

Clinical Practice Guidelines

Screening, Prevention and Management of Neonatal Hyperbilirubinemia

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National Neonatology Forum, India

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Executive Summary

Neonatal hyperbilirubinemia affects approximately 60% of term and 80% of preterm neonates in the first week of life. In neonates, unconjugated bilirubin above a threshold level, crosses the blood brain barrier and predisposes the neonate to acute or chronic bilirubin encephalopathy. Clinical recognition and assessment of jaundice can be difficult in neonates, especially in those with darker skin tone. Once jaundice is recognised there is uncertainty about when to treat, how to monitor and there is widespread variation in practices across the world regarding the use of phototherapy, monitoring under phototherapy and exchange transfusion. There is a need for more uniform evidence based and consensus based practice, where evidence is lacking. This guideline attempts to provide evidence based recommendations on screening and management of neonatal jaundice.

The guideline has been developed using standard methods adapted by National Neonatology Forum in accordance with the process described in the WHO handbook for guideline development. The detailed methods are described elsewhere in this compilation of guidelines. Table 1 summarizes the recommendations for practices questions prioritized by the guideline development group(GDG) in consultation with a wider group of NNF members.

Table 1: Summary of recommendations for screening and management of neonatal hyperbilirubinemia

S. No	Recommendations	Strength of recommendations	Quality of evidence
1.	<p>a. Either the American Academy of Pediatrics (AAP) guidelines based on postnatal age, gestation and presence or absence of risk factors or the National Institute for Health and Care Excellence (NICE), UK guidelines are used for deciding the need for phototherapy and exchange transfusion in neonates of gestation 35 weeks and more).</p> <p>b. Either Maisel's operational thresholds or the NICE, UK guidelines are used in preterm neonates born before 35 weeks of gestation.</p>	Weak	Not graded
2.	<p>Transcutaneous bilirubin (TcB) measurement may be used to screen for hyperbilirubinemia in term and preterm neonates.</p> <p><i>If TcB values fall within 2.9 mg/dL (~50 µmol/L) below or above the age appropriate phototherapy threshold, total serum bilirubin (TSB) should be measured to decide on the need for phototherapy or exchange transfusion.</i></p>	Weak, conditional	Moderate to low
3.	Discontinuation of breastfeeding is NOT recommended either for diagnosis or for treatment of breast milk jaundice in neonates.	Strong	Not graded
4.	Prophylactic phototherapy is not recommended for management of neonates with Rh immunization or ABO incompatibility.	Weak	Not graded
5.	Stable neonates with no other morbidity but having hyperbilirubinemia requiring phototherapy do not need to be admitted in the neonatal intensive care unit (NICU) or special care newborn unit (SCNU) for initiation of phototherapy; phototherapy should be initiated in them by their mothers' side.	Strong	Not graded

6.	Intensive phototherapy using either single or multiple phototherapy devices is to be employed in neonates requiring phototherapy. <i>Multiple phototherapy devices may be preferred when irradiance from a single device is low, or if serum bilirubin rises rapidly or fails to reduce as expected despite phototherapy.</i>	Weak, Conditional	Low to very low
7.	a. There is no role of routine fluid supplementation in neonates under phototherapy. b. <i>In neonates presenting with severe hyperbilirubinemia and requiring exchange transfusion, intravenous fluid supplementation may be considered while awaiting exchange transfusion. However, exchange transfusion should not be delayed for this purpose, particularly in presence of features of acute bilirubin encephalopathy.</i>	Weak, Conditional	Low to very low
8.	Routine periodic changes in body position – from supine to prone and vice versa – are not recommended in neonates receiving phototherapy.	Strong	Moderate to high
9.	Continuous phototherapy – except for interruptions during breast feeding and nappy changes – is employed in neonates with hyperbilirubinemia requiring phototherapy.	Weak	Low to very low
10.	a. In neonates with bilirubin value near exchange transfusion threshold, total serum bilirubin (TSB) may be measured every 4-6 hours after initiation of intensive phototherapy; once TSB starts declining and is no longer near exchange transfusion threshold, subsequent TSB may be measured every 8-12 hours. b. A follow-up total serum bilirubin (TSB) measurement may be done 12-24 hours after discontinuation of phototherapy in neonates with features of hemolysis.	Weak	Not graded
11.	Total serum bilirubin (TSB) is preferred over transcutaneous bilirubin (TcB) for monitoring of hyperbilirubinemia during phototherapy or in the first 24 hours after discontinuing phototherapy in term and preterm neonates.	Weak	Very low
12.	Intravenous immunoglobulin (IVIG) is NOT recommended, either prophylactically or	Strong	Very low

	therapeutically, in neonates with hyperbilirubinemia secondary to alloimmune hemolytic disease.		
13.	Phototherapy can be discontinued when TSB value is at least 2.9 mg/dL (nearly 50 µmol/litre) below the treatment threshold. A single value below this threshold is sufficient to discontinue phototherapy in neonates with non-hemolytic jaundice; two consecutive values below the threshold are usually required in neonates with hemolytic jaundice.	Weak	Not graded
14.	Albumin priming prior to or during exchange transfusion is not recommended in neonates with hyperbilirubinemia.	Strong	Moderate to low

Introduction

Physiological hyperbilirubinemia is a common problem in neonates with an incidence of 60-80%.¹ A significant proportion of these neonates develop pathological hyperbilirubinemia (PHB, defined as hyperbilirubinemia needing treatment) during the first week of life. Although the outcome for the majority is benign, infants with untreated, severe hyperbilirubinemia (defined as serum total bilirubin level >20 mg/dL) can develop signs of acute bilirubin encephalopathy (ABE). If not treated immediately, they might go on to develop kernicterus - a chronic, neurologically debilitating condition resulting from bilirubin toxicity. Management of hyperbilirubinemia includes detection of at-risk neonates, investigating cause of PHB, deciding thresholds for starting and stopping treatment and follow up of these neonates.

The published evidence-based guidelines on early detection, management and prevention of neonatal hyperbilirubinemia by organizations like American Academy of Pediatrics (1) and National Institute for Health and Clinical Excellence (2) primarily take care of the need of high-income countries. The low- and middle-income countries often follow these guidelines due to dearth of literature and absence of such evidence-based guidelines from their own settings. There is an increased incidence of significant hyperbilirubinemia in India due to inherent racial and genetic factors, widespread practice of exclusive breastfeeding, higher prevalence of G6PD deficiency, lower serum albumin at birth, higher bilirubin levels in summer season due to dehydration, blood group incompatibilities and infections (3, 4). This is compounded by lack of knowledge and awareness amongst family members and health workers about the possible consequences of severe neonatal jaundice (5).

