178–183.[PubMed]
15. Surmeli-Onay O, Korkmaz A, Yigit S, et al. Phototherapy rash in newborn infants: Does it differ between conventional and light emitting diode phototherapy? *Pediatr Dermatol* 2013;30:529–533.[PubMed]
16. Seidman DS, Moise J, Ergaz Z, et al. A new blue light-emitting phototherapy device: a prospective randomized controlled study. *J Pediatr* 2000;136:771–774.[PubMed]
17. Martins BM, De Carvalho M, Moreira ME, et al. Efficacy of new microprocessed phototherapy system with five high intensity light emitting diodes (Super LED). *J Pediatria (Rio J)* 2007;83:253–258.[PubMed]
18. Maisels MJ, Kring EA, DeRidder J, et al. Randomized controlled trial of light-emitting diode phototherapy. *J Perinatol* 2007;27:565–567.[PubMed]
19. Pishva N, Madani A. Effects of the different light-source distances from the skin surface in conventional phototherapy. *Iran J Med Sci* 2004;29:189–191.
20. Vandborg PK, Hansen BM, Greisen G, et al. Dose-response relationship of phototherapy for hyperbilirubinemia. *Pediatrics* 2012;130:e352–e357.[PubMed]
21. Mills JF, Tudehope D. Fibreoptic phototherapy for neonatal jaundice. In: The Cochrane Library, Issue 1, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2000.
22. Nuntnarumit P, Naka C. Comparison of the effectiveness between the adapted-double phototherapy versus conventional-single phototherapy. *J Med Assoc Thai* 2002;85:S1159–S1166.[PubMed]
23. Romagnoli C, Zecca E, Papacci P, et al. Which phototherapy system is most effective in lowering serum bilirubin in very preterm infants? *Fetal Diagn Ther* 2006;21:204–209.[PubMed]
24. Boonyarittipong P, Kriangburapa W, Booranavanich K, et al. Effectiveness of double-surface intensive phototherapy versus single-surface intensive phototherapy for neonatal hyperbilirubinemia. *J Med Assoc Thai* 2008;91:50–55.[PubMed]
25. Abd Hamid IJ, M Iyen MI, Ibrahim NR, et al. Randomised controlled trial of single phototherapy with reflecting curtains versus double phototherapy in term newborns with hyperbilirubinaemia. *J Paediatr Child Health* 2013;49:375–379.[PubMed]
26. Naderi S, Safdarian F, Mazloomi D, et al. Efficacy of double and triple phototherapy in term newborns with hyperbilirubinemia: the first clinical trial. *Pediatr Neonatol* 2009;50:266–269.[PubMed]
27. Wu PY, Lim RC, Hodgman JE, et al. Effect of phototherapy in preterm infants on growth in the neonatal period. *J Pediatr* 1974;85:563–566.[PubMed]
28. Niknafs P, Mortazavi A, Torabinejad M, et al. Intermittent versus continuous phototherapy for reducing neonatal hyperbilirubinemia. *Iran J Pediatr* 2008;18:251–256.
29. Lau SP, Fung KP. Serum bilirubin kinetics in intermittent phototherapy of physiological jaundice. *Arch Dis Child* 1984;59:892–894.[PubMed]
30. Pritchard MA, Beller EM, Norton B. Skin exposure during conventional phototherapy in preterm infants: a randomized controlled trial. *J Paediatr Child Health* 2004;40:270–274.[PubMed]
31. Jangaard KA, Vincer MJ, Allen AC. A randomized trial of aggressive versus conservative phototherapy for hyperbilirubinemia in infants weighing less than 1500 g: short- and long-term outcomes. *Paediatr Child Health* 2007;12:853–858.[PubMed]
32. Morris BH, Oh W, Tyson JE, et al; NICHD Neonatal Research Network. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *N Engl J Med* 2008;359:1885–1896.[PubMed]
33. 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;2:1211–1212.[PubMed]
34. Tyson JE, Pedroza C, Langer J, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Does aggressive phototherapy increase mortality while decreasing profound impairment among the smallest and sickest newborns? *J Perinatol* 2012;32:677–684.[PubMed]

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TABLE **GRADE evaluation of interventions for neonatal jaundice**

