Clinical Practice Guidelines

Feeding of Low Birth Weight Neonates

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National Neonatology Forum, India

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Executive Summary

Low birth weight (LBW) neonates are defined by the WHO as neonates born with a birth weight of less than 2.5 kg. This heterogenous group consists of neonates born with Extremely Low birth weight (ELBW) defined as less than 1kg; Very low birth weight neonates (VLBW) defined as birthweight less than 1.5kg; neonates with varying gestational maturity – term neonates 37-41 weeks with intra-uterine growth retardation, late preterm neonates with gestational ages 34-36 weeks, preterm neonates 28-33 weeks and extreme preterm neonates less than 28 weeks gestation. Each of these periods differ in organ maturity, nutrition needs and growth, and every attempt was made to study these subgroups where feasible. However, evidence is scant in many areas and subgroups have not been comprehensively studied. This review essentially summarizes currently available evidence in English literature on LBW feeding.

Nutrition in this critical period is essential for immediate outcomes such as changes in anthropometry (weight, length and head circumference) as well as adverse effects like necrotizing enterocolitis (NEC). Nutrition also effects long term adverse outcomes such as developmental delay, diplegic cerebral palsy, and death during infancy and childhood. This review has looked for the effects of nutrition in these areas. Further long-term outcomes like risk of adult onset diseases like myocardial infarction and stroke may also be related to nutrition of the LBW neonate but have not been included in this review.

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

The recommendations made by this group are summarized in Table 1.

Table 1: Summary of recommendations for feeding of low birth weight neonates

S.No.	Recommendations	Strength of recommendations	Quality of evidence
1.	Mother's own milk is strongly recommended for feeding the low birth weight infant. *Specific nutrient supplementation needs to be made in preterm very low birth weight infants (see below).*	Strong	Not graded
2.	(a). If mother's own milk is not available, pasteurized donor human milk from human milk bank, should be used for feeding low birth weight infants. *Applicable to settings with facilities for providing donor milk; associated with lower weight gain, linear growth and head growth and hence need monitoring and possibly fortification.* (b). If donor human milk is not available, formula milk is to be considered. *Formula milk will incur a higher cost and may also be associated with higher risk of necrotizing enterocolitis and sepsis.*	Strong, Conditional	Moderate
3.	Early trophic feeding started within 24 hours of life is recommended in preterm LBW neonates. *The recommendation may not be generalized to extreme preterm or extreme low birth weight neonates and those with intrauterine growth restriction for lack of sufficient evidence in this group of patients.*	Strong, Conditional	Low
4.	Stable preterm very low birthweight infants may preferably be initiated on progressive enteral feeding from the first day of life. *This recommendation may not be generalized to extreme preterm or extreme low birth weight neonates and those with intrauterine growth restriction.*	Strong, Conditional	Moderate
5.	Daily feed volumes are to be increased by 30-40mL/kg in stable preterm very low birth weight infants with no signs of feed intolerance.	Strong	High
6.	In the absence of other signs of feed intolerance in preterm LBW neonates, neither routine prefeed abdominal circumference nor prefeed gastric residue estimation is recommended for assessment of tolerance to enteral feeds.	Weak	Low

7.	Preterm infants who cannot feed directly from the breast should be fed by cup, *paladai* or *katori-spoon,* rather than by bottle, to fasten the transition to direct breast feeding.	Weak	Low
8.	Preterm very low birth weight infants who do not accept cup*, paladai* or *katori-spoon* feeds should be fed by either nasogastric or orogastric route of tube feeding.	Weak	Very low
9.	Intra-gastric route of tube feeding is preferred over transpyloric route in preterm infants	Weak	Low to moderate
10.	Continuous feeding is not recommended as a routine strategy for feeding preterm low birth weight infants receiving intragastric tube feeding.	Weak	Low to moderate
11.	Preterm low birth weight infants with birthweight >1250 grams and on cup, *paladai* or *katori-spoon* feeds or intragastric tube feeding may be given feeds every three hours.	Weak	Low to very low
12.	Checking of position of feeding tube (NG/OG) after placement and before commencement of first feed is recommended in LBW infants. *Of the available methods, abdominal x-ray seems to be the best method for checking the position of feeding tube.*	Weak, Conditional	Low
13.	Erythromycin is not to be used routinely for the management of feed intolerance in preterm LBW infants.	Weak	Very low
14.	Multi-nutrient fortification of breast milk can be initiated in preterm LBW infants with birthweight <1800 g and receiving enteral feeds of at least 50-80 mL/kg/day *For resource limited settings, fortification may be commenced only for those infants who fail to gain weight despite adequate breast milk feeding.*	Weak	Low to moderate
15.	Routine supplementation of docosahexaenoic acid (DHA) / long chain polyunsaturated fatty acid (LC-PUFA) is NOT recommended in preterm LBW infants.	Weak	Low
16.	Routine oral or intramuscular supplementation of vitamin A is NOT recommended in LBW infants.	Weak	Low