The previous guidelines published by National Neonatology Forum, India (NNF 2010) (6) provided a practical framework for managing neonatal hyperbilirubinemia in Indian setting, but these guidelines need to be updated to determine the optimal strategy for screening and management of hyperbilirubinemia in current context. Hence, it was important to conduct a systematic review of the current available evidence with the hope of highlighting and resolving controversies and standardizing practice.

Scope of the guideline and Target audience

Aim

The primary aim of this guideline is to improve the quality of care and outcomes for preterm and term infants by providing recommendations on the screening, prevention and management of hyperbilirubinemia

Target audience

The primary audience for this guideline includes health-care professionals (neonatologists, paediatricians, obstetricians, medical officers, nurses and other practitioners) who are responsible for delivering care for neonates in different levels of healthcare as well as health program managers and policy-makers in all settings. The information in this guideline will be useful for developing job aids and tools for training of health professionals to enhance the delivery of neonatal care.

Population of interest

The guidelines focus on screening, prevention and management of hyperbilirubinemia in neonates admitted to healthcare settings.

How to use these guidelines

This systematic review on screening, prevention and management of hyperbilirubinemia led to the development of 14 recommendations. Each recommendation was graded as **strong** when there was confidence that the benefits clearly outweigh the harms, or **weak** when the benefits probably outweigh the harms, but there was uncertainty about the trade-offs. A strong or weak recommendation was further classified as **conditional** if the benefits outweigh the harms in some situations but not in others. For example, some recommendations were relevant only to settings in low and middle-income countries where resources are very limited while others were considered relevant only to settings where certain types of facilities are available. To ensure that each recommendation is correctly understood and applied in practice, the context of all context-specific recommendations is clearly stated within each recommendation, and additional remarks are provided where needed. Users of the guideline should refer to these remarks, which are presented along with the evidence summaries within the guideline.

Methodology

Questions relevant to clinical practice

The guideline development group(GDG) in consultation with a wider group of NNF members identified 14 questions to be of the highest priority for development of recommendations. Most of the questions are relevant to both term and preterm infants. A list of potential outcomes of interest for each question was circulated to all members of the GDG, who scored the importance of each outcome on a scale of 1 to 9 . A score of 1-3 was considered *not important*; 4 – 6 as *important* and 7-9 *critical*. The average of the scores for each outcome was used to prioritize the outcomes and to select the most important outcomes for each PICO question.

The following questions have been addressed in this set of recommendations:

1. What is the bilirubin level for starting phototherapy among term and preterm neonates with hyperbilirubinemia?
2. Should transcutaneous bilirubin(TcB) vs. total serum bilirubin(TSB) be used to diagnose hyperbilirubinemia in term and preterm neonates less than 28 days of life?
3. Should discontinuation of breastfeeding vs. no discontinuation be used for treatment of breast milk jaundice?
4. Should prophylactic phototherapy versus no prophylactic phototherapy be used for the management of Rh immunized neonates or ABO incompatibility?
5. Should phototherapy be given by mother's side versus in NICU/SNCU for the management of significant hyperbilirubinemia in neonates?
6. Should single unit vs. multiple/double surface phototherapy be used for the management of neonatal hyperbilirubinemia?
7. Should fluid supplementation vs. no fluid supplementation be used to treat hyperbilirubinemia in neonates requiring phototherapy?
8. Should supine vs. turning position under phototherapy be used in term and late preterm infants with hyperbilirubinemia?

9. Should intermittent vs. continuous phototherapy be used for treatment of hyperbilirubinemia in neonates requiring phototherapy?
10. Should less frequently (> 12 hourly) versus conventional monitoring (6 to 8 hourly) of bilirubin be used for the monitoring of neonates under phototherapy?
11. Among term and preterm neonates being treated for hyperbilirubinemia, can transcutaneous bilirubin (TcB) be used for monitoring during and after phototherapy, in place of total serum bilirubin (TSB) ?
12. Or ABO Should intravenous immunoglobulin versus no intravenous immunoglobulin be used for the management of Rh isoimmunised neonates?
13. Should pre-decided bilirubin level cut off vs. nomogram-based bilirubin levels be used for stoppage of phototherapy in neonates with hyperbilirubinemia?
14. Should albumin versus no albumin be used prior to exchange transfusion for treatment of hyperbilirubinemia in neonates?

Outcomes of interest

For each question, the following 5 outcomes were considered to be *critical*:

1. Mortality
2. Bilirubin induced neurological damage (BIND : defined as acute clinical manifestations of bilirubin toxicity seen in the first weeks after birth, characterised by irritability and hypertonia, retrocollis and opisthotonus, together with any 1 of the following: drowsiness, poor feeding, alternating tone, high-pitched cry)
3. Abnormal neurodevelopmental outcome
4. Abnormal neuro-imaging, hearing impairment or a failed auditory brainstem response hearing screen
5. Need for phototherapy or exchange transfusion.

The following outcomes were considered to be *important*:

1. Duration of phototherapy
2. Duration of hospitalization
3. Readmission for jaundice
4. Mean difference and correlation between bilirubin levels measured by 2 methods
5. Need for blood sampling

Benefits and harms in critical outcomes formed the basis of the recommendations for each question.

A systematic review of literature was done and a standardized form was used to extract relevant information from studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results. The following quality characteristics were recorded for all studies: allocation concealment or risk of selection bias (observational studies), blinding of intervention or observers or risk of measurement bias, loss to follow up, intention to treat analysis or adjustment for confounding factors, and analysis adjusted for cluster randomization (the latter only for cluster-randomized controlled trials, RCTs).

Interpretation of strong and conditional recommendations

We used GRADE approach for assessing the quality of evidence and the recommendations. The quality of the set of included studies reporting results for an outcome was graded as: *high*, *moderate*, *low* or *very low*. The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. The decisions were made on the basis of evidence of benefits and harms, quality of evidence, values and preferences of policy-makers, health-care providers and parents and whether costs are qualitatively justifiable relative to benefits in low- and middle- income countries.

