OPTIMAL FEEDING OF LOW BIRTH WEIGHT INFANTS

Standard Treatment Guidelines

Neonatal Guideline Development Group
(Secretariat: Department of Pediatrics, AIIMS)

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FOREWORD

To be developed

Executive summary

Low birth weight (LBW) is defined as weight less than 2500g at birth. The World Health Organization estimates that 16% of allneonates—nearly 20 million—are born low birth weight(birth weight less than 2500 g) every year. In India, nearly one-third of live born babies are low birthweight—8 million every year. These neonates are at 11–13times increased risk of dying as compared to normal birthweight babies.

Low birth weight neonates may be gestation-wiseimmature (i.e. preterm) or may have sufferedintrauterine growth restriction (IUGR). The incidence of prematurity is fairlyconstant at 8–16% throughout the world. But the prevalence of IUGR varies widely – in South Asia, IUGR is responsiblefor two-thirds of LBW neonates.

LBW infants are at risk of short and long term morbidities. Short term morbidities include hypothermia, hypoglycemia, increased risk of sepsis and feeding difficulties among others. Feeding difficulties in LBW infants are often due to poor feeding skills because of prematurity per se, altered perfusion of the gut due to high resistance in uterine and umbilical arteries while *in utero,* and also due to non-availability of own mother's milk in adequate volume in the initial few days after birth. Providing optimal nutrition not only improves growth but also results in better neurodevelopmental outcome in these infants.

Optimal nutrition to LBW infants can be provided by parenteral or enteral means. While parenteral nutrition is essential when the infant is critically ill, enteral route is preferred over parenteral route once the infant is stabilized because of the cost and inherent risks involved with parenteral nutrition. Enteral feeding should be initiated and advanced as early as possible in LBW infants to optimize nutrition.

The objective of this standard treatment guidelines is to improve the quality of care received by LBW infants inhealth facilities of India through improved capacity of health care providers. These guidelines focus on optimal feeding of clinically stable LBW infants in India. They do not specificallyaddress the feeding of infants with a birth weight less than 1.0 kg (known as extremely LBW, ELBW),who are often clinically unstable and may require parenteral nutrition. Health care providers can adapt the recommendations to their setting and implement to improve short- and long-term outcomes of LBW infants.

The Guideline Development Group (GDG)searched the existing guidelines on feeding of low birth weight infants using a broad search strategy. After comparing the available guidelines using the standard approach, the GDG decided to use the WHO optimal feeding of LBW guidelines as the base for the present guidelines and adopt it using the National Neonatology Forum (NNF) guidelines.

The WHO guidelines had enlisted 18 priority research questions. The GDG identified eight additional RQs from the NNF practice guidelines, of which four were considered to be relevant and important for the present guidelines. In addition, the group conducted an electronic survey followed by telephonic discussion among healthcare providers from secondary level facilities to identify additional research questions.

The GDG finalized the recommendations by adopting or adapting the original recommendations from the WHO and NNF guidelines:

Recommendations on optimal feeding of low birth weight infants	
Recommendation	**Adopted/adapted from**
What to feed: Choice of milk	
Low birth weight (LBW) infants, including those with very low birth weight (VLBW), should be fed mother's own milk.	Adopted from the WHO guidelines
LBW infants, including those with VLBW, who do not have access to mother's own milk/ whose mother's own milk is insufficient,should be fed donor human milk.	Adapted from the WHO guidelines
LBW infants, including those with VLBW, who cannot be fed mother's own milk or donor human milk should be fed standard infant formula. VLBW infants who cannot be fed mother's own milk or donor human milk should be given preterm infant formula if they fail to gain weight despite adequate feeding with standard infant formula.	Adopted from the WHO guidelines
VLBW infants who are fed mother's own milk or donor human milk should not routinely be given bovine milk-based human milk fortifier. VLBW infants who fail to gain weight despite adequate breastmilk feeding should be given human-milk fortifiers, preferably those that are human milk based.	Adopted from the WHO guidelines
What to feed: Supplements	

