Background Document

Detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants

October 2016

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Introduction

Jaundice refers to the yellow discoloration of the skin and the sclera caused by the accumulation of a pigment (bilirubin) in the skin and mucous membranes. It is seen in neonates when the serum bilirubin levels exceed 5-7 mg/dL. Approximately 60% of term and 80% of preterm infants develop jaundice in the first week of life, and about 10% of breastfed infants are still jaundiced at 1 month.

Visible jaundice usually appears between 24 to 72 hours of age. The total serum bilirubin (TSB) level usually rises in term infants by 3 days of age and then falls. In preterm infants, the peak level occurs around 3 to 7 days after birth. It may take weeks before the TSB levels falls under 2 mg/dL in both term and preterm infants. Jaundice is not an indication of an underlying disease for most infants, and this early jaundice (termed 'physiological jaundice') is generally harmless.

Hyperbilirubinemia typically refers to serum bilirubin levels beyond the normal range and is a common problem in neonates. (1) A significant proportion of these neonates develop pathological jaundice (jaundice requiring treatment) during the first week of life (2). It is also one of the leading causes of hospitalization in the first week of life globally (3-5).The overall incidence of hyperbilirubinemia (>15 mg/dL) has been reported as 3.3% in intramural neonates and 22.1% in extramural neonates (2).

Timely and appropriate treatment with phototherapy and/or exchange transfusion is effective in decreasing excessive bilirubin levels. However, failure of instituting appropriate therapy results in acute bilirubin encephalopathy (ABE) which if not treated immediately, might go on to develop kernicterus and other long term neurological deficits including cerebral palsy, sensorineural hearing loss, intellectual difficulties or gross developmental delays (6-10). It is estimated that nearly 5,00,000 term and late preterm neonates globally are affected by severe hyperbilirubinemia annually and around one-fourth of them die and 63,000 survive with neurological disability (11). Three-fourth of these affected infants reside in sub-Saharan Africa and South Asia (12).

The purpose of the guideline

There is a need for a standard guideline for the management of neonatal hyperbilirubinemia in term and late preterm newborn infants in India**.** The context for the detection, management and prevention of neonatal hyperbilirubinemia in India is different from other countries.

The published evidence based guidelines on early detection, management and prevention of neonatal hyperbilirubinemia by various bodies including American Academy of Pediatrics **(**13**)** and National Institute for Health and Clinical Excellence **(**14**)** primarily takes care of the need of high income countries**.** The low and middle**-**income countries including India are following these guidelines due to dearth of literature and absence of such evidence based guidelines from their own setting**.**

There is an increased incidence of significant hyperbilirubinemia in India due to various risk factors including racial and genetic factors, widespread practice of exclusive breastfeeding, higher prevalence of G6PD deficiency in some parts of the country, more neonates with low albumin at birth, higher bilirubin levels in summer season due to dehydration, blood group incompatibilities and infections (15, 16). Lack of knowledge among mother and family members about jaundice (17) and poor transport facilities especially in rural areas often results in delay in seeking medical advice. The situation is further compounded by ñwhy worryò attitude among healthcare professionals especially in the dearth of substantial data documenting bilirubin induced neurological dysfunction (BIND) on arrival to health facility (18). Inadequate knowledge among healthcare professionals, limited facilities for clinical investigations, lack of standardised protocol for management (including absence of monitoring serum bilirubin while under phototherapy) and inconsistent functional status of available phototherapy devices, often results in inappropriate treatment thus resulting in BIND (19-22). Even the lack of exchange transfusion facilities at majority of the healthcare setting due to non-availability of blood or expertise results in permanent neurological dysfunction which could be easily avoided by doing early exchange transfusion.

Though the guidelines published by National Neonatology Forum, India **(**NNF 2010**) (**22**)** have tried to provide a practical framework for managing neonatal hyperbilirubinemia in Indian

setting, these guidelines are meant for only tertiary care health facilities**.** In view of the above stated reasons and opening of Special Care Newborn Units (SCNUs) and private health facilities delivering level II neonatal care in a big way; the current guideline has been developed for the management of neonatal hyperbilirubinemia in late preterm and term infants in the Indian context for health care facilities at all levels.

Approach of the guideline

The guidelines have been commissioned to enable a systematic cost-effective approach for the detection, management and evaluation of neonatal hyperbilirubinemia in late preterm and term infants in India. This guideline and its accompanying implementation tools in the form of a quick reference guide, flow charts, and quality standards will serve as a valuable reference material for healthcare providers, patients and administrators. While formulating these guidelines the main outcome measures taken into consideration have been mortality, incidence of acute bilirubin encephalopathy, incidence of chronic bilirubin encephalopathy, hearing Loss, incidence of exchange transfusion, incidence of severe hyperbilirubinemia, duration of phototherapy and incidence of readmissions required for hyperbilirubinemia

- This guideline has a primary care focus and a public health approach**.** The focus of the primary care is to improve the early detection and the timely treatment to prevent long term neurological deficits. Increasing awareness among public especially mother and family members at the time of discharge about the need for jaundice evaluation in first week of life in face of early discharges from health facilities in India will improve this dismal situation and result in improving intact survival.
- These guidelines will also facilitate effective advocacy and mobilisation of requisite resources for the optimal care of newborn infants with hyperbilirubinemia at all levels.
- The guideline presented covers detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants in primary, secondary and tertiary care setting and includes an algorithmic approach to a newborn with or at risk of hyperbilirubinemia.