Evidence review and Formulation of recommendations

Methodology

Using the assembled list of priority questions and critical outcomes from the scoping exercise, the GDG identified systematic reviews that were either relevant or potentially relevant and assessed whether they needed to be updated. A systematic review was considered to be out of date if the last search date was two years or more prior to the date of assessment. If any relevant review was found to be out of date, it was updated.

Search strategy

Cochrane systematic reviews were the primary source of evidence for the recommendations included in this guideline. In addition, key databases searched included the Cochrane database of systematic reviews of RCTs, the Cochrane controlled trials register and MEDLINE (1966 to August 2019). The reference lists of relevant articles and a number of key journals were hand searched. Details of search strategy are provided in the online annexure.

Data abstraction and summary tables of individual studies

A standardized form was used to extract information from relevant studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results. The following quality characteristics were recorded for RCTs: allocation concealment, blinding of intervention or observers, loss to follow up, intention to treat analysis, analysis adjusted for cluster randomization (the latter only for cluster RCTs). The quality characteristics recorded for observational studies were likelihood of reverse causality, selection bias and measurement bias, loss to follow-up and analysis adjusted for confounding. The studies were stratified according to the type of intervention or exposure, study design, birth weight and gestational age, where possible. Effects were expressed as relative risks (RR) or odds ratios (OR) for categorical data, and as mean differences (MD) or weighted mean differences (WMD) for continuous data where possible. All studies reporting on a critical outcome were summarized in a table of individual studies.

Pooled effects

Pooled effects for developing recommendations were considered, wherever feasible. If results of three or more RCTs were available for an outcome, and the overall quality of evidence using the GRADE approach was at least "low", observational studies were not considered. Pooled effects from published systematic reviews were used if the meta-analysis was appropriately done, and the reviews were up to date. However, if any relevant published study not included in the systematic review or a methodological problem with the meta-analysis was identified, the results were pooled in RevMan 5. For pooling, the author-reported adjusted effect sizes and confidence intervals (CIs) were used as far as possible. Random effects models for meta-analysis were used if there was an important inconsistency in effects, and the random effects model was not unduly affected by small studies. Where pooling of results was not possible, the range of effect sizes observed in the individual studies was used in the development of recommendations.

Quality assessment

Quality assessment of the body of evidence for each outcome was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE approach was used for all the critical outcomes identified in the PICOs, and a GRADE profile was prepared for each quantitative outcome within each PICO. Accordingly, the quality of evidence for each outcome was rated as "high," "moderate," "low," or "very low" based on a set of criteria. As a baseline, RCTs provided "high-quality" evidence, while non-randomized trials and observational studies provided "low-quality" evidence. This baseline quality rating was then downgraded based on consideration of risk of bias, inconsistency, imprecision, indirectness and publication bias. For observational studies, other considerations, such as magnitude of effect, could lead to upgrading of the rating if there were no limitations that indicated a need for downgrading.

Risk of bias

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas quality was downgraded when the results were in different directions and confidence limits showed minimal overlap.

Indirectness: Rating of the quality of evidence were downgraded where there were serious or very serious concerns regarding the directness of the evidence, i.e. where there were important differences between the research reported and the context for which the recommendations are being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes.

Imprecision: The degree of uncertainty around the estimate of effect was assessed. As this was often a function of sample size and number of events, studies with relatively few participants or events (and thus wide confidence intervals around effect estimates) were downgraded for imprecision.

Publication bias: Quality rating could also be affected by perceived or statistical evidence of bias that may have led to underestimation or overestimation of the effect of an intervention as a result of selective publication based on study results. Where publication bias was strongly suspected, evidence was downgraded by one level.

GRADE profile software was used to construct "Summary of Findings" tables for each priority question; these tables include the assessments and judgements relating to the elements described above and the illustrative comparative risks for each outcome. Relevant information and data were extracted in a consistent manner from the systematic reviews relating to each priority question by applying the following procedures. First, up-to-date review documents and/or data (e.g. RevMan file) were obtained from the Cochrane Library. Secondly, analyses relevant to the critical outcomes were identified and selected. The data were then imported from the RevMan file (for Cochrane reviews) or manually entered into the GRADE profilers (for non-Cochrane reviews). For each outcome, GRADE assessment criteria (as described above) were applied to evaluate the quality of the evidence. In the final step of the assessment process, GRADE evidence profiles were generated for each priority question.

Document review

The GDG met face to face on two occasions and prepared a draft of the full guideline document with revisions to accurately reflect the deliberations and decisions of the GDG participants. The draft guideline was then shared electronically between the GDG members for further comments. The inputs of the peer reviewers were included in the guideline document and further revisions were made to the guideline draft as needed. After the peer review process, the revised version was prepared.

Questions, Evidence summaries and Recommendations

Practice question 1 : What is the bilirubin level for starting phototherapy among term and preterm neonates with hyperbilirubinemia?

Table 2: Summary of previous guidelines

Association/ Professional body	Recommendation	Remarks
Canadian Pediatric Society 1999(7)	Bilirubin levels based on postnatal age for healthy term infants with presence or absence of risk factors. <i>Risk factors –</i> Gestation < 37 weeks & birth weight < 2500 g, hemolysis due to maternal isoimmunization, G6PD deficiency, spherocytosis, or other causes, jaundice at less than 24 hours of age, sepsis and need for resuscitation at birth	Not updated since 1999.
AAP Guidelines 2004(8)	<i>In neonates ≥ 35 weeks -</i> Postnatal age, gestation and risk factor-based guidelines. Three risk groups include Higher risk (35-37 ^{6/7} wk + risk factors), Medium risk (\geq 38 wk + risk factors or 35-37 ^{6/7} wk and well) and Lower risk (\geq 38 wk and well) <i>Risk factors -</i> Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis or albumin < 3.0 g/dl	Consensus guidelines based on limited evidence. Use total bilirubin. Use "Intensive phototherapy" (irradiance in the blue-green spectrum of at least 30 $\mu\text{W}/\text{cm}^2/\text{nm}$).
European Society of Pediatric Research – AAP 2008(9)	<i>In neonates ≥ 35 weeks -</i> Endorsed the AAP Guidelines	Consensus guidelines based on expert opinion
UK-NICE Guideline 2010 (updated in 2016) (10)	Treatment threshold table/graph based on gestational age Use total bilirubin Do not use bilirubin/albumin ratio for making decisions on starting phototherapy	Consensus guidelines based on expert opinion. Thresholds chosen with a wide margin of safety, with the threshold for phototherapy well below that for exchange transfusion
NNF Guidelines 2011 (6)	<i>In neonates ≥ 35 weeks -</i> AAP Guidelines based on postnatal age, gestation and risk factors with modifications for Indian neonates (higher incidence of G6PD deficiency, SGA neonates and non-availability of intensive phototherapy in many neonatal units) <i>In neonates < 35 weeks -</i> Start phototherapy when TSB is 0.5% and 0.75% of the body weight in sick and healthy infants respectively	Consensus guidelines based on limited evidence. Limited evidence on prevalence of BIND among Indian neonates. Lower albumin concentration and albumin binding capacity in sick preterm neonates. No role of aggressive phototherapy in ELBW.
Norwegian Guidelines 2011(11)	Treatment based on birth weight, postnatal age and TSB levels. Treatment recommendations for low, very low and extremely low birth weight infants	Based on expert opinion and pragmatism with a limited evidence base.
Academy of Breastfeeding Medicine protocol 2017(12)	Recommend using treatment thresholds for phototherapy as per existing US, Canadian, UK and other national guidelines.	Expert opinion