LBW infants (1500-2499 g) should be given vitamin D supplements at a dose of 400 IU per day until 6 months of age. VLBW infants (<1500 g) should be given vitamin D supplements at a dose of 800 IU per day until 6 months of age.	Adapted from the WHO and NNF guidelines
VLBW infants who are fed mother's own milk or donor human milk should be given daily calcium (120-140 mg/kg per day) and phosphorus (60-90 mg/kg per day) supplementation until term gestation (40 weeks' postmenstrual age).	Adapted from the WHO guidelines
VLBW infants fed mother's own milk or donor human milk should be given 2-4 mg/kg per day iron supplementation starting at 2 weeks until 6 months of age. Other LBW infants (1500-2499 g) fed mother's own milk or donor milk should be given 2-3 mg/kg per day iron starting at 6-8 weeks until 6 months of age.	Adapted from the WHO and NNF guidelines
Routine zinc supplementation for LBW infants who are fed mother's own milk or donor human milk is not recommended at the present time, because there is not enough evidence of benefits to support such a recommendation.	Adopted from the WHO guidelines
When to initiate feeding?	
LBW infants **(**birth weight $\geq$ 1200 g)who are able to breastfeed should be put to the breast as soon as possible after birth when they are clinically stable.	Adopted from the WHO guidelines
LBW infants with birth weight <1200 g should be given 10 mL/kg per day of enteral feeds, preferably expressed breast milk, starting from the first day of life, with the remaining fluid requirement met by intravenous fluids.	Adapted from the WHO guidelines
How to feed?	
LBW infants who need to be fed by an alternative oral feeding method should be fed by cup (or *palladai*, which is a cup with a beak) or spoon.	Adopted from the WHO guidelines
VLBW infants requiring intragastric tube feeding should be given bolus intermittent feeds.	Adopted from the WHO guidelines
In VLBW infants who need to be given intragastric tube feeding, the intragastric tube may be placed either by oral or nasal route, depending upon the preferences of health-care providers.	Adopted from the WHO guidelines
VLBW infants on intragastric tube feeding should be fed 2 hourly. Other LBW infants (1500-2499 g) on intragastric tube feeding should be fed 3-hourly.	Adapted from the NNF guidelines
LBW infants who are fully or mostly fed by an alternative oral feeding method should be fed based on infants' hunger cues, except when the infant remains asleep beyond 3 hours since the last feed.	Adopted from the WHO guidelines

How much to feed?	
LBW infants with birth weight >=1200 g should be initiated on 60-80 mL/kg per day of enteral feeds, preferably expressed breast milk, on the first day of life.	Adapted from the NNF guidelines
In VLBW infants who need to be fed by an alternative oral feeding method or given intragastric tube feeds, feed volumes can be increased by up to 30 ml/kg per day with careful monitoring for feed intolerance.	Adopted from the WHO guidelines
LBW infants who need to be fed by an alternative oral feeding method or given intragastric tube feeds, should be fed up to 180-200 mL/kg per day after 1-2 weeks of life.	Adapted from the NNF guidelines
Optimal duration of exclusive breastfeeding	
LBW infants should be exclusively breastfed until 6 months of age.	Adopted from the WHO guidelines
Miscellaneous issues	
Non-nutritive sucking (NNS) is recommended in VLBW infants on intragastric tube feeding to improve transition from gavage to breast feeding.	Adapted from the NNF guidelines
Growth monitoring	
LBW infants should be monitored for optimal growth by serial weight and head circumference measurement at least once weekly in the first weeks of life, using an appropriate growth chart like Fenton's chart.	Adapted from the NNF guidelines

Introduction

Low birth weight (LBW) is defined as weight less than 2500g at birth. The World Health Organization estimates that 16% of allneonates—nearly 20 million—are born low birth weight(birth weight less than 2500 g) every year. The highest burdenof low birth weight (LBW) neonates is in South Asia, wherean estimated 31% neonates are born low birth weightcontributing to nearly one half of the global burden.In India, nearly one-third of live born babies are low birthweight—8 million every year. These neonates are at 11–13times increased risk of dying as compared to normal birthweight babies and are also predisposed to a variety of adult onsetdiseases.

Low birth weight neonates may be gestation-wiseimmature (i.e. preterm) or may have sufferedintrauterine growth restriction (IUGR). The incidence of prematurity is fairlyconstant at 8–16% throughout the world. But the prevalence of IUGR varies widely – in South Asia, IUGR is responsiblefor two-thirds of LBW neonates.LBW infants are also classified as very low birth weight (VLBW) if their birth weight is less than 1.5 kg, and as extremely low birth weight (ELBW) if their birth weight is less than 1 kg. All these infants have a higher mortality risk than infants who do not have LBW.

LBW infants are at risk of short and long term morbidities. Short term morbidities include hypothermia, hypoglycemia, increased risk of sepsis and feeding difficulties among others. Feeding difficulties in LBW infants are often due to poor feeding skills because of prematurity per se, altered perfusion of the gut due to high resistance in uterine and umbilical arteries while *in utero,* and also due to non-availability of own mother's milk in adequate volume in the initial few days after birth. Providing optimal nutrition not only improves growth but also results in better neurodevelopmental outcome in these infants.

Optimal nutrition to LBW infants can be provided by parenteral or enteral means. Even though parenteral nutrition is essential when the infant is critically ill, enteral route is preferred over parenteral once the infant is stabilized because of the cost and inherent risks involved with parenteral nutrition. Enteral feeding should be initiated and advanced as early as possible in LBW infants to optimize nutrition.

However, LBW feeding is fraught with controversies resulting in wide variations in clinical practice.

Formulating a standard feeding guidelines based on current best evidence would help to streamline enteral feeding practices in LBW infants. Health care providers can adapt the recommendations to their setting and implement to improve short term outcomes of LBW infants.

Guideline Development Group (GDG)

The following experts were involved in the development of these guidelines: Vinod Paul (AIIMS, New Delhi), Ashok Deorari (AIIMS, New Delhi), M Jeeva Sankar (AIIMS, New Delhi), Ruchi Nanavati (KEM, Mumbai), Jayashree Mondkar (LTMMC, Sion, Mumbai), Ramesh Agarwal (AIIMS, New Delhi), Nandkishore Kabra (AIIMS, New Delhi), Ashish Jain (MAMC, Delhi), and N Chandrakumar (AIIMS, New Delhi).