Full Guideline Title: Detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants

Population

Groups that will be covered

a) Neonates ≥ 35 weeks

Groups that will not be covered

a) Preterm neonates < 35 weeks
b) Neonates with conjugated hyperbilirubinemia

Health Care Setting

a) Primary care
b) Secondary and tertiary care

Disease or risk condition

At risk or having jaundice

Key Clinical issues that will be covered in this guideline

A. Screening and Diagnosis

1.1 What should be the screening protocol for detection of jaundice in neonates?
1.2 Which neonates are at a higher risk of hyperbilirubinaemia?
1.3 What is the accuracy of transcutaneous bilirubinometry in recognizing neonatal hyperbilirubinaemia and how should it be done?
1.4 How will you interpret serum bilirubin levels and manage hyperbilirubinaemia?
1.5 What should be optimum discharge and follow-up timing and the assessment policy to minimize the subsequent risk of severe hyperbilirubinemia and acute bilirubin encephalopathy?
1.6 What should be included in the formal assessment of a neonate with neonatal hyperbilirubinaemia?
1.7 How can we prevent severe hyperbilirubinemia?

B. Treatment of hyperbilirubinemia

2.1 Phototherapy
2.2 Exchange transfusion
2.3 Other modalities
2.4 What should be the frequency of long term follow up of neonates with hyperbilirubinemia and what all should be evaluated at follow up?
2.5 Information and support which should be given to parents/care givers of neonates with neonatal hyperbilirubinaemia?

Methodology of Development of Guideline

A Task Force was constituted in December 2014 to guide the development of Standard Treatment Guidelines (STG) in India for application in the National Health Mission. The Task Force subsequently approved the draft STG development manual of India (Part 1) for development of adapted guidelines. In addition, it approved a list of 14 topics recommended by a subgroup of the task force appointed to select prioritized topics for STG development. These 14 topics are from 10 clinical specialties for which the first set of STGs will be developed. The topic of detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants was dealt by the neonatology sub-group.

Formation of the STG group

A multidisciplinary group composed of a mix of primary care practitioners, family medicine practitioners, teaching faculty, practicing and academic neonatologists, nurse practitioners, voluntary sector representatives, and a patient representative was formed by September 2015. The composition of the subgroup is mentioned in the table below.

Facilitator: Prof Praveen Kumar

Writing Team: Dr Anu Sachdeva, Dr Neeraj Arora, Dr Srinivas Murki, Dr Aparna Chandrasekaran, Dr Shridhar Gopalakrishnan, Dr Deepak Chawla, Dr Mangla Bharti

Experts: Prof Vinod K Paul, Prof Ashok K Deorari

Primary care Practioner:

Nursing Practioner: Ms Meena Joshi

Patient participant

Scoping the STG

The scope of the STG was discussed at the first clinical subgroup meeting in Delhi in September 2015

Declaration of interests

All the members of the GDG declare no conflict of interest.

Funding source

NHSRC…

Scheduled review

We plan to update the STG every 3 years.

Search and selection of evidence based guidelines

In view of the paucity of time available to develop this guideline, a decision was taken by the Task Force for the Development of STGs for the National Health Mission that these STGs would be adopted and/or adapted from existing evidence based guidelines to make them relevant to our context, resource settings and priorities.

Search and select guidelines

We searched the electronic database MEDLINE via PubMed and the websites www.who.int (World Health Organization), http://www.guideline.gov (National Guideline Clearing House of US), http://www.nice.org.uk (National Institute for Clinical & Care Excellence, UK), www.aap.org (American Academy of Pediatrics), http://www.cps.ca/(Canadian Pediatric Society), and www.nnfi.org (National Neonatology Forum, India) to search for existing guidelines on detection, management and prevention of hyperbilirubinemia of term and late preterm infants.

Step 1
We used the following search strategy: ("jaundice, neonatal"[MeSH Terms] OR ("jaundice"[All Fields] AND "neonatal"[All Fields]) OR "neonatal jaundice"[All Fields] OR ("neonatal"[All Fields] AND "jaundice"[All Fields])) AND guideline [ptyp]which revealed 16 citations of which six were relevant citations. Additional search revealed two additional guidelines. In addition, we identified another guideline – by National Neonatology Forum, India – by hand searching.

Step 2
We evaluated the technical quality and the process of development of these guidelines by the AGREE-GRS instrument (http:// www.agreetrust.org) (Table 1)

Table 1: Comparison of existing guidelines on detection, management and prevention of hyperbilirubinemia of term and late preterm infants.