	Emphasize the continuation of breastfeeding or supplementation with expressed breast milk or infant formula during phototherapy	
Maisels 2012(13)	<p>In neonates < 35 weeks</p> <p>Based on operational thresholds or therapeutic normal bilirubin levels (a level beyond which specific therapy will likely do more good than harm).</p> <p>Risk factors –</p> <ul style="list-style-type: none"> Lower gestational age Serum albumin levels <2.5 g dl Rapidly rising TSB levels, suggesting hemolytic disease and neonates who are clinically unstable 	<p>Consensus based guidelines</p> <p>Not based on good evidence and are lower than those suggested in the UK-NICE and Norwegian guidelines</p>

RECOMMENDATION 1

All the available guidelines emphasize the rare occurrence of BIND/ Kernicterus and its uncertain incidence/prevalence. In light of the limited evidence available for treatment thresholds for hyperbilirubinemia, the following is the **consensus-based guideline** for Indian neonates, based on expert opinion -

1. In **neonates ≥ 35 wk**, either the **AAP guideline** based on postnatal age, gestation and presence or absence of risk factors, or the **UK-NICE guideline** are used for deciding the need for phototherapy and exchange transfusion. Conjugated bilirubin , if measured, should not be deducted from total serum bilirubin for decision making.
2. The risk factors for bilirubin neurotoxicity include isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis and serum albumin < 3.0 g/dL.
3. The additional factors to be considered among Indian neonates include a higher incidence of G6PD deficiency (not diagnosable without lab testing and commonly prevalent in female infants as well), SGA neonates, increasing adoption of delayed cord clamping and variable quality of phototherapy (type of lamps – tube lights/CFL/LED, irradiance not checked routinely and ineffective phototherapy).
4. Among **neonates < 35 wk**, either **Maisels operational thresholds** for bilirubin level or the **UK-NICE guidelines** are used.

Weak recommendation, Not graded

Practice question 2 : Should transcutaneous bilirubin (TcB) vs. total serum bilirubin (TSB) be used to diagnose hyperbilirubinemia in term and preterm neonates less than 28 days of life?

Summary of evidence

- We identified 2 RCTs which compared TcB versus visual examination and serum bilirubin when deemed appropriate in identifying significant jaundice (16,17).
- There was moderate quality evidence to show that there is a 37% reduction in the need for blood sampling for serum bilirubin (Relative Risk [RR] 0.63; 95% confidence intervals [CI]: 0.55 to 0.73) with the use of transcutaneous bilirubin as against using visual assessment along with total serum bilirubin wherever appropriate. The use of TcB was associated with 179 fewer blood samples (95% CI from 218 fewer to 131 fewer) required per 1,000 TcB assessments .
- There was low quality of evidence to show no significant difference (RR 0.29; 95% CI: 0.06 to 1.39) in the incidence of severe hyperbilirubinemia between the two groups.
- Based on the available evidence, one may conclude that a TcB reading which is more than 2.9 mg/dL (50 μ mol/L) below the age appropriate phototherapy threshold (American Academy of Pediatrics 2004) for an infant may be considered safe for not initiating phototherapy in an otherwise well preterm, late preterm or term neonate without the need for TSB estimation.
- A TcB reading above the phototherapy threshold may be sufficient to initiate phototherapy. However, a confirmation by TSB will help in monitoring and decision to stop phototherapy.
- A TcB reading falling within than 2.9 mg/dL (50 μ mol/L) below the age appropriate phototherapy threshold (American Academy of Pediatrics 2004) should be confirmed with TSB before initiating phototherapy.

RECOMMENDATION 2

Transcutaneous bilirubin(TcB) measurement may be used to screen for hyperbilirubinemia in term and preterm neonates.

If TcB values fall within 2.9 mg/dL (~50 μ mol/L) below or above the age appropriate phototherapy threshold, total serum bilirubin (TSB) should be measured to decide on the need for phototherapy or exchange transfusion.

(Weak conditional recommendation, based on moderate to low quality evidence for no significant difference in critical outcomes and cost and availability considerations in low- and middle-income countries)

Practice question 3 : Should discontinuation of breastfeeding vs. no discontinuation be used for treatment of breast milk jaundice?

Table 3: Summary of available reviews/ guidelines

Author	Recommendations	Remarks
Gartner 2001(22)	Breastfeeding must be continued without interruption. When serum bilirubin approaches 25 mg/dL, the use of phototherapy while continuing breastfeeding, or the interruption of breastfeeding for 24 hours, substituting formula, may be indicated.	Breast milk jaundice is an extension of physiologic jaundice of the newborn
Preer 2011(23)	The interruption of breastfeeding for diagnosis or treatment is not recommended.	Temporary cessation of breastfeeding may mask other causes of jaundice in the infant and interfere with return to exclusive breastfeeding subsequently
Soldi 2011(24)	Breastfeeding interruption for diagnosis is not recommended because of low specificity.	Temporary breastfeeding interruption may mask other underlying causes for jaundice and may be falsely reassuring. It also disrupts the maternal-infant bonding and interferes with the return to exclusive breastfeeding subsequently.
Academy of Breastfeeding Medicine Clinical Protocol 2017(25)	Breastfeeding cessation is not recommended for diagnosis or treatment.	Differentiates early suboptimal breastfeeding jaundice from breast milk jaundice. In individual cases, based on clinical judgement, temporary additional feedings with expressed breast milk, donor human milk, or infant formula; or very rarely, temporary interruption of breastfeeding and replacement feeding with infant formula may be required in addition to phototherapy in the treatment of neonatal hyperbilirubinemia.
Bratton S 2019(26)	If the serum bilirubin level remains below 12 mg/dL, continue breastfeeding and expect resolution of jaundice by 12 weeks	Treatment is not necessary for breast milk jaundice unless the serum bilirubin level is greater than 20 mg/dL. A brief 24-hour cessation of breastfeeding often leads to a sharp decline in the bilirubin levels.