Team from NHSRC, NICE, (NHSRC team to fill the names and their roles)

The guideline development group (GDG) met once in September 2015 to deliberate on the steps and timelines. A working group comprising three members of the GDG (MJS, NC, and RN) developed the draft guidelines based on the agreed plan. Thisdraft was reviewed electronically and approved by the other GDG members.

Declaration of interests

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

Funding source

National Health Systems Resource Center (NHSRC), New Delhi

Scheduled review

We plan to update the STG every 3 years.

Scope of the guidelines

Target audience

The primary audience for these guidelines is intended to be healthcare workers in primary and secondary level health facilities as well as referral hospitals. The

guidelines are also expected to be used by policy-makers, program managers, and health facility managers to set up a system for optimal care of LBW infants.

Further, many of the recommendations will be relevant for community health workers providing care to LBW infants at home. The information in these guidelines will be included in several capacity strengthening courses for health workers, such as for Essential Newborn Care and Integrated Management of Newborn and Childhood Illness (IMNCI), and in community health worker training on caring for the newborn at home.

Population of interest

The guidelines focus on the feeding of clinically stable LBW infants being cared for in a health facility or at home. Some of the recommendations focus only on very low birth weight infants (VLBW; birth weight less than 1.5 kg). The guidelines do not specifically address the feeding of infants with a birth weight less than 1.0 kg (extremely low birth weight; ELBW), who are often clinically unstable and may require parenteral nutrition. Further, the guidelines do not provide separate recommendations for the two groups of LBW infants – term small-for-gestational age (SGA) and preterm – because of lack of evidence.

Critical outcomes

Four outcomes were considered to be critical by the GDG: mortality, severe morbidity, neurodevelopment, and anthropometric status. Mortality and severe morbidity over the short term (e.g. during initial hospital stay after birth) or long term (e.g. infant mortality) were considered to be critical. Neurodevelopment and anthropometric status were considered critical only if measured at age 6 months or more.

Benefits and harms in critical outcomes formed the basis of the recommendations. When information on critical outcomes was not available, other non-critical outcomes were considered. Examples of these other outcomes include breastfeeding duration or exclusivity, short-term growth, duration of hospital stay, hemoglobin levels and bone mineralization.

Methodology

Step 1: Search and select guidelines

The GDG 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), www.cps.ca(Canadian Pediatric Society), and www.nnfi.org (National Neonatology Forum, India) to search for existing guidelines on feeding of low birth weight infants.

The following search strategy "(feeding[All Fields] AND ("infant, low birth weight"[MeSH Terms] OR ("infant"[All Fields] AND "low"[All Fields] AND "birth"[All Fields] AND "weight"[All Fields]) OR "low birth weight infant"[All Fields] OR ("low"[All Fields] AND "birth"[All Fields] AND "weight"[All Fields] AND "infants"[All Fields]) OR "low birth weight infants"[All Fields])) AND Guideline[ptyp]" was used for searching PubMed. A similar search strategy was used to search the websites of national and international organizations.

Two relevant citations – one each by the World Health Organization and Chinese Society of Parenteral and Enteral Nutrition (CSPEN) – were identified. In addition, the GDG identified another guideline – by National Neonatology Forum, India –by hand searching. Another review-cum-guidelines – published recently in 2015 – by an expert group from McMaster University, Canada was also identified by hand searching.

Step 2: Compare and sift guidelines

Table 1 depicts the key features of the three guidelines (WHO, CSPEN, and NNF).

Of the three guidelines, only one – by the World Health Organization – has been evaluated thoroughly by the National Guideline Clearinghouse of the US (www.guideline.gov). The technical quality and the process of development of the other two guidelineswere evaluated by two members of the GDG using the AGREE-GRS instrument (http://www.agreetrust.org/).

Both the guidelines scored3 to 5 in the 7-point scale for individual items (lowest quality being 1). On the overall guideline assessment, one guideline (CSPEN) scored 2 while the NNF guidelines scored 6 (strongly disagree=1; strongly agree=7 in a 7-point scale).

The GDGunanimously decided to use the WHO feeding guidelines as the base for the present guidelines and adopt it using the NNF guidelines, if there was a need to adopt the recommendations to Indian context.

Table 1: Comparison of guidelines			
Guideline Title	**Guidelines on optimal feeding of low birth-weight infants in low- and-middle income countries**	**CSPEN guidelines for nutrition support in neonates**	**NNF Clinical Practice Guidelines**
Date Released	2011	2013	2010
Adaptation	Not applicable: The guideline was not adapted from another source.	Not applicable	Not applicable
Guideline Developer(s)	World Health Organization (WHO) - International Agency	Chinese Society of Parenteral and Enteral Nutrition, Chinese Society of Pediatrics	National Neonatology Forum, India
Source(s) of Funding	These guidelines were developed using funding to the Department of Maternal, Newborn, Child and Adolescent Health from the United States Agency for International Development.	? None	National Neonatology Forum, India
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.	Not clear
Disease/Condition(s)	• Low birth weight (LBW) (<2.5 kg) • Very low birth weight (VLBW) (1.0 to 1.5 kg)	Neonates NOT restricted to LBW neonates	LBW neonates (one section in the document is on 'Feeding of LBW Infants')
Intended Users	Advanced Practice Nurses Allied Health Personnel Dietitians Health Care Providers Health Plans Hospitals Managed Care Organizations Nurses Physician Assistants Physicians Public Health Departments	Not mentioned	Not mentioned
Guideline Objective(s)	To improve the quality of care received by low birth weight (LBW) infants in	To provide proposed advisable ranges for nutrient	To have Neonatal practice Guidelines which are evidence based relevant to