Guideline Title	Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation (AAP)(13)	ABM Clinical Protocol #22: Guidelines for Management of Jaundice in the Breastfeeding Infant Equal to or Greater Than 35 Weeks' Gestation (23)	NNF guidelines (22)	Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (24)	Recommendations on newborn health (25)	Neonatal jaundice: prevention, assessment and management (26)	Neonatal Jaundice (14)
Date Released	2004	2010	2010	2007 Reaffirmed 2011	2013	2012	2010; updated May 2016
Adaptation	Not applicable	Not applicable	Adapted from AAP	Adapted from AAP	Not applicable: The guideline was not adapted from another source.	Not applicable	Not applicable
Guideline Developer(s)	American Academy of Pediatrics	The Academy of Breastfeeding Medicine Protocol Committee	National Neonatology Forum, India	Canadian Pediatric Society (fetus and newborn Committee)	World Health Organization - International Agency	Queensland Maternity and Neonatal Clinical Guidelines Program	National Institute of Health and care excellence
Source(s) of Funding	? None	? None	? None	? None	These guidelines were developed using funding to the Department of Maternal, Newborn, Child and Adolescent Health from the United States Agency for International Development.	Queensland Health, Centre for Healthcare Improvement.	NICE

Guideline Title	Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation	ABM Clinical Protocol #22: Guidelines for Management of Jaundice in the Breastfeeding Infant Equal to or Greater Than 35 Weeks' Gestation	NNF guidelines	Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants	Recommendations on newborn health	Neonatal jaundice: prevention, assessment and management	Neonatal Jaundice
Financial Disclosures /Conflicts of Interest	None of the members of the Guideline Development Group (GDG) declared any conflicts of interest.	None declared any conflict of interest.	? None	? None	? None	? None	None
Disease/Condition(s)	Newborn Infant 35 or MoreWeeks of Gestation with jaundice	Breastfeeding Infant Equal to or Greater Than 35 Weeks' Gestation with jaundice	All neonates with jaundice	Term And Late Preterm Newborn Infants with jaundice	All neonates with jaundice	All neonates with jaundice	All neonates with jaundice
Intended Users	Hospitals and paediatricians, neonatologists, family physicians, physician assistants, and advanced practice nurses who treat newborn infants in the hospital and as outpatients.	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Guideline Objective(s	To reduce the incidence of severe	1. To provide guidance in	To have Neonatal practice Guidelines which are	1. Can severe hyperbiliru	1. What health	Not mentioned	1. Offer parents or

)	hyperbilirubinemia andbilirubin encephalopathy while minimizing the risks of unintended harm such as maternal anxiety, decreased breastfeeding, and unnecessary costs or treatment.	distinguishing those causes of jaundice in the newborn that are directly related to breastfeeding from those that are not directly related to breastfeeding. 2. To guide monitoring of jaundice and bilirubin concentration and management of these conditions in order to preserve breastfeeding while protecting the infant from potential risks of toxicity from hyperbilirubinemia. 3. To provide a protocol for hospital and office procedures for optimal management of jaundice and hyperbilirubinemia the breastfed newborn and young infant.	evidence based relevant to India, acceptable to local needs and developed by a large group with wider representation	binemia be accurately predicted? 2. Who should have their bilirubin concentration measured, 3. when and by what method? 4. How can the risk of severe hyperbilirubinemia be reduced? 5. When should severe hyperbilirubinemia be treated?	interventions should the newborn, child receive and when should s/he receive it?		carers information about neonatal jaundice that is tailored to their needs and expressed concern 2. Care for all babies and additional care for babies at high risk of hyperbilirubinemia 3. Measurement and methodology of bilirubin measurement 4. Care of a baby with prolonged jaundice

Target Population	Newborn Infant 35 or MoreWeeks of Gestation	Breastfeeding Infant Equal to or Greater Than 35 Weeks' Gestation	All neonates	Term And Late Preterm Newborn Infants	All neonates	All neonates	All neonates
Major Outcomes Considered	Clear and mentioned	Not clear	Not clear	Not clear	Not clear	Not clear	Clear and mentioned
Cost Analysis Performed /Reviewed ?	Yes	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned	Yes
Methods Used to Collect/Select the Evidence	Hand-searches of Published Literature (Primary Sources) Hand-searches of Published Literature (Secondary Sources) Searches of Electronic Databases	Not mentioned	A search of medical literature using specific search terms was made using PubMed, Medline, Cochrane trial register, Google Scholar and 'Ovid'. Abstracts of the retrieved studies were inspected and selected studies were perused in detail and relevant data extracted. This search was conducted independently by the three authors in each group and the references were subsequently pooled to widen the reference base.	A search was carried out in MEDLINE and the Cochrane library and was last updated in January 2007. Search terms in MEDLINE were hyperbilirubinemia and newborn, and the clinical queries filter of Haynes et al was applied using the broad, sensitive option. Other searches without the filter were carried out to find	Hand-searches of Published Literature (Primary Sources) Hand-searches of Published Literature (Secondary Sources) Searches of Electronic Databases Hand-searches of Published Literature (Primary Sources) Hand-searches of Published Literature (Primary Sources) Hand-searches of Published Literature (Secondary	Not mentioned	Hand-searches of Published Literature (Primary Sources) Hand-searches of Published Literature (Secondary Sources) Searches of Electronic Databases Hand-searches of Published Literature (Primary Sources) Hand-searches of Published Literature (Secondary Sources) Searches of Electronic Databases