Discontinuation of breast feeding, even temporarily decreases the success of breast feeding. It also has an impact on maternal-infant bonding and can create unnecessary guilt and blame for the mother.

RECOMMENDATION 3

In view of the scarce evidence available on stopping breastfeeding as treatment for breast milk jaundice, the recommendation is based on expert opinion and consensus. Breast milk jaundice is usually a benign and self-limited condition. **Breastfeeding discontinuation is NOT recommended either for diagnosis or for treatment of breast milk jaundice in neonates.** All attempts must be made to rule out other causes of jaundice and phototherapy begun as per existing guidelines. All mothers must be provided lactation support and counselling for ensuring exclusive breastfeeding as per the existing IYCF guidelines. (27)

Strong recommendation, Not graded

Practice question 4 : Should prophylactic phototherapy versus no prophylactic phototherapy be used for management of Rh immunized neonates or ABO incompatibility ?**Summary of findings**

There is lack of evidence in form of randomised controlled trials comparing prophylactic phototherapy with criteria based therapeutic phototherapy in Rh isoimmunised infants. Most of the randomised controlled trials conducted in Rh isoimmunised infants have used a pre-specified cut off criteria (as shown in summary table of individual studies) for initiation of phototherapy and in all trials, intensive phototherapy was provided with LED phototherapy units. The only randomised study comparing effect of prophylactic phototherapy (initiated within 4 hours of life) in infants with ABO incompatibility found decrease in serum bilirubin levels up to 48 hours of life but not beyond that (28). Furthermore, the obtained benefits were not clinically significant enough to change existing practice.

RECOMMENDATION 4

Prophylactic phototherapy (initiated before cut off for phototherapy is reached) **is not recommended for the management of neonates with Rh isoimmunisation or ABO incompatibility.** Instead, clinicians should be vigilant and monitor serial bilirubin values frequently (4-6 hourly) for deciding early initiation of phototherapy.

Phototherapy should be initiated only when the cut off for phototherapy is reached (see Recommendation 1 for cut-offs). Unnecessary phototherapy is likely to interfere with maternal-infant bonding and establishment of breast feeding.

Weak recommendation, Not graded

Practice question 5 : Should phototherapy be given by mother's side versus in NICU/SNCU for management of significant hyperbilirubinemia in neonates?

Summary of evidence

There are no randomized controlled trials to address this question. NICE clinical guidelines update 2016 provides guidance on this issue (2). Separation of the neonate from mother just for the purpose of phototherapy compromises breast feeding and maternal-infant bonding. In addition, this creates avoidable overcrowding in NICU/SNCU and denial of scarce beds for sicker neonates.

RECOMMENDATION 5

Stable neonates with no other morbidity but having hyperbilirubinemia requiring phototherapy do not need to be admitted in the neonatal intensive care unit (NICU) or special care newborn unit (SCNU) for initiation of phototherapy ; phototherapy should be initiated in them by their mothers' side .

Parents and caregivers should be offered verbal and written information on phototherapy including all of the following:

- (i) Why phototherapy is being started
- (ii) The possible adverse effects of phototherapy
- (iii) The need for eye protection and routine eye care

Mothers should be reassured that short breaks for feeding, nappy changing and cuddles are encouraged. They also need to be counselled what might happen if phototherapy fails, about rebound jaundice and potential impact on breastfeeding and how to minimise this.

They should be informed that intensified phototherapy and transfer to NICU/SNCU may be required if :

- (i) The serum bilirubin level is rising rapidly (more than 0.5 per mg/hour)
- (ii) The serum bilirubin is at a level within 2.9 mg/dL below the threshold at which exchange transfusion is indicated
- (iii) The bilirubin level fails to respond to initial phototherapy (that is, the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting phototherapy)

Strong recommendation, Not graded

Practice question 6 : Should single unit vs. multiple unit/double surface phototherapy be used for management of neonatal hyperbilirubinemia?

Summary of evidence (29-34)

Balance of benefits and harms

1. When compared to single phototherapy, double phototherapy leads to a small decrease in the duration of phototherapy. Double phototherapy also results in a greater decrease in serum bilirubin and rate of fall of bilirubin but not to a clinically meaningful level. The quality of evidence is low to very low.
2. No major harms were observed with the use of double phototherapy between the groups with respect to frequency of stooling and percentage of weight loss, frequency of defecation etc. One study that used an intensive phototherapy ($30 \mu\text{W}/\text{cm}^2/\text{nm}$) reported greater body temperature with double units.

Values and preferences

1. The mean duration of phototherapy is only a surrogate outcome of efficiency of phototherapy and not a very precise outcome on which to base a decision. The majority of evidence is of low to very low quality due to study design issues (unclear randomisation methods and allocation concealment), lack of blinding and small sample size. These factors increase the uncertainty in drawing any conclusion.
2. Multiple units are likely to provide higher level of irradiance and cover more surface area than single units. However, with modern LED devices, this can be achieved by simply adjusting the level of irradiance in a device without adding additional devices. Therefore, the term 'multiple unit phototherapy' may no longer be relevant to current practice when most phototherapy units provide high irradiance.
3. Most neonatal units in India are now using LED devices because they provide higher irradiance with a very long lamp life, produce less glare, generate less heat, are compact and easier to maintain. If conventional fluorescent devices are used, adding multiple/double surface units may provide benefit.

Costs

1. No economic studies were identified that compared the cost effectiveness of single vs multiple phototherapy units. It is logical that using multiple or double surface phototherapy will require extra devices and lamps but may decrease the duration of phototherapy.

RECOMMENDATION 6

Intensive phototherapy using either single or multiple phototherapy devices is to be employed in neonates requiring phototherapy.

Multiple phototherapy devices may be preferred when irradiance from a single device is low, or if serum bilirubin rises rapidly or fails to reduce as expected despite phototherapy.