17.	Oral iron supplements in a daily dose of 2–4 mg/kg of elemental iron is recommended in LBW infants from 2-4 weeks of life to 12 months of age.	Weak	Low
18.	Multi-strain probiotics may be initiated in preterm low birth weight infants from as early as day 1 of life and continued until 36-37 weeks post-menstrual age or discharge (whichever is earlier), *in neonatal units with high baseline incidence of necrotizing enterocolitis.*	Weak, Conditional	Moderate
19.	VLBW infants should be given vitamin D supplements at a dose ranging from 400 IU to 1000 IU per day from the day of reaching full enteral feeds to 6 months of age.	Strong	Moderate

Introduction

World Health Organization (WHO) has defined low birth weight (LBW) as neonates who are born with birth weight of less than 2.5 kg, very low birth weight (VLBW) less than 1.5 kg and extremely low birth weight (ELBW) less than 1 kg. LBW can be a result of preterm birth (before 37 completed weeks of gestation), small size for gestational age (SGA, defined as weight for gestation less than 10th percentile), or a combination of both. Overall, 15% to 20% of all births worldwide are low birth weight, representing more than 20 million births a year with more than 96% in low and middle income (LMIC) countries.[1] Regional estimates of low birth weight include 28% in south Asia, 13% in sub-Saharan Africa and 9% in Latin America.[2] Every year, 1.1 million babies die from complications of preterm birth and prematurity is the most common direct cause of neonatal mortality.[3] In India, the main cause of neonatal death in 2015 was prematurity (43.8%) followed by birth asphyxia and birth trauma (18.9%), and sepsis (13.6%).[4] LBW infants are at higher risk of fetal and neonatal mortality and morbidity, early growth restriction, infection, developmental delay, death during infancy and childhood, and an increased risk of chronic diseases later in life.[5]

By improving the care of LBW infants, global neonatal and infant mortality rates can be reduced significantly. Optimal nutrition during the neonatal period is essential for growth and development throughout infancy and into childhood. Experience from both developed and developing countries has clearly shown that appropriate care of low birth weight (LBW) infants, with adequate attention to feeding can improve their survival, immediate and longer-term health and well-being of the individual infant and at population level.[6] Nutritional needs of infants vary based on gestational age, metabolic state, and physiological complications. This review focuses on nutrition of relatively well admitted low birth weight neonate without a major illness.

Scope of the guidelines and target audience

Aim

The primary aim of this guideline is to guide the feeding of low birth weight infants based on the available evidence by providing recommendations which may be applied in clinical practice.

Target audience

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

Population of interest

The guidelines focus on feeding of low birth weight neonates in healthcare settings.

How to use these guidelines

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

Methodology

Nutrition in this critical period is essential for immediate outcomes such as changes in anthropometry (weight, length and head circumference) as well as adverse effects like necrotizing enterocolitis (NEC). Nutrition also effects long term adverse outcomes such as developmental delay, diplegic cerebral palsy, and death during infancy and childhood. This review has looked for the effects of nutrition in these two areas. Further long-term outcomes like risk of adult onset diseases like myocardial infarction and stroke may also be related to nutrition of the LBW neonate but have not been included in this review.

The group decided to focus on five areas of feeding the LBW neonate:

1. What is the best milk for the LBW?
2. What is the best time to initiate feeds, ideal quantity, maximum volume of increment, and method of detecting feed intolerance.
3. What is the best method of feeding- orogastric, nasogastric, transpyloric, spoon, cup, *paladai*, etc.
4. Feeding policy and technique in a sick neonate
5. Nutrition supplements

Post discharge nutrition was not included as part of this review. The group framed 53 questions and of these 22 questions were shortlisted by a priority poll amongst the members of the GDG in consultation with a wider group of NNF members. Finally, 20 questions were taken up for a detailed review.

Questions relevant to clinical practice

1. Should Mother's own milk vs. Formula milk/Donor human milk be used for feeding preterm or low birth weight infants?
2. What is the best choice of milk for feeding when Mother's milk is not available?
3. What is the role of trophic feeding?