				publications addressing specific issues. The hierarchy of evidence from the Centre for Evidence-Based Medicine was applied using levels of evidence for both treatment and prognosis. The reference lists of recent publications were also examined – in particular, the evidence-based review by Ip et al and a more extensive review by the same author performed for the Agency for Healthcare Research and Quality of the US Department of Health and Human Services. The references of the recent	Sources) Searches of Electronic Databases		

				statement of the American Academy of Pediatrics were also examined.			
Description of Methods Used to Collect/Select the Evidence	We searched the Medline database on September 25, 2001, for publications from 1966 to the present using relevant medical subject heading terms ("hyperbilirubinemia"; "hyperbilirubinemia, hereditary"; "bilirubin"; "jaundice, neonatal"; and "kernicterus") and text words ("bilirubin," "hyperbilirubinemia," "jaundice," "kernicterus," and "neonatal"). The abstracts were limited to human subjects and English-language studies focusing on newborns between birth and 1 month of age. In addition, the same text	Not mentioned	A search of medical literature using specific search terms was made using PubMed, Medline, Cochrane trial register, Google Scholar and 'Ovid'. In addition, relevant cross-references were looked at in detail. Abstracts of conference proceedings of National and International meetings (NNF, IAP,PAS, ESPR) and recommendations of various professional bodies were also reviewed. A hand search of MD &DM dissertations and non-indexed journals like Journal of Neonatology was performed.	Same as above	Not mentioned in summary document retrieved	Not mentioned	Mentioned and clear

	words used for the Medline search were used to search the PreMedline database. The strategy yielded 4280 Medline and 45 PreMedline abstracts. We consulted domain experts and examined relevant review articles for additional studies. A supplemental search for case reports of kernicterus in reference lists of relevant articles and reviews was performed also.						
Methods Used to Assess the Quality and Strength of the Evidence	The Steering Committee on Quality Improvement and Management categorizes evidence quality in 4 levels: 1. Well-designed, randomized, controlled trials or diagnostic studies on relevant populations	Not mentioned	Literature was assessed for appropriateness of study design, limitations in employed study design, and inconsistency across different studies, and applicability to Indian neonates. Evidence provided by individual studies was classified as per standard recommendations. Based on evidence guidelines are provided for practice and research issues.	Literature was assessed for appropriateness of study design, limitations in employed study design, and inconsistency across different studies, and applicability to Indian neonates. Evidence provided by	Not mentioned in the summary document	Not mentioned	

<table>
<tr>
<td></td>
<td>2. Randomized, controlled trials or diagnostic studies with minor limitations; overwhelming, consistent evidence from observational studies
3. Observational studies (case-control and cohort design)
4. Expert opinion, case reports, reasoning from first principles</td>
<td></td>
<td></td>
<td>individual studies was classified as per standard recommendations. Based on evidence guidelines are provided for practice and research issues.</td>
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<tr>
<td>Rating Scheme for the Strength of the Evidence</td>
<td>The AAP defines evidence-based recommendations as follows:1
• Strong recommendation: the committee believes
that the benefits of the recommended approach
clearly exceed the harms of that approach and that the quality of the supporting evidence is either excellent or impossible to</td>
<td>Not mentioned</td>
<td>GRADE recommendations were used to summarize evidence on therapeutic questions.
<table><tr><th>Level of evidence</th><th>Type of study</th></tr><tr><td>1a</td><td>Systematic review of randomized controlled trials</td></tr><tr><td>1b</td><td>Individual randomized controlled trial (with narrow confidence interval)</td></tr><tr><td>1c</td><td>All cases affected before intervention, some or none affected after intervention</td></tr></table></td>
<td>Grade recommendations (as Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=1047 (Version current at March 28, 2007).</td>
<td>A modified GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for assessing the quality of evidence was used. The quality of the set of included studies reporting</td>
<td>Not mentioned</td>
<td>Grade recommendations (as Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=1047 (Version current at March 28, 2007).</td>
</tr>
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	obtain. Clinicians should follow these recommendations unless a clear and compelling rationale for an alternative approach is present. • Recommendation: the committee believes that the benefits exceed the harms, but the quality of evidence on which this recommendation is based is not as strong. Clinicians should also generally follow these recommendations but should be alert to new information and sensitive to patient preferences. In this guideline, the term "should" implies a recommendation by the committee. • Option: either the		<table><tr><td>2a</td><td>Systematic review of cohort studies</td></tr><tr><td>2b</td><td>Individual cohort study (including low-quality randomized controlled trial)</td></tr><tr><td>2c</td><td>'Outcomes' research</td></tr><tr><td>3a</td><td>Systematic review of case-control studies</td></tr><tr><td>3b</td><td>Individual case-control study</td></tr><tr><td>4</td><td>Case series (and poor-quality cohort and case-control studies)</td></tr></table> <table><tr><th>Grades of recomm.</th><th>Levels of study</th></tr><tr><td>A</td><td>Consistent level 1 studies</td></tr><tr><td>B</td><td>Consistent level 2 or 3 studies or extrapolations from level 1 studies</td></tr><tr><td>C</td><td>Level 4 studies or extrapolations from level 2 or 3 studies</td></tr><tr><td>D</td><td>Level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td></tr></table>		results for an outcome was graded as: high, moderate, low or very low. The interpretation of the grades in these guidelines is: **High**: One can be sure that the intervention is beneficial, has no effect or is harmful. The results, including the magnitude of the pooled effect, are unlikely to change with new studies. **Moderate**: One can be reasonably sure that the intervention is beneficial, has no effect or is harmful. However, the magnitude of the pooled		