When using double surface phototherapy, the infant should be placed on a comfortable translucent pad which will not significantly decrease the transmitted irradiance of the under-surface unit.

Weak Conditional recommendation, based on low to very low quality of evidence and consensus among experts in Indian scenario where conventional CFL phototherapy is still used and irradiance of phototherapy lamps may not be monitored regularly.

Practice question 7 : Should fluid supplementation vs. no fluid supplementation be used to treat hyperbilirubinemia in neonates requiring phototherapy?

Summary of evidence (35-42)

In the comparison between IV fluid supplementation and no supplementation for neonates presenting with severe hyperbilirubinemia, none of the infants in either group developed bilirubin encephalopathy in the only study that reported this outcome.

- Serum bilirubin was lower at 4 hours post intervention for infants who received IV fluid supplementation (MD 34 µmol/litre lower (52.29 lower to 15.71 lower; low quality of evidence, downgraded one level for indirectness and one level for suspected publication bias).
- Serum bilirubin was lower at 8 and 12 hours post intervention for infants who received IV fluid supplementation but the quality of evidence was graded as very low or low.
- Duration of phototherapy was significantly shorter for fluid-supplemented infants, but the estimate was affected by heterogeneity which was not clearly explained [MD 7.9 h lower (12.3 h lower to 3.6 h lower)]
- Fluid-supplemented infants were less likely to require exchange transfusion [RR 0.39 (0.22 to 0.71) 128 per 1,000; 78 fewer per 1,000 (100 fewer to 37 fewer); 563 participants (7 RCT); very low quality evidence]
- No harmful effects in terms of infection or significant hyponatremia were reported.

There was no evidence of effects on the critical outcomes of bilirubin-induced brain dysfunction, as no infant in either group developed this. There was very low to low quality evidence for all major outcomes. Three main factors affected the quality of evidence: first, the use of bilirubin, a laboratory measurement, as the main outcome, rather than direct clinical outcomes that matter to patients; second, inconsistent study results; and third, unpublished studies that might change the review findings for the relevant outcomes.

In summary, IV fluid supplementation in neonates with severe hyperbilirubinemia reduces the need for exchange transfusion and duration of phototherapy without significant side effects.

For neonates with mild to moderate hyperbilirubinemia under phototherapy, NICE guideline on 'Postnatal care' recommends that 'breastfed babies should not be routinely supplemented with formula, water or dextrose water for the treatment of jaundice'. Our group also recommends that the need for additional fluids during phototherapy should be considered only on an individual clinical basis. Routine supplementation with additional fluids in every case is not recommended (NICE 2015).

RECOMMENDATION 7

- **There is no role of routine fluid supplementation in all neonates under phototherapy.**
- In neonates presenting with severe hyperbilirubinemia and requiring exchange transfusion, intravenous fluid supplementation may be considered while awaiting exchange transfusion. However, exchange transfusion should not be delayed for this purpose, particularly in presence of features of acute bilirubin encephalopathy.

Weak Conditional recommendation, based upon Low to very low quality evidence

Practice question 8 : Should supine vs. turning position under phototherapy be used in term and late preterm infants with hyperbilirubinemia?

Summary of evidence (43-48)

Table 4 : Summary of studies comparing fixed supine to turning position under phototherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with turning position under phototherapy	Risk with supine			
Duration of phototherapy	The mean duration of phototherapy was 0	MD 0.15 higher (2.09 lower to 2.4 higher)	-	231 (4 RCTs)	⊕⊕⊕⊕ HIGH
Percent fall in bilirubin at 24 hours of starting phototherapy	The mean percent fall in bilirubin at 24 hours of starting phototherapy was 0	MD 0.27 lower (2.98 lower to 2.43 higher)	-	193 (3 RCTs)	⊕⊕⊕○ MODERATE ^a
Rate of fall of serum total bilirubin at 24 hours of starting phototherapy (mg/dL/h)	The mean rate of fall of serum total bilirubin at 24 hours of starting phototherapy (mg/dL/h) was 0	MD 0.02 higher (0.02 lower to 0.06 higher)	-	100 (1 RCT)	⊕⊕⊕○ MODERATE ^b
Serum total bilirubin at 24 hours of starting phototherapy	The mean serum total bilirubin at 24 hours of starting phototherapy was 0	MD 0.19 higher (0.36 lower to 0.74 higher)	-	292 (4 RCTs)	⊕⊕⊕⊕ HIGH

Explanations

a. Significant statistical heterogeneity was noted. The study by Shinwell et al reported a significantly lower rate of fall of serum total bilirubin in 24 h, while the other two studies included in the meta-analysis did not show any significant difference

b. 95% CI is -0.02 to 0.06

There is moderate to high quality evidence that there is no difference in clinically important outcomes between supine versus turning position under phototherapy in term and late-preterm

infants with hyperbilirubinemia. Important outcomes like mortality, incidence of BIND, abnormal neurodevelopmental outcome, abnormal neuroimaging, hearing impairment, need for exchange transfusion and duration of hospitalization were not reported in the included studies. Results of this systematic review apply mainly to neonates born at late preterm or term gestation who are receiving phototherapy for non-hemolytic hyperbilirubinemia. On pooling the results, no significant difference was observed in the duration of phototherapy (4 studies, 231 participants, mean difference: 0.15 h, 95% CI: -2.09 to 2.40 h), percent fall in bilirubin at 24 h of starting phototherapy, rate of fall of serum total bilirubin at 24 h of starting phototherapy and serum bilirubin at 24 hours.

It is obvious that change in body position is relevant only if the neonate is receiving single-surface phototherapy. The posture of the baby under phototherapy is also governed by nursing preferences and the risk of sudden infant death syndrome (SIDS) in prone position.

RECOMMENDATION 8

Routine periodic changes in body position – from supine to prone and vice versa – are not recommended in neonates receiving phototherapy.

Strong recommendation, Moderate to High quality evidence

Practice question 9 : Should intermittent vs. continuous phototherapy be used for treatment of hyperbilirubinemia in neonates requiring phototherapy?

Summary of evidence

Intermittent phototherapy as compared to continuous phototherapy had statistically significant beneficial effects in terms of decreased duration of phototherapy as well as higher fall of bilirubin. The evidence is generated from 3 small studies: all of them were non-blinded and 2 of them were conducted 4 decades ago and the method of randomization is not mentioned. Out of the 3 studies, 1 had preterm infants and other 2 included term infants. All 3 started phototherapy at lower threshold. None of them had evaluated the effect of intermittent phototherapy in moderate to severe jaundice. The type of phototherapy devices and irradiance used in older phototherapy devices was quite different as compared to what is used now. Hence, overall quality of evidence is very low.