4. What is the optimum time for initiation of progressive enteral feeding in very low birth weight infants? (early vs. late)
5. What is the optimum time to achieve full volume feeding in LBW infants? (slow vs. rapid advancement of feeding)
6. Is there any role of monitoring prefeed abdominal circumference and/or gastric aspiration before giving the feed?
7. If direct breastfeeding is not possible then what is the best mode of enteral feeding? (tube feeding/ cup feeding/ *paladai*/ spoon/ syringe)
8. What is the best route of tube feeding in VLBW/LBW infants (orogastric vs. nasogastric)?
9. What is the best route of tube feeding in VLBW/LBW infants (transpyloric vs. intragastric)?
10. What is the best schedule of feeding in VLBW infants (continuous vs. bolus)?
11. What is the best schedule of feeding in VLBW infants (2 hourly vs. 3 hourly)?
12. Should we check the position of NG/OG tube before each feeding and how?
13. Is there any role of prokinetics in feeding intolerance?
14. What is the role of human milk fortifier in LBW neonates?
15. Is there a role of supplementing DHA in LBW neonates?
16. Do we need to give Vitamin A supplementation to LBW neonates?
17. Is there role of Iron supplementation in LBW neonates?
18. Is there any role of Probiotics in LBW neonates?
19. Is there role of Vitamin D supplementation in LBW infants?

Outcomes of interest

For each question, the following outcomes were considered *critical*

1. Mortality
2. Necrotizing enterocolitis

The following outcomes were considered to be *important*

1. Growth and anthropometry
2. Neuro-developmental disability
3. Duration of hospital stay

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

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

Interpretation of strong and conditional recommendations

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

Evidence Review and Formulation of recommendations

Methodology

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

Search strategy

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

Data abstraction and summary tablsof individual studies

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

Pooled effects

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

Quality assessment

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

Risk of bias

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

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

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

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

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

Document review

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

Questions, Evidence summaries and Recommendations

Practice Question 1 : Should Mother's own milk vs. Formula milk/Donor human milk be used for feeding preterm or low birth weight infants?[7–13]

Table 2: Summary of previous guidelines

Association / Professional body	Recommendation	Remarks
WHO Optimal feeding of Low birth weight infants Technical review 2006[11]	Breast feeding or mother's own expressed milk is the best option.	Extensive review of data.
ESPGHAN 2010[8]	Recommended human milk with need for added nutrients	Focused on nutrient requirement of preterm neonates
NNF feeding guideline 2011[6]	Breast feeding or mother's own milk	Consensus guidelines no grading of evidence
WHO Optimal feeding of LBW in low and middle income countries 2011[7]	LBW infants should be fed Mother's own milk	Strong recommendation based on moderate quality of evidence.

The WHO recommendations[7] on optimal feeding of low birth weight infants had reviewed all the cohort studies till then and concluded that there is strong evidence to recommend mother's own milk. Following this no further trials were found that have addressed this issue and it is unlikely that any further trials will be conducted as the evidence is overwhelming.

Maternal breast milk remains the default choice of enteral nutrition for the LBW neonate. Observational studies, and meta-analyses of trials comparing cohorts of neonates fed with formula versus breast milk, suggest that feeding with breast milk has the following benefits and need supplementation as below.

1. There was no study which examined the impact of mother's own milk feeding on mortality.
2. Mother's own milk has been associated with reduced risk of infection RR 0.44 – 0.56 (0.24, 0.82)[7]
3. Mother's own milk feeding is associated with increased cognitive development scores adjusted mean difference about 5, including in SGA term infants.[7]
4. Mother's own milk feeding is reported with slower growth in length and weight compared to formula fed neonates but this difference has not been found significant at 18 months follow up.[7]
5. LBW Neonates fed exclusively on un-supplemented mother's own milk have been reported in case series to develop iron deficiency, osteopenia, zinc deficiency vitamin A and vitamin D deficiency. Hence ESPGHAN[8] has recommended appropriate supplementation of these nutrients particularly in the Very low birth weight neonates.

Based on the existing data WHO, UNICEF and European Society of Pediatric Gastroenterology and Nutrition (ESPGHAN) strongly recommend that use of Mother's Own Milk for the Low birth weight infant. It is unlikely that any further trials will be conducted to confirm or refute this

conclusion. This recommendation strongly endorses the use of Mother's own milk for the low birth weight infant.