	developing countries through improved capacity of health workers who care for these infants	intakes in neonates	India, acceptable to local needs and developed by a large group with wider representation
Target Population	Clinically stable low birth weight (LBW)* infants in low- and middle-income countries, including infants born at term (after 37 and before 42 completed weeks of gestation) and preterm (born up to 37 completed weeks of gestation) *Weighing between 1.0 and 2.5 kg at birth **Note**: The recommendations do not specifically address the feeding of infants with a birth weight less than 1.0 kg (known as extremely LBW, ELBW), who are often clinically unstable and may require parenteral nutrition.	All neonates including preterm and most sick term neonates	All neonates
Major Outcomes Considered	• Mortality • Severe morbidity • Neurodevelopment • Anthropometric status	Not clear	Not clear
Cost Analysis Performed/Reviewed ?	Yes	No	No
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	Based on the 'considered review of available scientific reports on the subject, and on expert consensus for which the available scientific data are considered inadequate' Further details not available	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.
Description of Methods Used to Collect/Select the Evidence	**Search Strategy** A series of systematic reviews were conducted and published by the World Health Organization (WHO) as *Optimal feeding of low-birth-weight infants: technical review* in 2006. The databases searched included the Cochrane Database of Systematic Reviews of randomized controlled trials (RCTs), the Cochrane Controlled Trials Register, the Cochrane Database of Abstracts of Reviews of Effectiveness (DARE), the Cochrane neonatal collaborative review group specialized register, MEDLINE (1966 to 2005), and EMBASE (1966 to 2005). The reference lists of relevant articles and a number of key journals were hand searched. Every effort was made to include relevant non-English language articles and abstracts. This approach was complemented by an additional search in August-September 2010 to identify relevant research papers published between January 2005 and August 2010. The first set of search terms ("all fields" and "MESH terms") was related to the population of interest: low-birth-weight (LBW) infant, preterm infant, premature infant, SGA infant, fetal growth retardation, intrauterine growth retardation, intrauterine growth restriction. The studies identified also needed to have at least one of the search terms in the second set related to issues in feeding of LBW infants. The	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.

<table>
<tr><td></td><td>second set of search terms included: feeding, enteral nutrition, breastfeeding, breast milk, human milk, donor milk, formula, human-milk fortifier, vitamin, micronutrient, vitamin A, vitamin D, calcium, phosphorus, zinc, iron, cup, bottle, spoon, tube, feeding tolerance, trophic feeding, minimal enteral nutrition and gut priming.</td><td></td><td></td></tr>
<tr><td>Methods Used to Assess the Quality and Strength of the Evidence</td><td>Weighting According to a Rating Scheme (Scheme Given)</td><td>The quality and strength of the supporting literature was graded according to American Society for Parenteral and Enteral Nutrition (ASPEN). The grade of recommendation depends on the scientific quality of the studies reported. Meta-analyses were used to organize information and to draw conclusions about overall treatment effect from multiple studies on a particular subject.</td><td>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.</td></tr>
<tr><td>Rating Scheme for the Strength of the Evidence</td><td>Quality of the Evidence
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 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</td><td>Level of evidence
I: Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error
II: Small, randomized trials with uncertain results; moderate to high risk of false-positive (alpha) and/or false-negative (beta) error</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></table></td></tr>
</table>

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 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.

III: Nonrandomized, contemporaneous controls
IV: Nonrandomized, historical controls
V: Case series, uncontrolled studies, and expert opinion

Grade of recommendation
A: Supported by at least two level I investigations
B: Supported by one level I investigation
C: Supported by level II investigations only
D: Supported by at least two level III investigations
E: Supported by level IV or level V evidence

1b	Individual randomized controlled trial (with narrow confidence interval)
1c	All cases affected before intervention, some or none affected after intervention
2a	Systematic review of cohort studies
2b	Individual cohort study (including low-quality randomized controlled trial)
2c	'Outcomes' research
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)

Grades of recomm.	**Levels of study**
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or

				extrapolations from level 2 or 3 studies
			D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level
Description of the Methods Used to Analyze the Evidence	**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 randomized controlled trials (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	Meta-analyses were used to organize information and to draw conclusions about overall treatment effect from multiple studies on a particular subject. Further details not available.		