Table 5 : Summary of studies comparing intermittent vs. continuous phototherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with continuous phototherapy	Risk with Intermittent			
Rate of fall of bilirubin (mg/dl/hr)	The mean rate of fall of bilirubin (mg/dl/hr) was 0	MD 0.86 higher (0.37 higher to 1.35 higher)	-	97 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}
Peak serum bilirubin (mmol/L)	The mean peak serum bilirubin (mmol/L) was 0	MD 1.64 lower (11.93 lower to 8.65 higher)	-	97 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}
Total duration of phototherapy	The mean total duration of phototherapy was 0	MD 7.06 lower (12.06 lower to 2.06 lower)	-	97 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}

Explanations

a. Both are unblinded study with poor methodology b. Sample size small

RECOMMENDATION 9

Continuous phototherapy – except for interruptions during breast feeding and nappy changes – is employed in neonates with hyperbilirubinemia requiring phototherapy.

Weak recommendation, Low to very low quality evidence

Practice question 10 : Should less frequently (> 12 hourly) versus conventional monitoring (6 to 8 hourly) of bilirubin be used for the monitoring of neonates under phototherapy?**Summary of previously available guidelines**

We could not find any relevant studies (observational studies or randomized controlled trials) comparing various schedule of monitoring of bilirubin during and after discontinuation. Studies have used monitoring frequency varying from 6 to 24 hours without any underlying evidence. Hence, we looked at existing guidelines by international organizations and their recommendations which are summarized below in tabular form. Most of these recommendations are based on expert consensus. The existing guidelines vary in their recommendations.

Table 6: Summary of existing guidelines

Recommending body	During phototherapy	After discontinuation of phototherapy
Canadian Pediatric Society(7)	First serum bilirubin should be done at 6–12 hours after the start of phototherapy	First serum bilirubin after discontinuation of phototherapy at 24–48 hours
American Academy of paediatrics(8)	For babies with gestational age \geq 35 weeks, serum bilirubin to be repeated every 2–3 hourly until levels fall, after which it should be repeated 8–12 hourly	After discontinuation, serum bilirubin can be measured after 24 hours to check for rebound jaundice (optional).
Israel Neonatal society(49)	For babies of gestational age \geq 35 weeks, serum bilirubin measurement to be repeated at least twice daily depending on clinical assessment. Phototherapy should be discontinued at 205–222 $\mu\text{mol/litre}$.	In high-risk babies, serum bilirubin should be measured 12–24 hours after discontinuation of phototherapy.
NICE guideline 2010 (Amended 2016) (10)	<p><i>For starting phototherapy</i> In babies with a gestational age 38 weeks or more whose bilirubin is in the 'repeat bilirubin measurement' category as per NICE chart, a repeat bilirubin is warranted at 6–12 hours and those with 'consider phototherapy' category repeat the bilirubin in 6 hours regardless of whether or not phototherapy has been started.</p> <p><i>During phototherapy</i> Repeat serum bilirubin measurement 4–6 hours after initiating and 6–12 hourly when the serum bilirubin level is stable or falling.</p>	Check for rebound with a repeat serum bilirubin measurement 12–18 hours after stopping phototherapy. Babies do not necessarily have to remain in hospital for this to be done.
Spanish Association of Pediatrics (50)	The serum concentration of bilirubin should be assessed 2–6 hours after initiation of PT. Once the bilirubin level is stable or decreasing, measurements should be repeated every 6–12 hours.	No mention
Previous NNF guideline 2010 (6)	In neonates with higher bilirubin value (near exchange range) repeat measurement should be done after 4–6 hours of initiation of intensive phototherapy. Once a declining trend has been documented and levels are no longer near exchange transfusion threshold, subsequent values may be repeated every 8–12 hourly	If phototherapy is used for infants with hemolytic diseases or is initiated early and discontinued before the infant is 3 to 4 days old, a follow-up bilirubin measurement within 24 hours after stopping of phototherapy is recommended. However, discharge should not be delayed for the same.

RECOMMENDATION 10

The following is the consensus for frequency of measuring serum bilirubin during and after stoppage of phototherapy:

1. In neonates with bilirubin value near exchange transfusion threshold, total serum bilirubin (TSB) may be measured every 4-6 hours after initiation of intensive phototherapy; once TSB starts declining and is no longer near exchange transfusion threshold, subsequent TSB may be measured every 8-12 hours.
2. A follow-up total serum bilirubin (TSB) measurement may be done 12-24 hours after discontinuation of phototherapy in neonates with features of hemolysis.

Weak recommendation, Not graded

Practice question 11 : Among term and preterm neonates being treated for hyperbilirubinemia, can transcutaneous bilirubin (TcB) be used for monitoring during and after phototherapy, in place of total serum bilirubin (TSB) ?

Summary of evidence (51-57)

Term and late preterm neonates

The results of the review show that TcB devices are much less accurate in estimating serum bilirubin values in infants under phototherapy as compared to their documented accuracy in the pre-phototherapy period. The limited data available from studies assessing agreement between TcB and TSB tests following discontinuation of phototherapy show somewhat improved accuracy in the post phototherapy phase.

Preterm neonates

Varying results have been reported regarding correlation of TcB with TSB in preterm infants. Results have reported R values between moderate (0.47) to good (0.97). Some studies report underestimation by TcB even under covered site as compared to TSB whereas one of the study mentions overestimation.

RECOMMENDATION 11

Total serum bilirubin (TSB) is preferred over transcutaneous bilirubin (TcB) for monitoring of hyperbilirubinemia during phototherapy or in the first 24 hours after discontinuing phototherapy in term and preterm neonates.

Weak recommendation, Very low quality evidence

Practice question 12 : Should intravenous immunoglobulin (IVIG) versus no intravenous immunoglobulin be used for management of Rh or ABO isoimmunised neonates?**Summary of evidence (58)**

Balance of benefits and harms

1. When compared to placebo therapy, IVIG therapy does not need reduce exchange transfusions, need for top-up transfusions, duration of phototherapy, peak serum bilirubin levels or the incidence of long term side effects of neonatal hyperbilirubinemia (kernicterus, deafness and cerebral palsy). The quality of evidence is very low.
2. Although all 9 studies in Cochrane review had included or subsequently provided data for adverse effects, the exact protocols used for identifying adverse effects are not clear. Furthermore studies from other uses of IVIG have reported several common side effects of IVIG infusion in neonates (febrile reaction, rash, hypotension) and occasional life threatening side effects like anaphylaxis.