RECOMMENDATION 1

Mother's own milk (MOM) is strongly recommended for feeding the low birth weight infant. *Specific nutrient supplementation needs to be made in preterm very low birth weight infants.*

Strong recommendation, not graded

Practice Question 2 : If Mother's own milk is NOT available should formula milk vs. donor milk be used for feeding preterm or low birth weight infants? [7–9,14]

Summary of Evidence

The outcomes assessed in this meta-analysis were growth, necrotizing enterocolitis, all-cause mortality and neurodevelopmental disability. Presently available evidence of 11 trials (1809 infants) fulfilling the inclusion criteria showed that formula-fed infants had higher in-hospital rates of weight gain, linear growth and head growth (moderate quality evidence).
However, formula feeding was associated with a significantly increased risk of necrotizing enterocolitis (moderate quality evidence). There was no evidence of an effect on long-term growth or neurodevelopment with either of the interventions. Considering the low socio-economic status and poor hygienic condition of our country, there should be a word of caution for the use of formula milk, as incidence of sepsis is already very high in majority of the neonatal care units of India. Another prohibitive factor is the high cost associated with formula feeding, which often leads to a tendency of over-dilution and poor nutrition.

Only pasteurized donor human milk from human milk bank is recommended for feeding. Moreover, it needs adequate fortification for feeding preterm low birth weight infants.

RECOMMENDATION 2

(a). If mother's own milk is not available, pasteurized donor human milk from human milk bank, should be used for feeding low birth weight infants.

Applicable to settings with facilities for providing donor milk; associated with lower weight gain, linear growth and head growth and hence need monitoring and possibly fortification.

(b). If donor human milk is not available, formula milk is to be considered.

Formula milk is costly and may also be associated with higher risk of necrotizing enterocolitis and sepsis. Utmost care should be taken for maintenance of asepsis and proper dilution.

Strong Conditional recommendation, based on Moderate quality evidence

Practice Question 3 : Should trophic feeding vs. enteral fasting be used for very preterm or very low birth weight infants ?[15]

Summary of Evidence

In a metanalysis of nine randomized controlled trials, 754 infants were included. The metanalysis looked at the effect of early trophic feeding versus enteral fasting on feed tolerance, growth and development, and the incidence of NEC and invasive infection and mortality in very preterm or VLBW infants. The metanalysis showed that there is no difference in days to reach full feeds (feed intolerance) (MD) -1.05 (95% (CI) -2.61 to 0.51) days. The evidence was downgraded to low because of risk of bias and significant inconsistency.

Similarly low quality evidence suggests, no significant difference for NEC (RR) 1.07 (95% CI 0.67 to 1.70). The quality of evidence was downgraded to low because of risk of bias and imprecision (wide CI). The other outcomes like mortality, short term growth, invasive infections and duration of hospital stay also did not show significant difference between the early trophic versus fasting group. The quality of the evidence for these outcomes was downgraded to low because of serious risk of bias, imprecision and inconsistency.

When trophic feeds are started within the first 96 hours and continued for at least one week, it did not increase the feeding tolerance and did not increase the risk of NEC. Early trophic feeds is preferred to increase gastrointestinal maturation, to reduce cholestasis and phototherapy requirement. Early introduction of trophic feeds compared to fasting had a trend towards reaching full feeds earlier but in a non-significant way (MD)− 1.05 days (95% CI −2.61, 0.51).

RECOMMENDATION 3

Early trophic feeding started within 24 hours of life is recommended in preterm LBW neonates.

The recommendation may not be generalized to extreme preterm or extreme low birth weight neonates and those with intrauterine growth restriction for lack of sufficient evidence in this group of patients.

Strong Conditional recommendation, Low quality evidence

Practice Question 4: Should delayed vs. early introduction of progressive enteral feeding be used for very low birth weight infants?[16]

Summary of Evidence

Analyses of data from nine randomized controlled trials with 1106 infants did not provide evidence that delayed introduction of progressive enteral feeds reduced the risk of NEC. Meta-analysis of data from these trials did not indicate an effect on all- cause mortality (RR) 1.18, 95% (CI) 0.75 to 1.88. Meta-analysis did not detect a statistically significant effect for NEC (RR) 0.93, 95% (CI) 0.64 to 1.34. The quality of this evidence was downgraded to moderate for significant risk of bias.

The median time to establish full enteral feeding was longer in the delayed introduction group but the reports did not provide data to allow quantitative synthesis. For other outcomes moderate evidence suggested no difference in invasive infections, feed intolerance and growth between early and delayed introduction of enteral feeding. The duration of hospital stay was also not different between the groups, but the quality of evidence of this is low because of risk of bias and significant inconsistency.

Four trials recruited only infants with intrauterine growth restriction and abnormal flow velocities detected on antenatal Doppler studies. Meta-analysis did not detect any statistically significant differences in the incidence of NEC or mortality. The quality of evidence was downgraded to moderate for risk of bias.

RECOMMENDATION 4

Stable preterm very low birthweight infants may preferably be initiated on progressive enteral feeding from the first day of life.

This recommendation may not be generalized to extreme preterm or extreme low birth weight neonates and those with intrauterine growth restriction.