Important outcomes	Mortality, neurological/neurodevelopmental, need for exchange transfusion, duration of treatment, serum bilirubin levels, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of different wavelengths of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants?									
1 (72) [6]	Duration of treatment	Fluorescent *v* blue fluorescent	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for no statistical analysis between groups
1 (72) [6]	Serum bilirubin levels	Fluorescent *v* blue fluorescent	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for no statistical analysis between groups
1 (262) [7]	Duration of treatment	Blue fluorescent *v* green fluorescent	4	0	0	–1	0	Moderate	Directness point deducted for restricted population
2 (356) [7] [8]	Serum bilirubin levels	Blue fluorescent *v* green fluorescent	4	–1	0	–1	0	Low	Quality point deducted for subgroup analysis (no overall analysis reported) in 1 RCT; directness point deducted for restricted population
1 (40) [11]	Duration of treatment	Blue-green fluorescent *v* blue fluorescent	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (266) [9] [10] [11]	Serum bilirubin levels	Blue-green fluorescent *v* blue fluorescent	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results; consistency point deducted for conflicting results
1 (58) [15]	Mortality	Blue LED *v* conventional quartz-halogen	4	–2	0	0	0	Low	Quality points deducted for sparse data and unclear randomisation/allocation concealment
2 (322) [13] [14]	Duration of treatment	Blue LED *v* conventional quartz-halogen	4	0	–1	–1	0	Low	Consistency point deducted for significant heterogeneity in meta-analysis; directness point deducted for variation in interventions and protocols for phototherapy affecting generalisability of results
3 (261) [13] [14] [15]	Serum bilirubin levels	Blue LED *v* conventional quartz-halogen	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for variation in interventions and protocols for phototherapy affecting generalisability of results
1 (79) [12]	Duration of treatment	Blue-green LED *v* conventional quartz-halogen	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (79) [12]	Serum bilirubin levels	Blue-green LED *v* conventional quartz-halogen	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of different intensities of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants?									
1 (774) [19]	Duration of treatment	Close phototherapy *v* distant light-source phototherapy	4	0	0	–1	0	Moderate	Directness point deducted for small number of comparators
1 (151) [20]	Serum bilirubin levels	Close phototherapy *v* distant light-source phototherapy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

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Important outcomes	Mortality, neurological/neurodevelopmental, need for exchange transfusion, duration of treatment, serum bilirubin levels, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (42) [21]	Need for exchange transfusion	Double phototherapy *v* single phototherapy	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of events (2 in total) indicating weak power to demonstrate difference between groups
9 (749) [21] [23] [22]	Duration of treatment	Double phototherapy *v* single phototherapy	4	–2	0	–1	0	Very low	Quality points deducted for inclusion of quasi-randomised trials, and variation in inclusion criteria and outcome criteria; directness point deducted for inconsistent interventions between trials (BiliBlanket, Wallaby, conventional phototherapy)
10 (809) [21] [22] [23] [24]	Serum bilirubin levels	Double phototherapy *v* single phototherapy	4	–2	0	–1	0	Very low	Quality points deducted for inclusion of quasi-randomised trials, and variation in inclusion criteria and outcome criteria; directness point deducted for inconsistent interventions between trials (BiliBlanket, Wallaby, conventional phototherapy)
1 (40) [26]	Serum bilirubin levels	Triple phototherapy *v* double phototherapy	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of comparators
What are the effects of different total doses of light in hospital phototherapy as treatment for unconjugated hyperbilirubinaemia in term and preterm infants?									
1 (34) [29]	Duration of treatment	Intermittent phototherapy *v* continuous phototherapy	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for restricted population
3 (228) [27] [28] [29]	Serum bilirubin levels	Intermittent phototherapy *v* continuous phototherapy	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for small number of events in some analyses (1 and 5 in two analyses) indicating weak power to demonstrate differences between groups
1 (59) [30]	Duration of treatment	Increased skin exposure *v* standard skin exposure phototherapy	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of comparators
1 (59) [30]	Serum bilirubin levels	Increased skin exposure *v* standard skin exposure phototherapy	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of comparators
What are the effects of starting hospital phototherapy at different thresholds in term and preterm infants?									
1 (83) [31]	Neurological/neurodevelopmental	Prophylactic *v* threshold phototherapy	4	–2	0	–1	0	Very low	Quality point deducted for sparse data and no intention-to-treat analysis; directness point deducted for composite outcome (death and cerebral palsy)
1 (unclear, <96) [31]	Duration of treatment	Prophylactic *v* threshold phototherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (at least 92) [31]	Serum bilirubin levels	Prophylactic *v* threshold phototherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (1974) [32]	Mortality	Low threshold *v* high threshold phototherapy	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
1 (1854) [32]	Neurological/neurodevelopmental	Low threshold *v* high threshold phototherapy	4	–1	0	0	0	Moderate	Quality point deducted for no intention-to-treat analysis

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Important outcomes	Mortality, neurological/neurodevelopmental, need for exchange transfusion, duration of treatment, serum bilirubin levels, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (unclear) [32]	Need for exchange transfusion	Low threshold *v* high threshold phototherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (unclear) [32] [33]	Duration of treatment	Low threshold *v* high threshold phototherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (unclear) [32]	Serum bilirubin levels	Low threshold *v* high threshold phototherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Type of evidence: 4 = RCT.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.

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