	continuous data where possible. Where results adjusted for potential confounders were available, particularly for observational studies, they were used in preference to unadjusted results. Where results adjusted for potential confounders were not available, unadjusted results were used. All studies reporting on a critical outcome were summarized in a table of individual studies (see the Annexes in the original guideline document). **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 Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was at least "low", observational studies were not considered. However, if there were less than three RCTs for an outcome or the quality of evidence was "very low", the effects from RCTs were pooled with those from available cohort and case-control studies. 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 using the "metan" command in Stata 11.0. 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 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. **Grading the Quality of Evidence** A modified GRADE approach for assessing the quality of evidence was used (see the "Rating Scheme for the Strength of the Evidence" field). One of the difficulties in using GRADE is that the evidence base for an outcome may include studies with varying methodological quality and sample size. Therefore, the weight of the studies in the estimation of the pooled effect was included to make judgments about the quality of the set of included studies. The criteria used to grade the quality of evidence are shown in Table I in the original guideline document. The following briefly describes how these criteria were used: *Study Design* The included studies were classified as: 1 RCTs –including RCTs or cluster-RCTs 2 Non-randomized experimental studies		

	3 Observational studies, including cohort studies and case-control studies (studies with other observational designs were not included) If a majority of evidence was from RCTs, indicated by over 50% weight in the pooled effect, a score of 0 was given. A score of -0.5 was given if a majority of evidence was from non-randomized experimental studies, and -1.0 if the evidence was from observational studies. See the original guideline document for the limitations and other details of these methods.		
Methods Used to Formulate the Recommendations	Expert Consensus Other	Not provided	Not provided
Description of Methods Used to Formulate the Recommendations	**Formulation of Recommendations** The external guideline panel formulated the first version of the recommendations based on the technical review published in 2006. This version of guidelines was field tested in health facilities in four countries - Ghana, India, Pakistan and Uganda - in 2008-9. After the evidence base was updated in 2010 and its quality graded using the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the World Health Organization (WHO) staff prepared the second version of recommendations in a format consistent with the new WHO *Handbook for Guideline Development* (see the "Availability of Companion Documents"	Not provided	Not provided

	field). The Guideline Development Group (GDG) met once to review the evidence synthesized in a technical review. The WHO working group and a consultant developed the draft guidelines based on this evidence. This draft was reviewed electronically by the GDG members and approved by them. The GRADE system for grading recommendations was used. 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 compared to the benefits in low- and middle-income countries.		

The WHO guidelines were published in year 2011. Because the evidence behind the recommendations was relatively old, the GDG planned to examine the recently published systematic review on feeding of LBW infants to update the evidence and to decide on the need to modify the recommendations.

Step 3: Search and select recommendations

Before searching and selecting the recommendations, the GDG examined the research questions (RQ) addressed by the WHO and NNF guidelines in the meeting held in Delhi in late 2015. The group deliberated and enlisted the following steps:

1) Examine the appropriateness and relevance of RQs in WHO feeding guidelines
2) Identify other relevant RQs in NNF Clinical Practice Guidelines to complement those in WHO guidelines
3) Discuss with other stakeholders – particularly healthcare providers from secondary level health facilities – to identify research questions that are relevant to their settings.

Examining WHO LBW feeding guidelines

The WHO guidelines had enlisted 18 priority research questions:

1. *In LBW infants (P), what is the effect of feeding mother's own milk (I) compared with feeding infant formula (C) on critical outcomes - mortality, severe morbidity, neurodevelopment and anthropometric status (O)?*
2. *In LBW infants who cannot be fed mother's own milk (P), what is the effect of feeding donor human milk (I) compared with feeding infant formula (C) on critical outcomes (O)?*
3. *In LBW infants who cannot be fed mother's own milk or donor human milk (P), what is the effect of feeding preterm infant formula (I) compared with feeding standard infant formula (C) on critical outcomes (O)?*
4. *In LBW infants who cannot be fed mother's own milk or donor human milk (P), what is theeffect of feeding nutrient-enriched infant formula from hospital discharge until 6 months ofage (I) compared with feeding standard infant formula (C) on critical outcomes (O)?*
5. *In VLBW infants who are fed mother's own milk or donor human milk (P), what is the effectof multi-component fortification of breast milk (I) compared with no fortification of breastmilk (C) on critical outcomes (O)?*
6. *In VLBW infants who are fed mother's own milk or donor human milk (P), what is the effectof giving 2-4 Recommended Daily Allowance (RDA) of*

vitamin D supplements (I) comparedwith 1 RDA of vitamin D supplements (C) on critical outcomes (O)?