Strong Conditional recommendation, Moderate quality evidence

Practice Question 5: Should slow vs. faster rates of feed advancement be used for very low birthweight infants?[17,18]

Summary of Evidence

A meta-analysis of 10 RCTs in which a total of 3753 infants participated (2804 infants participated in one large trial). Most participants were stable very preterm infants of birth weight appropriate for gestation. About one-third of all participants were ELBW, and about one-fifth were small for gestational age (SGA), growth-restricted, or compromised in utero, as indicated by absent or reversed end-diastolic flow velocity (AREDFV) in the fetal umbilical artery. Trials typically defined slow advancement as daily increments of 15 to 20 mL/kg, and faster advancement as daily increments of 30 to 40 mL/kg.

Meta-analyses did not show effects on risk of NEC (RR) 1.07, 95% (CI) 0.83 to 1.39; or all-cause mortality (RR) 1.15, 95% (CI)0.93 to 1.42. Subgroup analyses of extremely preterm or ELBW infants, or of SGA or growth-restricted or growth-compromised infants, showed no evidence of an effect on risk of NEC or death.

Slow feed advancement delayed establishment of full enteral nutrition by between about one and five days. Meta-analysis showed borderline increased risk of invasive infection (RR) 1.15, 95% (CI) 1.00 to 1.32. The quality of evidence for these primary outcomes were moderate, downgraded from high because of lack of blinding in the included trials. The included trials did not show consistent evidence of an important effect on duration of hospital admission and the reports did not provide data to allow quantitative synthesis.

We could not include a very recent publication from October 2019 as the search was restricted to August 2019 and practical constraints. But the outcomes of this study compliments the above findings.[18] The SIFT trial[18] study showed that there was no significant difference in survival without moderate or severe neuro- developmental disability at 24 months in very preterm or very-low-birth-weight infants with a strategy of advancing milk feeding volumes in daily increments of 30 ml per kilogram as compared with 18 mL per kilogram.

RECOMMENDATION 5

Daily feed volumes are to be increased by 30-40 mL/kg in stable preterm very low birth weight infants with no signs of feed intolerance.

Current evidence suggests that this recommendation is also applicable to subgroups of neonates with IUGR, extremely low birth weight, and those with absent or reversed end diastolic flow .

Strong recommendation, High quality evidence

Practice Question 6a.: Should pre feed abdominal circumference measurement vs. no abdominal circumference be used for VLBW infants?[19]

Summary of Evidence

There are no randomized controlled trials ascertaining the role of abdominal circumference (AC) measurement as a sole parameter, in feeding outcomes and NEC.

In a single prospective study with 50 participants the abdominal distension (labelled as abdominal circumference >1.5 cm) did not have predictive value for time to reach full feeds. The mean number of days with abdominal distention prior to full gavage feedings being achieved was 0.03 +/- 0.07 (range 0.00– 0.30). The quality of evidence is graded as low as it is a single prospective study.
We considered two randomized controlled trials comparing AC with Gastric residual volume (GRV). In both the studies NEC has not been reported as primary outcome, and time to reach full feeds has been reported in comparison (AC vs GRV) and not as AC vs no AC or GRV vs no GRV. This was a limitation in considering these studies for the purpose of answering this question and grading evidence. In addition, the current available evidence is suggesting minimal role for GRV as predictor for feeding intolerance and NEC.
Evidence also suggests that there is significant inter and intra-observer variability in measuring AC and that there can be up to 3.5 cm variation in AC during a feeding cycle in preterm babies.

Practice Question 6b.: Should routine pre-feed gastric residual volume testing vs no routine gastric residual volume testing be done to assess feed intolerance in low birth weight and very low birthweight infant?[20–23]

Summary of Evidence

We identified three RCT's (620 neonates) which compared routine gastric residual volume (GRV) testing versus no routine GRV testing in low and very low birth weight neonates. Sepsis and NEC were considered as critical outcomes. The meta-analysis of the 3 trials has shown that there is no effect of selective gastric residue aspiration on incidence of sepsis, NEC>= stage 2, and length of hospital stay. The quality of evidence was graded as low due to imprecision and serious risk of bias. The other important outcomes were time to reach full feeds, length of hospital stay and any stage NEC. There is low-quality evidence from 3 RCT's (downgraded due to risk of bias in assessing NEC and imprecision as the risk difference is almost negligible) that routine pre-feed gastric residue estimation leads to increased risk of NEC. This finding was consistent in all three trials. Also, all three trials consistently reported that routine gastric residual testing delays the time to reach full feeds (downgraded as low-quality evidence due to risk of bias and lack of meaningful clinical precision). There was no difference in the length of the hospital stay (judged as very low quality due to imprecision, risk of bias, and inconsistency). Since, the event rate for the critical outcomes (sepsis and NEC>/= stage 2) is very low (< 5%) and the risk estimates for these outcomes are imprecise. So, for these outcomes, the overall certainty is low.