	quality of the evidence that exists is suspect or well-performed studies have shown little clear advantage to one approach over another. Patient preference should have a substantial role in influencing clinical decision-making when a policy is described as an option. • No recommendation: there is a lack of pertinent evidence and the anticipated balance of benefits and harms is unclear				effect may change with new studies. **Low**: Although it is likely that the intervention is beneficial, has no effect or is harmful, one cannot be sure. The magnitude of the pooled effect is uncertain and is likely to change with new studies. **Very low**: One cannot be certain about the effects of the intervention. The criteria used to grade the quality of evidence are shown in Table I of the original guideline document.		
Description of the Methods	In this report, 2 statistical analyses were performed in	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Described in detail (https://www.

Used to Analyze the Evidence	which there were sufficient data: the NNT and receiver operating characteristics (ROC) curve. NNT The NNT can be a clinically meaningful metric to assess the benefits of clinical trials.8 It is calculated by taking the inverse of the absolute risk difference. The absolute risk difference is the difference between the event rates between the treatment and control groups. For example, if the event rate is 15% in the control group and 10% in the treatment group, the absolute risk difference is 5% (an absolute risk reduction of 5%). The NNT then would be 20 (1 divided by 0.05), meaning that 20 patients will need						nice.org.uk/article/pmg6/chapter/4-Developing-review-questions-and-planning-the-systematic-review)

	to be treated to see 1 fewer event. In the setting of neonatal hyperbilirubinemia, NNT might be interpreted as the number of newborns needed to be treated (with phototherapy) at 13 to 15 mg/dL to prevent 1 newborn from reaching 20 mg/dL. ROC Curve ROC curves were developed for individual studies in question 4 if multiple thresholds of a diagnostic technology were reported. The areas under the curves (AUCs) were calculated to provide an assessment of the overall accuracy of the tests. Meta-analyses of Diagnostic Test Performance Meta-analyses were performed to quantify the TcB measurements for						

	which the data were sufficient. We used 3 complementary methods for assessing diagnostic test performance: summary ROC analysis, independently combined sensitivity and specificity values, and meta-analysis of correlation coefficients.						
Methods Used to Formulate the Recommendations	Expert Consensus Other	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	(https://www.nice.org.uk/article/pmg6/chapter/4-Developing-review-questions-and-planning-the-systematic-review)
Description of Methods Used to Formulate the Recommendations	Not provided	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	(https://www.nice.org.uk/article/pmg6/chapter/9-Developing-and-wording-guideline-recommendations)

Adaptation and adoption of recommendations

The Clinical practice guideline 'Subcommittee on Hyperbilirubinemia' for Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation was published by American Academy of Pediatrics in 2004. Thereafter the National Neonatology Forum, India published the guidelines in 2010 which were adapted from American Academy of Pediatrics guidelines. The National Collaborating Centre for Women's and Children's Health commissioned by the National Institute for Health and Clinical Excellence published the NICE guidelines for Neonatal jaundice in May 2010.

We have adopted and/or adapted from existing evidence based guidelines (Neonatal Jaundice, NICE 2010; updated May 2016, Clinical practice guideline 'Subcommittee on Hyperbilirubinemia for Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation', American Academy of Pediatrics, 2004, National Neonatology Forum, India guidelines, 2010) and tried to make them relevant to our context, resource settings and priorities.

S. No.	Key recommendation	Source guideline(s)	
	Screening and assessment		
1.	What should be the screening protocol for detection of jaundice in neonates? (14)		
	1. Healthcare professionals should all look for jaundice (visual inspection) in babies 2. Assessment of all newborns for jaundice should be done every 12 hours especially in the initial 3 to 5 days. 3. Monitoring for development of severe neonatal jaundice may be needed till end of first week of postnatal life.	Neonatal Jaundice, NICE 2010; updated May 2016	Adapted. The original recommendation is 'examine the baby for jaundice at every opportunity especially in the first 72 hours'. We have given an objectivity to the words 'at every opportunity' by giving a time frame. This will give clear message to all healthcare professionals and will ensure jaundice evaluation at least q 12 hourly in first 72 hours to avoid missing any case of neonatal jaundice.
2.	Which neonates are at a higher risk of hyperbilirubinaemia? (13)		
	Identify neonates as being more likely to develop significant hyperbilirubinaemia if they have **ANY** of the following factors: • Gestational age under 38 weeks • A previous sibling with neonatal jaundice requiring phototherapy • Mother's intention to breastfeed exclusively • Visible jaundice in the first 24 hours of life. • Visible jaundice at discharge • Setting of blood group incompatibility • High prevalence of G6PD deficiency, primipara mother • Weight loss at discharge >3% per 24 h of age or >7% cumulative weight loss	Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP 2004	• Visible jaundice at discharge (Adapted): Just the words have been reframed to make it simple. The original words are 'Jaundice observed before discharge' • 'Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive.' We have given the weight cut-offs to help healthcare professionals in objectively defining excessive weight loss. • The original recommendation is 'Blood group incompatibility with positive direct antiglobulin test (DAT)'. In India, direct coomb's test (DCT)/DAT test facility is not