7. *In VLBW infants who are fed mother's own milk or donor human milk (P), what is the effect of calcium and phosphorus supplementation (I) compared with no supplementation (C) oncritical outcomes (O)?*
8. *In VLBW infants who are fed mother's own milk or donor human milk (P), what is the effectof starting iron supplementation at 2 weeks of age (I) compared with starting ironsupplementation at 2 months of age (C) on critical outcomes (O)?*
9. *In VLBW infants who are fed mother's own milk or donor human milk (P), what is the effectof daily oral vitamin A supplementation (I) compared with no supplementation (C) on criticaloutcomes (O)?*
10. *In LBW infants who are fed mother's own milk or donor human milk (P), what is the effect ofzinc supplementation (I) compared with no supplementation (C) on critical outcomes (O)?*
11. *In LBW infants who are able to breastfeed (P), what is the effect of initiation of breastfeeding in the first day of life (I) compared with delaying breastfeeding for more than 24 hours (C) on critical outcomes (O)?*
12. *In VLBW infants born in settings where total parenteral nutrition is not possible (P), what is the effect of starting small amounts of oral feeds (about 10 ml/kg per day) in the first few days of life (I) compared with no enteral feeding (C) on critical outcomes (O)?*
13. *In LBW infants (P), what is the effect of exclusive breastfeeding for 6 months (I) compared with an exclusive breastfeeding duration of 4 months or less (C) on critical outcomes (O)?*
14. *In LBW infants who need to be fed by an alternative oral feeding method (P), what is the effect of feeding by a cup or palladai (I) compared with bottle-feeding (C) on critical outcomes (O)?*
15. *In VLBW infants who need to be given intragastric tube feeding (P), what is the effect of bolus intermittent feeding (I) compared with continuous feeding (C) on critical outcomes (O)?*
16. *In VLBW infants who need to be given intragastric feeding (P), what is the effect of orogastric tube feeding (I) compared with nasogastric tube feeding (C) on critical outcomes (O)?*
17. *In LBW infants who are fully or mostly fed by an alternative oral feeding method (P), what is the effect of feeding based on infants' hunger cues (I) compared with strict scheduled feeding (C) on critical outcomes (O)?*
18. *In VLBW infants who need to be fed by an alternative oral feeding method or given intragastric feeds (P), what is the effect of rapid (>30 ml/kg per day)*

progression of feeds (I)compared with slow (<20 ml/kg per day) progression (C) on critical outcomes (O)?

After reviewing the 18 questions, the GDG decided to retain allbut two RQ (question no. 4 on post-discharge formula and no. 9 on vitamin A supplementation) for the present guidelines.

Identifying complementary questions from NNF guidelines

The GDG identified eight additional RQs from the NNF practice guidelines. Of these, the following four were considered to be relevant and important:

1. *What should be the frequency of feeds for LBW infants - 2-hourly vs. 3-hourly?*
2. *What should be the volume of feeds in LBW infants?*
3. *What is the role of non-nutritive sucking?*
4. *How to monitor growth of LBW infants?*

Discussion with other stakeholders

The GDG conducted an electronic survey followed by telephonic discussion among healthcare providers from secondary level facilities to identify additional research questions. The group did not identify any relevant additional questions.

Recommendations

After enlisting the research questions, the GDG finalized the recommendations by adopting or adapting the original recommendations from the WHO and NNF guidelines:

- *Adopting a recommendation entails transferring the recommendations verbatim to the new guideline.*
- *Adapting a recommendation entails making some changes to the recommendation. This could be a minor edit in order to ensure local compatibility with the country setting, or adding precisions to the wording to clarify the recommendation.*

Table 2 enlists all the new recommendations:

Table 2: Final recommendations			
New recommendations	**Adopted/ adapted**	**Recommendations in original guidelines**	**Reasons for adaptation**
What to feed: Choice of milk			
1. Low birth weight (LBW) infants, including those with very lowbirth weight (VLBW), should be fed mother's own milk.	Adopted from the WHO guidelines	Low-birth-weight (LBW) infants, including those with very lowbirth weight (VLBW), should be fed mother's own milk.	Nil
2. LBW infants, including those with VLBW, who do not have access to mother's own milk/ whose mother's own milk is insufficient, should be fed donor human milk *(recommendation relevant for settings where safe and affordable milk-banking facilities are available or can be set up).*	Adapted from the WHO guidelines	LBW infants, including those with VLBW, who cannot be fed mother's own milk should be fed donor human milk (recommendation relevant for settings where safe and affordable milk-banking facilities are available or can be set up).	The GDG felt it is not appropriate to use the words 'who cannot be fed mother's own milk'. The words have been modified to convey the message in a more appropriate manner.
3. LBW infants, including those with VLBW, who cannot be fedmother's own milk or donor human milk should be fed standardinfant formula. **VLBW infants who cannot be fed mother's own milk or donorhuman milk should be given preterm infant formula if they fail togain weight despite adequate feeding with standard infantformula.**	Adopted from the WHO guidelines	LBW infants, including those with VLBW, who cannot be fed mother's own milk or donor human milk should be fed standard infant formula (recommendation relevant for resource-limited settings). VLBW infants who cannot be fed mother's own milk or donor human milk should be given preterm infant formula if they fail to gain weight despite adequate feeding with standard infant formula.	Nil
4. VLBW infants who are fed mother's own milk or donor human milk should not routinely be given bovine milk-based human milkfortifier. **VLBW infants who fail to gain weight despite adequate breastmilk feeding should be given human-milk fortifiers,**	Adopted from the WHO guidelines	VLBW infants who are fed mother's own milk or donor human milk should not routinely be given bovine milk-based human milk fortifier (recommendation relevant for resource-limited settings). VLBW infants who fail to gain weight despite	Nil