There is low-quality evidence that routine pre-feed gastric residue estimation leads to increased risk of NEC (any stage) and delays the time to reach full feeds (120 ml/kg/day). Therefore, the evidence is against the practice of routine pre feed GRV aspiration.
There are no costs associated with abandoning the practice of routine prefeed GRV testing in LBW neonates which do not have any other signs of feed intolerance.

RECOMMENDATION 6

In the absence of other signs of feed intolerance in preterm LBW neonates, neither routine prefeed abdominal circumference nor prefeed gastric residue estimation is recommended for assessment of tolerance to enteral feeds.

Weak recommendation, based on Low quality evidence

Practice Question 7: Should cup feeding vs. other modes of supplemental enteral feeding (bottle/tube feeding) be used in preterm infants unable to fully breast feed? [24–34]

Summary of Evidence

The critical outcomes considered were rates of mortality, sepsis, breastfeeding rates at discharge, and weight gain during the hospital stay. From the existing literature, there is no information on the comparison of the mortality rate or sepsis rate among the various methods. Four randomized controlled trials (957 infants) assessed any breastfeeding (not exclusive) at discharge. The meta-analysis of these 4 trials showed that the breastfeeding rates at the time of hospital discharge are better with the cup-feeding as compared to other supplemental modes of feeding. The evidence was downgraded to low-quality due to serious risk of bias and inconsistency of the definitions used and the results among the studies.

Only one trial assessed the daily weight gain and found that there was no difference in weight gain (very low-quality evidence). Only one study assessed the gestational age at discharge and found that there was no difference in the gestational age at discharge (very low-quality evidence). Two studies assessed average time per feed and did not find any difference (meta-analysis was not done due to significant heterogeneity). Two studies assessed the length of hospital stay and found considerable variation in results and in the direction of effect (meta-analysis was not done due to significant heterogeneity). Only one trial reported desaturations during feeding and didn't find any difference (very high risk of bias and selective reporting).

So overall, there is very low-quality evidence to suggest that breastfeeding rates at discharge and on follow-up are better with cup feeding as compared to bottle or other supplemental modes of feeding. No trials were found which compared the use of palladai / spoon feeds versus cup or bottle feeds. The group however feels that there is a high probability that *katori-spoon* and *paladai* feeding resembles cup feeding strongly enough to universalize this recommendation to both these indigenous methods till further studies are available.

There are concerns about bacterial contamination of milk in bottles, therefore WHO and UNICEF recommend cup feeding in low-resource settings.

RECOMMENDATION 7

Preterm infants who cannot feed directly from the breast should be fed by cup, *paladai* or *katori-spoon*, rather than by bottle, to fasten the transition to direct breast feeding.

Weak recommendation, based on Low quality evidence

Practice Question 8: Should nasogastric vs. orogastric tube feeding be used in feeding LBW infants[35–44]

Summary of Evidence

Very few studies have tried to look into superiority of either nasogastric or orogastric feeding tube placement for enteral feeding in preterm or low birth weight infants in relation to feeding tolerance, growth and development, and adverse events.

Critical outcomes considered in this meta-analysis were time to establish full enteral tube feeds, time to regain birth weight and need for oxygen supplementation. Only a single randomized controlled trial (RCT) of small sample size (n = 46) and poor methodological quality assessed these outcomes. No significant difference in any of the outcomes was found.

Another two poor quality RCTs assessed the incidences of apnea, bradycardia and desaturation episodes in association with nasogastric versus orogastric placement of feeding tubes. Though there was no immediate difference, one RCT documented significantly more recorded episodes of apnea in nasogastric tube group on the seventh day. Because of significant heterogeneity (wide variability of study design and definitions used for apnea), meta-analysis of the outcomes could not be undertaken.

So, overall, very low-quality evidence does not establish superiority of any mode of feeding tube placement (nasogastric vs. orogastric) in preterm low birth weight infants. However, there are concerns of apnea, bradycardia and desaturation episodes in relation to prolonged (7 days and more) nasogastric tube feeding.

RECOMMENDATION 8

Preterm very low birth weight infants who do not accept cup, *paladai* or *katori-spoon* feeds should be fed by either nasogastric or orogastric route of tube feeding.