Costs

IVIG therapy is costly (Rs. 5000-10000). The need for continuous slow infusion and monitoring requires close nursing supervision.

Values and preferences

IVIG therapy has doubtful beneficial effects , is not free from adverse effects, is expensive and requires close monitoring and expert supervision.

RECOMMENDATION 12

Intravenous immunoglobulin (IVIG) is NOT recommended, either prophylactically or therapeutically, in neonates with hyperbilirubinemia secondary to alloimmune hemolytic disease.

Strong recommendation, Very low quality evidence

Practice question 13 : Should pre-decided bilirubin level cut off vs. nomogram based bilirubin levels be used for stoppage of phototherapy in neonates with hyperbilirubinemia?**Summary of evidence**

We could not identify any randomised controlled trial or observational study that has tried to answer this question. The following recommendation is based on review of international guidelines and consensus.

Table 7 : Summary of previous guidelines

Association/ Professional body	Recommendation on stopping phototherapy and monitoring TSB	Remarks
AAP Guidelines 2004 (1)	<p>In neonates \geq 35 weeks -</p> <p>If TSB > 25 mg/dl (428 $\mu\text{mol/L}$), repeat TSB within 2-3 h</p> <p>If TSB 20–25 mg/dl (342–428 $\mu\text{mol/L}$), repeat within 3–4 h. If TSB < 20 mg/dl (342 $\mu\text{mol/L}$), repeat in 4–6 h. If TSB continues to fall, repeat in 8–12 h.</p> <p>Discontinue phototherapy when TSB is 13–14 mg/dl (239 $\mu\text{mol/L}$)</p>	Consensus guidelines based on limited evidence. Frequency of monitoring advised in the guideline may not be feasible in resource limited and crowded settings in our country.
UK-NICE Guideline 2010 (updated in 2016) (2)	<p>During phototherapy:</p> <ul style="list-style-type: none"> repeat serum bilirubin measurement 4–6 hours after initiating phototherapy repeat serum bilirubin measurement every 6–12 hours when the serum bilirubin level is stable or falling. <p>Phototherapy can be stopped once serum bilirubin has fallen to a level at least 50 $\mu\text{mol/litre}$ below the treatment threshold table/graph based on gestational age</p>	Consensus guidelines based on expert opinion. Frequency of monitoring advised in the guideline may not be feasible in resource limited and crowded settings in our country.
NNF Guidelines 2011 (6)	<p>If initial TSB levels are near exchange transfusion range, repeat measurement may be done after 4-6 h of intensive PT. Once a declining trend has been documented and levels are no longer near BET threshold, TSB may be monitored every 8-12 h. Phototherapy may be discontinued when serum bilirubin level has fallen below 2mg/dl lower than the age appropriate PT threshold for that postnatal age.</p>	Consensus guidelines based on limited evidence.
Maisels 2012 (13)	<p>In neonates $<$ 35 weeks</p> <p>No recommendation on frequency of monitoring</p> <p>Discontinue phototherapy when TSB is 1–2 mg/dl below the initiation level for the infant's postmenstrual age.</p>	Consensus based guidelines

RECOMMENDATION 13

- **Phototherapy can be discontinued when TSB value is at least 2.9 mg/dL (50 $\mu\text{mol/L}$) below the treatment threshold.**
- A single value below this threshold is sufficient to discontinue phototherapy in neonates with non-hemolytic jaundice; two consecutive values below the threshold are usually required in neonates with hemolytic jaundice.

Weak recommendation, Not graded

Practice question 14 : Should albumin versus no albumin be used prior to exchange transfusion for treatment of hyperbilirubinemia in neonates?

Summary of evidence(59-62)

Table 8: Pre-exchange albumin vs no albumin in treatment of hyperbilirubinemia

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty
	Risk with no albumin	Risk with albumin			
Duration of phototherapy	The mean duration of phototherapy was 0	MD 14.14 lower (18.99 lower to 9.3 lower)	-	142 (3 RCTs)	 LOW ^{a,b}
Requirement of exchange transfusion	63 per 1,000	69 per 1,000 (14 to 282)	OR 1.12 (0.21 to 5.89)	92 (2 RCTs)	 MODERATE ^c
Post exchange serum bilirubin	The mean post exchange serum bilirubin was 0	MD 0.61 lower (0.9 lower to 0.32 lower)	-	92 (2 RCTs)	 MODERATE
Serum bilirubin 6 hours post exchange	The mean serum bilirubin 6 hours post exchange was 0	MD 5.57 lower (6.39 lower to 4.75 lower)	-	92 (2 RCTs)	 MODERATE
Hospital stay	The mean hospital stay was 0	MD 2.3 lower (6.06 lower to 1.46 higher)	-	42 (1 RCT)	 MODERATE ^e

Explanations

a. Mitra et al and Shahian et al (contribution 40.7% & 40.8% respectively) showed a decline in the duration of phototherapy while Dash et al reported no difference (-4.00 [-12.97, 4.97] hours) c. Only two neonates each in Dash et al and only one neonate in Mitra et al required exchange .

Albumin infusion also causes volume expansion, which could independently lead to a reduction in bilirubin levels after administration. The confounding effect of the volume expansion property of albumin infusion was taken care of in 1 trial which used an isotonic fluid in the comparator arm and reported no difference in any of the outcomes measured in the two groups. Overall, none of the trials found any significant benefit priming with 1 g/kg during exchange transfusion. Therefore, its use cannot be recommended.

RECOMMENDATION 14

Albumin priming prior to or during exchange transfusion is not recommended in neonates with hyperbilirubinemia.

Strong recommendation, Moderate to low quality evidence

Abbreviations

GA: Gestational age	BIND: Bilirubin induced neurological damage	AAP: American Academy of Pediatrics
NICE: National Institute for Health and Care Excellence	TSB: Total Serum Bilirubin	TcB: Transcutaneous bilirubin
SNCU Special newborn care unit	NICU: Neonatal Intensive Care Unit	CFL: Compact fluorescent lamp
LED: Light-emitting diode	IV: Intravenous	SIDS: Sudden infant death syndrome
IVIG: Intravenous immunoglobulin		

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