preferably those that are human milk based.		adequate breastmilk feeding should be given human-milk fortifiers, preferably those that are human milk based.	
What to feed: Supplements			
5. LBW infants(1500-2499 g) should be given vitamin D supplements at a dose of 400 IU per day until 6 months of age. **VLBW infants (<1500 g) should be given vitamin D supplements at a dose of 800 IU per day until 6 months of age.**	Adapted from the WHO and NNF guidelines	VLBW infants should be given vitamin D supplements at a dose ranging from400 IU to 1000 IU per day until 6 months of age.	The WHO guidelines do not address the issue of vitamin D supplements in LBW infants with BW of 1500-2499 g; the recommendation is adapted based on the NNF guidelines; The ESPGHAN guidelines recommend 800-1000 IU for preterm infants; recent evidence also favors a higher dose for preterm VLBW infants.
6. VLBW infants who are fed mother's own milk or donor humanmilk should be given daily calcium (120-140 mg/kg per day) andphosphorus (60-90 mg/kg per day) supplementation until term gestation (40 weeks' postmenstrual age).	Adapted from the WHO guidelines	VLBW infants who are fed mother's own milk or donor humanmilk should be given daily calcium (120-140 mg/kg per day) andphosphorus (60-90 mg/kg per day) supplementation during thefirst months of life.	The WHO guidelines do not specify the duration of calcium and phosphorus supplements.
7. VLBW infants fed mother's own milk or donor human milk should be given 2-4 mg/kg per day iron supplementation startingat 2 weeks until 6 months of age. **Other LBW infants (1500-2499 g) fed mother's own milk or donor milk should be given 2-3 mg/kg per day iron startingat 6-8 weeks until 6 months of age.**	Adapted from the WHO and NNF guidelines	VLBW infants fed mother's own milk or donor human milk should be given 2-4 mg/kg per day iron supplementation starting at 2 weeks until 6 months of age.	The WHO guidelines do not address the issue of iron supplements in LBW infants with birth weights of 1500-2499 g; the recommendation is adapted based on the NNF guidelines

8. Routine zinc supplementation for LBW infants who are fedmother's own milk or donor human milk is not recommended atthe present time, because there is not enough evidence ofbenefits to support such a recommendation.	Adopted from the WHO guidelines	Routine zinc supplementation for LBW infants who are fed mother's own milk or donor human milk is not recommended at the present time, because there is not enough evidence of benefits to support such a recommendation.	Nil
When to initiate feeding?			
9. LBW infants (birth weight ≥ 1200 g) who are able to breastfeed should be put to the breast as soon as possible after birth when they are clinicallystable.	Adopted from the WHO guidelines	LBW infants who are able to breastfeed should be put to the breast as soon as possible after birth when they are clinically stable.	Nil
10. LBW infants with birth weight <1200 g should be given 10 mL/kg per day of enteral feeds, preferably expressed breast milk, starting from the first day of life, with the remaining fluid requirement met by intravenous fluids.	Adapted from the WHO guidelines	VLBW infants should be given 10 ml/kg per day of enteral feeds,preferably expressed breast milk, starting from the first day oflife, with the remaining fluid requirement met by intravenousfluids (recommendation relevant for resource-limited settings).	Recommendation has been adapted to be in sync with NNF guidelines – stable infants with BW of 1200-1499 g can be initiated on full enteral feeds from day 1 of life.
How to feed?			
11. LBW infants who need to be fed by an alternative oral feeding method should be fed by cup (or *palladai*, which is a cup with abeak) or spoon.	Adopted from the WHO guidelines	LBW infants who need to be fed by an alternative oral feedingmethod should be fed by cup (or *palladai*, which is a cup with a beak) or spoon.	Nil
12. VLBW infants requiring intragastric tube feeding should be givenbolus intermittent feeds.	Adopted from the WHO guidelines	VLBW infants requiring intragastric tube feeding should be given bolus intermittent feeds.	Nil
13. In VLBW infants who need to be given intragastric tube feeding, the intragastric tube may be placed either by oral or nasal route,depending upon	Adopted from the WHO guidelines	In VLBW infants who need to be given intragastric tube feeding,the intragastric tube may be placed either by oral or nasal route,depending upon the preferences of	Nil

the preferences of health-care providers.		health-care providers.	
14. VLBW infants on intragastric tube feeding should be fed 2-hourly. **Other LBW infants (1500-2499 g) on intragastric tube feeding should be fed 3-hourly.**	Adapted from the NNF guidelines	Frequency of feeding is decided by the gestational age, weight and the clinical condition of the baby (GRADE B).	The NNF guidelines recommend 3 hourly feeding for infants with BW of >1600 g; for convenience and to align with other recommendations, the GDG modified it to weight of 1500 g
15. LBW infants who are fully or mostly fed by an alternative oral feeding method should be fed based on infants' hunger cues, except when the infant remains asleep beyond 3 hours since the last feed *(recommendation relevant to settings with an adequate number of health-care providers)*	Adopted from the WHO guidelines	LBW infants who are fully or mostly fed by an alternative oral feeding method should be fed based on infants' hunger cues, except when the infant remains asleep beyond 3 hours since the last feed *(recommendation relevant to settings with an adequate number of health-care providers)*	Nil
How much to feed?			
16. LBW infants with birth weight >=1200 g should be initiated on 60-80 mL/kg per day of enteral feeds, preferably expressed breast milk, on the first day oflife.	Adapted from the NNF guidelines	The volume of feeds should be decided taking into consideration the gestational age, postnatal age and clinical status.	The NNF guidelines have suggested 60-80 mL/kg/day in infants with BW >=1200 g
17. In VLBW infants, who need to be fed by an alternative oral feeding method or given intragastric tube feeds, feed volumes can be increased by up to 30 ml/kg per day with careful monitoring for feed intolerance.	Adopted from the WHO guidelines	In VLBW infants who need to be fed by an alternative oral feeding method or given intragastric tube feeds, feed volumes can be increased by up to 30 ml/kg per day with careful monitoring for feed intolerance	Nil
18. LBW infants who need to be fed by an alternative oral feeding method or given intragastric tube feeds, should be fed up to 180-200 mL/kg per day after	Adapted from the NNF guidelines	The volume of feeds should be decided taking into consideration the gestational age,postnatal age and clinical status. The maximum volume of feeds may reach up to	The GDG adapted the NNF guidelines' recommendation to make it more clear and avoid ambiguity