Weak recommendation, based on Very low quality evidence

Practice Question 9 : Should transpyloric route vs. Gastric route be used for tube feeding in preterm infants?[45–52]

Summary of Evidence

Outcomes considered for this meta-analysis were growth (weight, length and head-circumference gain velocity), death prior hospital discharge, adverse events such as gastrointestinal disturbances including diarrhea, necrotizing enterocolitis and aspiration pneumonia.

Four RCTs (n = 93) of low methodological quality documented significantly higher weight and length gain velocity in association with transpyloric feeding in preterm infants. Two RCTs (n = 75) of low methodological quality did not find any difference in head-circumference gain velocity with either of the two methods. Similarly, five RCTs (n = 165) of low methodological quality did not find any difference in mortality during hospital stay with either intervention.

Six RCTs (n = 219) of moderate methodological quality documented significantly higher incidences of gastrointestinal disturbances including diarrhea in association with transpyloric feeding, though the incidences of necrotizing enterocolitis (7 RCTS, n = 198, moderate-quality evidence) and aspiration pneumonia (6 RCTs, n = 171, low- quality evidence) were similar with both the interventions.

However, insertion and maintenance of transpyloric tube placement requires considerable expertise, which is not available in Level II nursery set-ups of India. Therefore, though transpyloric tube feeding is associated with better weight and length gain velocity, it is associated with higher incidences of gastrointestinal disturbances including diarrhea (low to moderate-quality evidence), and requires considerable expertise.

RECOMMENDATION 9

Intra-gastric route of tube feeding is preferred over transpyloric route in preterm infants .

Weak recommendation, based on low to moderate quality of evidence

Practice Question 10: Should continuous intragastric tube feeding vs. intermittent bolus tube feeding be used for preterm low birthweight infants?[53–65]

Summary of Evidence

Major outcomes analyzed in this meta-analysis are days to reach full feeds, full enteral feeding achieved in 28 days, days to regain birth weight, growth (weight, length, head circumference, triceps skin fold thickness gain velocity), duration of mechanical ventilation, necrotizing enterocolitis, apneic episodes, sepsis and death.

Five RCTs (n = 424) did not find any significant difference between continuous intragastric tube feeding and intermittent bolus tube feeding in preterm low birth weight infants in days to reach full feeds (moderate quality evidence). One (n = 246) and five (6 = 647) RCT(s) did not find any difference between the interventions with respect to full enteral feeding achieved in 28 days and days to regain birth weight, respectively (both moderate quality evidence).

Moderate quality evidence showed that there was no difference in improvement in growth parameters (per day or per week weight gain, length gain, head circumference gain and change in triceps skinfold thickness), duration of mechanical ventilation (two RCTs, n = 326) and complications including NEC (Bell's Stage II and beyond) (five RCTs, n = 516), number of apneic episodes/day (two RCTs, n = 307), sepsis (one RCT, n = 246) and mortality (one RCT, n = 246) between continuous and intermittent bolus feeding.

One study reported significantly lower mean daily gastric residual volumes and number of patients with feeding interruptions in association with intermittent bolus feeding compared to continuous feeding (low quality evidence).

Continuous bolus feeding requires the facility for syringe pump, involves large cost and continuous supervision. Therefore, it may not be feasible in Level II neonatal care set ups.

RECOMMENDATION 10

Continuous feeding is not recommended as a routine strategy for feeding preterm low birth weight infants receiving intragastric tube feeding.

Weak recommendation, based on low to moderate quality evidence

Practice Question 11: Should three hourly feeding vs Two hourly feeding be used for stable very low birthweight infants?[66–70]

Summary of Evidence

The metanalysis of the four trials has shown that there is no difference in any stage NEC, feed intolerance, hypoglycemia, and time to reach full enteral feeds among two groups (low-quality evidence, downgraded for serious risk of bias and imprecision). The meta-analyses of three trials (including 350 neonates) have shown that the three hourly feeding groups help in regaining birth weight faster as compared to 2 hourly feeding schedules (low-quality evidence, downgraded due to serious risk of bias and inconsistency among the reported results in the individual trials. One trial (92 neonates) from India has shown that three hourly feeding schedules can reduce the total time spent in feeding by the nurses by 22 minutes (very low-quality evidence). So, the overall effects seem to be trivial benefit by three hourly feeding schedules.

The event rate for the critical outcome (NEC) is low (7.3 and 7.8%) and the risk estimates for these outcomes are imprecise. Also, the sample size is small (n-411). Therefore, the overall

certainty of the evidence for critical outcomes like NEC will be very low. Similarly, for adverse effects like feed intolerance and hypoglycemia, the certainty will be very low (small sample, imprecise results, and risk of bias). For favorable outcomes like time to reach full feeds and nursing time spent the certainty will be low to very low. Therefore, the overall certainty was judged as very low.