			available at primary and secondary level of health care settings and at some of the tertiary care centres. Therefore, if mother's blood group is O positive or Rh Negative, then infants fall in high risk category unless one has a documented DCT/DAT report being negative.
3.	What is the accuracy of transcutaneous bilirubinometry in recognising neonatal hyperbilirubinaemia and how should it be done?		
3.1	Clinical examination for jaundice		
	1. Examine the baby in bright natural light. Alternatively, the baby can be examined in white fluorescent light. Make sure there is no yellow/ off white background. 2. Make sure the baby is naked. 3. Examine blanched skin and gums or sclerae 4. Depth of jaundice (degree of yellowness) should be carefully noted as it is an important indicator of level of jaundice and it does not figure out in Kramer's rule (27) 5. A deep yellow staining (even in absence of yellow soles or palms) is often associated with sever jaundice and therefore TSB should be estimated in such circumstances.	Neonatal Jaundice, NICE 2010; updated May 2016	Adopted
3.2	Transcutaneous and total serum bilirubin		
	Transcutaneous bilirubinometry **(**TcB**)** 1. TcB can be used in infants of 35 weeks or more of gestation after 24 hr. 2. TcB becomes unreliable once TSB level goes beyond 14 mg/dL. 3. Hour specific TcB can be used for prediction of subsequent hyperbilirubinemia. TcB value below 50th centile for age would rule out the risk of subsequent hyperbilirubinemia with high probability (high negative predictive value)(28) 4. Trends in TcB values by measuring 12 hr apart would have a better predictive value than a single value. Measurement of Total serum bilirubin (TSB)	Neonatal Jaundice, NICE 2010; updated May 2016	Adapted Å Interpret bilirubin levels according to the baby's postnatal age in hours and manage hyperbilirubinaemia according to the graphs (adopted from Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the

	1. Indication of TSB measurement: i. Jaundice in first 24 hour ii. Beyond 24 hr: if visually assessed jaundice is likely to be more than 14 mg/dL *or* approaching the phototherapy range *or* beyond. iii. If you are unsure about visual assessment iv. During phototherapy, for monitoring progress and after phototherapy to check for rebound in select cases (such as those with hemolytic jaundice) 2. Frequency of TSB measurement depends upon the underlying cause (hemolytic versus non-hemolytic) and severity of jaundice as well as host factors such as age and gestation. In general, in non-hemolytic jaundice in term babies, TSB can be performed every 12 to 24 hr depending upon age of the baby. As opposed to this, a baby with Rh isoimmunisation would require TSB measurement every 6 to 8 hours during initial 24 to 48 hours or so.		Newborn Infant 35 or More Weeks of Gestation, AAP 2004)
4.	How will you interpret serum bilirubin levels and manage hyperbilirubinaemia?		
	Interpret serum bilirubin levels according to the baby's postnatal age in hours and manage hyperbilirubinaemia as per the guidelines. 1. American Academy of Pediatrics (AAP) criteria should be used for making decision regarding phototherapy or exchange transfusion in these infants. AAP provides two age-specific nomograms- one each for phototherapy and exchange transfusion. The nomograms have lines for three different risk categories of neonates (Figure 3 and 4). These lines include one each for lower risk babies (38 wk or more and no risk factors), medium risk babies (38 wk or more with risk factors, or 35 wk to 37 wk and without any risk factors) and higher risk (35 wk to 37 wk and with risk factors). 2. TSB value is taken for decision making and direct fraction should **NOT** be reduced from it. The babies at lower and higher risk have their cut-offs at approximately 2 mg/dL higher or 2 mg/dL lower than that for medium risk babies, respectively. 3. Risk factors include presence of isoimmune hemolytic anemia,	Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP 2004	Adopted