1-2 weeks of life.		180-200ml/kg/day (GRADE D).	
Optimal duration of exclusive breastfeeding			
19. LBW infants should be exclusively breastfed until 6 months of age.	Adopted from the WHO guidelines	LBW infants should be exclusively breastfed until 6 months of age.	Nil
Miscellaneous issues			
20. Non-nutritive sucking (NNS) is recommended in VLBW infants on intragastric tube feeding to improve transition from gavage to breast feeding.	Adapted from the NNF guidelines	Non-nutritive sucking accelerates the maturation of the sucking reflex and has beenobserved to shorten the transition time from gavage to breast feeding. NNS helps in initiation andmaintenance, of successful breast feeding, during hospital stay and after discharge.	The NNF guidelines did not make a clear recommendation. The GDG made a recommendation after examining the evidence.
Growth monitoring			
21. LBW infants should be monitored for optimal growth by serial weight and head circumference measurement at least once weekly in the first weeks of life, using an appropriate growth chart like Fenton's chart.	Adapted from the NNF guidelines	All LBW infants should be checked for weight (daily), head circumference (weekly)and length (weekly or fort-nightly) during their NICU stay. Serial growth monitoring allows earlyidentification of growth faltering. Fenton's growth charts can be used for preterm babies. WHO Growth charts (2006) should be used from corrected age of 40 weeks into childhood.	The GDG adapted the NNF guidelines' recommendation to make it simple and easy to use in even resource restricted settings

Implementation tools

The GDG has already developed the quick reference guide for wider dissemination. The guide, along with the standard treatment guidelines, shall be finalized after incorporating the comments of the external consultation/peer review (timeline: 2 months). Concurrently, the group shall develop patient information document and quality standards (if applicable) in the next 4-6 months.

External consultation/peer review

To be developed

BIBLIOGRAPHY

1. Bang AT, Reddy HM, Bang RA, Deshmukh MD. Why do neonates die in rural Gadchiroli, India? (Part II): estimating population attributable risks and contribution of multiple morbidities for identifying a strategy to prevent deaths. J Perinatol. 2005 Mar;25 Suppl 1:S35-43
2. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H et al. CHERG Small-for-Gestational-Age-Preterm Birth Working Group. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet. 2013 Aug 3;382(9890):417-25.
3. Dickson KE, Simen-Kapeu A, Kinney MV, Huicho L, Vesel L, Lackritz E, de Graft Johnson J, von Xylander S, Rafique N, Sylla M, Mwansambo C, Daelmans B, Lawn JE; Lancet Every Newborn Study Group. Every Newborn: health-systems bottlenecks and strategies to accelerate scale-up in countries. Lancet. 2014;384(9941):438-54.
4. India Newborn Action Plan. Available at http://www.newbornwhocc.org/INAP_Final.pdf. Accessed on October 24, 2016.
5. Status of India's Newborn 2014. Available at: http://www.newbornwhocc.org/SOIN_PRINTED%2014-9-2014.pdf. Accessed on October 24, 2016.
6. World Health Organization. Guidelines on optimal feeding of low birth weight infants in low- and middle-income countries. Geneva, Switzerland: World Health Organization; 2011. Available at: http://www.who.int/maternal_child_adolescent/documents/infant_feeding_low_bw/en/. *Accessed October 24, 2016*
7. Dutta S, Singh B, Chessell L, Wilson J, Janes M, McDonald K, Shahid S, Gardner VA, Hjartarson A, Purcha M, Watson J, de Boer C, Gaal B, Fusch C. Guidelines for feeding very low birth weight infants. Nutrients. 2015 Jan 8;7(1):423-42
8. Sankar MJ, Agarwal R, Mishra S, et al. Feeding of low birth weight infants. Indian J Pediatr 2008;75(5):459–469.
9. Working Group Of Pediatrics Chinese Society Of Parenteral And Enteral Nutrition, Working Group Of Neonatology Chinese Society Of Pediatrics, Working Group Of Neonatal Surgery Chinese Society Of Pediatric Surgery. CSPEN guidelines for nutrition support in neonates. Asia Pac J Clin Nutr. 2013;22(4):655-63.
10. Management of Feeding in Low Birth Weight Infants. In: Evidence based clinical practice guidelines. National Neonatology Forum, India 2010.