<table>
<tr><td></td><td>G6PD deficiency, asphyxia, temperature instability, hypothermia, sepsis, significant lethargy, acidosis and hypoalbuminemia.*
*Routine estimation of serum albumin is not recommended</td><td></td><td></td></tr>
<tr><td>5.</td><td colspan="3">What should be optimum discharge and follow-up timing and the assessment policy to minimize the subsequent risk of severe hyperbilirubinemia and acute bilirubin encephalopathy? (22)</td></tr>
<tr><td></td><td>Table 1: Suggested follow-up policy
<table>
<tr><th>Scenario</th><th>Age at discharge</th><th>Follow-up</th></tr>
<tr><td rowspan="2">None of risk factors* present</td><td>24-72 h</td><td>48 h after discharge</td></tr>
<tr><td>>72 h</td><td>Follow-up optional</td></tr>
<tr><td rowspan="2">Any risk factor* present</td><td>24-48 h</td><td>24 h after discharge</td></tr>
<tr><td>After 48 hours</td><td>48 h after discharge</td></tr>
</table>
*History of jaundice needing treatment in previous sibling, setting of blood group incompatibility, visible jaundice at discharge, gestation <38 completed weeks, high prevalence of G6PD deficiency, primipara mother, weight loss at discharge >3% per 24 h of age or >7% cumulative weight loss,
**may need a repeat visit depending on physician's assessment</td><td>NNF guidelines 2010</td><td>Adopted</td></tr>
<tr><td>6.</td><td colspan="3">What should be included in the formal assessment of a neonate with neonatal hyperbilirubinaemia?</td></tr>
<tr><td></td><td>All neonates should undergo a complete clinical examination including evaluation of intensity of jaundice (27), breast feeding adequacy#, pallor, splenomegaly, cephalhematoma or other signs of birth trauma, and evaluation for lethargy, poor feeding, general activity and tone.
1. All pregnant women should be tested for ABO and Rh (D) blood types. (14)
2. If a mother has not had prenatal blood grouping or is Rh-negative, a direct anti-body test (or Coombs' test), blood type, and an Rh (D) type on the infant's (cord) blood are strongly recommended. (14)
3. DO NOT use the albumin/bilirubin ratio when making decisions about the management of hyperbilirubinaemia (14)</td><td>Neonatal Jaundice, NICE 2010; updated May 2016</td><td>Adapted;
1. The approach mentioned in the current guideline includes a complete clinical examination for possible risk factors of jaundice which have not been mentioned in the NICE guidelines
2. The words have been simplified so that it is better understood. The rest content is the same.</td></tr>
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<td></td>
<td>
4. Do not subtract conjugated bilirubin from total serum bilirubin when making decisions about the management of hyperbilirubinaemia. (14)
5. In addition to a full clinical examination by a suitably trained healthcare professional, carry out the following tests in babies with hyperbilirubinaemia (Table 2) as part of an assessment for underlying disease and treatment threshold graphs.
Table 2: Tests to be done in babies with hyperbilirubinaemia
<table>
<tr><th>Indications</th><th>Assessments</th></tr>
<tr><td>Infant receiving phototherapy</td><td>Measure TSB; blood type and DCT (if mother is ‘O’ or Rh negative); G6PD status; peripheral smear and reticulocyte count</td></tr>
<tr><td>Jaundice present beyond 3 weeks of age*</td><td>Total and direct (or conjugated) bilirubin level, thyroid profile (T3, T4, TSH), urine for reducing substances (galactosemia), urine r/m, urine c/s</td></tr>
</table>
Important Note*

Exclude cephalohematoma on examination
Exclude Rh isoimmunisation
Excessive weight loss (more than 10%)
Breast feeding jaundice due to inadequate breast feeding is common
Presence of direct hyperbilirubinemia (direct bilirubin more than 2 mg/dL at any age) requires specific investigations and care which is beyond the scope of this guideline

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<tr>
<td>7.</td>
<td colspan="3">How can we prevent severe hyperbilirubinemia? (13, 14)</td>
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<tr>
<td></td>
<td>1. All women should be encouraged to breastfeed 8 to 12 times a day
2. Supplementation is recommended only for dehydrated newborns and where weight loss from birth is >10%. Expressed breastmilk is the preferred supplementation.</td>
<td>Neonatal Jaundice, NICE 2010; updated May 2016 and Clinical practice guideline Subcommittee on</td>
<td>Adopted</td>
</tr>
</table>

	3. Routine supplementation with intravenous fluids, honey or dextrose water for newborns with jaundice is not recommended 4. No interruption of breastfeeding should be done for any jaundice.	Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP 2004	
2.	*Management and treatment*		
2.1	**Phototherapy for the management of hyperbilirubinemia**		
	Å Phototherapy can be delivered by light - emitting diode (LED) or fibreoptic or fluorescent lamps or tubes or bulbs.[#] Å Do not use sunlight as treatment for hyperbilirubinaemia. Exposing the baby to sunlight does not help in treatment of jaundice and is associated with risk of sunburn and therefore should be avoided.	Neonatal Jaundice, NICE 2010; updated May 2016	Adopted
	For starting phototherapy		
	Å Use serum bilirubin levels **ONLY** for decision making for starting phototherapy Å Intensive phototherapy must be ensured for neonates nearing exchange transfusion threshold. Phototherapy can be intensified by adding another light source or increasing the irradiance of the initial light source used. Å Phototherapy thresholds presented on seventh day may be used for rest of the neonatal period	Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP 2004	Adopted
	Å It is not necessary to measure spectral irradiance before each use of phototherapy; however it is important to perform periodic checks of phototherapy units to make sure that an adequate irradiance is being delivered	Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP	Adopted

		2004	
	For stopping phototherapy		
	Å There is no standard for discontinuing phototherapy. For infants who are readmitted after their birth hospitalization (usually for TSB levels of 18 mg/dL or higher), phototherapy may be discontinued when the serum bilirubin level falls below 13 to 14 mg/dL.	Clinical practice guideline Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP 2004	Adopted
	Discharge and follow up after phototherapy		
	Å 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 discharge is recommended. Å For infants who are readmitted with hyperbilirubinemia and then discharged, significant rebound is rare, but a repeat TSB measurement or clinical follow-up 24 hours after discharge is a clinical option. Å Checking serum bilirubin 24 h after discharge to check for rebound is optional	NNF Guidelines 2010	Adopted
	Tips for delivering safe and effective phototherapy		
	Å Protect the eyes with eye patches/covers Å Keep the baby naked with a small nappy to cover the genitalia Å Place the baby as close to the lights as the manufacturers' instructions allow. Å Routine position change while the baby is under phototherapy is not recommended. Å Phototherapy does not have to be continuous and can be interrupted for feeding, clinical procedures, and to allow maternal bonding. Å Using white cloth or aluminum foil around the light source to reflect light back onto the baby, making sure not to impede the	Neonatal Jaundice, NICE 2010; updated May 2016	Adapted with minor language changes to make the reading simple

	airflow that cools the bulbs is optional Å Do not place anything over the top of the phototherapy unit. This may block air vents or light and items may fall on the baby Å Encourage frequent breastfeeding. Unless there is evidence of dehydration, supplementing breastfeeding or providing IV fluids is unnecessary Å Giving frequent feeding will prevent excessive weight loss and temperature from rising Å Visual assessment of jaundice during phototherapy is unreliable Å Ensure all phototherapy equipment is maintained and used according to the manufacturers' guidelines.		
	Failure of phototherapy		
	Å For those infants in the exchange or pre-exchange bilirubin zone, failure of phototherapy has been defined as an inability to observe a decline in bilirubin of 1-2 mg/dL after 4-6 hours and/or to keep the bilirubin below the exchange transfusion level. Å Exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. Å For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours. However, an exchange transfusion (ET) should be performed at the slightest suspicion of bilirubin encephalopathy irrespective of the bilirubin value.	NNF Guidelines 2010	Adopted
2.2	**Exchange Transfusion**		
	Å Exchange transfusion should be done by central or peripheral route aiming replacement of double the baby's blood volume and by skilled personnel in a well-equipped centre. Å Immediate EBT is recommended if infant shows signs of ABE or if TSB is ≥25 mg/dL above the recommended age and risk specific cut off TSB Å For Rhesus isoimmunization, the best choice would be O (Rh) negative packed cells suspended in AB plasma. O (Rh) negative whole blood or cross-matched baby's blood group (Rh negative)	Neonatal Jaundice, NICE 2010; updated May 2016	Adopted

	may also be used. Å For ABO isoimmunization, O group (Rh compatible) packed cells suspended in AB plasma or O group whole blood (Rh compatible with baby) should be used. Å In other situations baby's blood group should be used. All blood must be cross matched against maternal plasma. Å Blood volume used: 2 x (80-100 ml/kg) x birth weight in kg.		
2.3	**Other modalities for management of hyperbilirubinemia**		
	Å No role of phenobarbitone, tin mesoporphyrin, Agar, Albumin, charcoal, cholestyramine, clofibrate, glycerine, chinese herbs, homeopathy, acupuncture, riboflavin or manna in management of hyperbilirubinemia Å Routine use of Intravenous immunoglobulin (IVIg) for Rh haemolytic disease of newborn and ABO disease is not recommended as evidence from studies with low risk of bias indicates no benefit in Rh haemolytic disease of newborn and studies suggesting benefit in ABO incompatibility had a high risk of bias. (26)	Neonatal Jaundice, NICE 2010; updated May 2016	Adapted the recommendation on Intravenous immunoglobulin (IVIg) in light of a recent systematic review (29).
2.4	**What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia?**		
	Offer parents or care givers information about neonatal jaundice but should be tailored to their needs and expressed concerns. This information should be provided through verbal discussion backed up by written information whenever possible. (14) Care should be taken to avoid causing unnecessary anxiety to parents or care-givers. **Information should include:** Å factors that influence the development of significant hyperbilirubinaemia Å how to check the baby for jaundice Å what to do if they suspect jaundice Å the importance of recognizing jaundice in the first 24 hours and of seeking urgent medical advice Å the importance of checking the baby's nappies for dark urine or pale chalky stools	Neonatal Jaundice, NICE 2010; updated May 2016	Adopted

	Å the fact that neonatal jaundice is common, and reassurance that it is usually transient and harmless when treated appropriately Å reassurance that breastfeeding should continue **Information about treatment including phototherapy** Å anticipated duration of treatment Å reassurance that breastfeeding, nappy-changing and cuddles can usually continue. Å Encourage mothers of with jaundice to breastfeed frequently, and to wake the baby for feeds if necessary. Å Provide lactation/feeding support to mothers whose baby is visibly jaundiced. Å why phototherapy is being considered Å why phototherapy may be needed to treat significant hyperbilirubinaemia Å the possible adverse effects of phototherapy Å the need for eye protection and routine eye care Å reassurance that short breaks for feeding, nappy changing and cuddles will not alter course of jaundice and efficacy of phototherapy Å what might happen if phototherapy fails Å rebound jaundice Å potential long-term adverse effects of phototherapy **Information on exchange transfusion** Å Offer parents or care givers information on exchange transfusion including: Å the baby be admitted to an intensive care bed Å why an exchange transfusion is being considered Å the possible adverse effects of exchange transfusions Å when it will be possible for parents or care givers to see and hold the baby after the exchange transfusion. Å when it will be possible for parents or care givers to see and hold the baby after the exchange transfusion.		

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