As the ELBW population in trials was very less and subgroup analysis was not done, these results cannot be applied to those infants. One study has shown that the extremely low-birth-weight infants reach full enteral feeds earlier when fed 2-hourly compared with 3-hourly. Therefore, we suggest to continue 2 hourly feeding schedules in ELBW population.

RECOMMENDATION 11

Preterm low birth weight infants with birthweight >1250 grams and on cup, *paladai* or *katori-spoon* feeds or intragastric tube feeding may be given feeds fed every three hours.

Weak recommendation, based on low to very-low quality evidence

Practice Question 12: Should checking of position of feeding tube vs. no checking of position of feeding tube be used for preterm infants before feeding?[71–92]

Summary of Evidence

Though confirmation of the position of feeding tube before enteral feeding or any other procedure in preterm infants have been advocated by many studies, there is paucity of good quality evidence for the method of checking the same. Various observational studies have assessed a variety of different methods for verifying placement of enteral feeding tubes in newborns including gastric secretion aspiration, epigastric region auscultation, checking aspirated secretion's pH, pepsin, trypsin and bilirubin, secretion color, presence of CO2 test, acid test with litmus paper, ultrasonography, reading diaphragm's electrical activity, electromagnetic tracing and the use of indigo carmine at 0.01%.

Since there was no RCT or good quality case-control study, meta-analysis of evidence was not possible.

Though abdominal radiographs are considered "gold standard" for verifying placement of feeding tubes, but the risks of radiation exposure, availability of portable x-ray machine and handling of infants often limit the use of radiographs in neonatal age group. pH analysis of fluid aspirated from feeding tubes to verify the placement in stomach has been evaluated in several studies and found to be an easy and effective methods. Though checking the mark of the feeding tube, aspiration to check the contents and injection of air and listening to the sound over stomach are widely practiced across the neonatal care units, these practices are not supported by evidence.

Existing International guidelines recommend the use of pH test indicators as the method of choice to correctly verify the position of naso/orogastric tubes. A minimum of 0.5 – 1 mL of gastric content should be aspirated and a reading between 0-5.5 in pH indicator strips is confirmatory for the intra-gastric position of the feeding tube.

RECOMMENDATION 12

Checking of position of feeding tube (NG/OG) after placement and before commencement of first feed is recommended in LBW infants.

Of the available methods, abdominal x-ray seems to be the best method for checking the position of feeding tube.

Weak recommendation, based on Low quality evidence

Practice Question 13: Should Erythromycin vs. placebo/ no erythromycin be used for feed intolerance in preterm infants as a rescue therapy?[93–102]

Summary of Evidence

We included randomized trials where erythromycin was used as rescue therapy only. The trials with prophylactic erythromycin were not included in the review. We divided the population into < 32 weeks and >/= 32 weeks preterm infants and low dose (< 12 mg/kg/day) vs high dose (> 12 mg/kg/day) erythromycin. This division is important as per the physiology and MOA of erythromycin. As the mechanism of the low and high dose is different, it will be inappropriate to combine the studies of low dose and high dose. Our critical outcomes were sepsis, NEC, and death.

Less than 32 weeks gestation

There were 6 RCTs for high dose and 2 for low dose. Of them only 4 from high dose and one from low dose trials reported our critical outcomes. The low dose does not have any impact on sepsis, NEC, or death (moderate-quality evidence, downgraded due to imprecision). The high dose also does not have any impact on sepsis, NEC (low-quality evidence, downgraded due to serious risk of bias and imprecision). There is moderate-quality evidence that high dose erythromycin does not have any impact on the mortality rate (moderate-quality evidence, downgraded due to imprecision).

There is very low-quality evidence (downgraded due to serious risk of bias and extreme heterogeneity of 76%) that high dose erythromycin in infants less than 32 weeks, helps in

reaching full enteral feeds earlier by 6.82 days (95 % CI 5.37- 8.28). For any other positive outcome, there was no advantage of erythromycin over placebo.
There is concern about the TPN related cholestasis secondary to prolonged use of TPN in infants with frequent feed intolerance. There is low-quality evidence (downgraded due to very serious risk of bias due to variation in the definition of cholestasis and lack of blinding for assessing outcome in some trials) that the use of high dose erythromycin in less than 32 weeks infants leads to 50% reduction in the risk of cholestasis. There are concerns about the emergence of antibiotic resistance against erythromycin. Although there was no difference in the sepsis rates among the two groups, this aspect has not been addressed well in the trials.

More than / equal to 32 weeks gestation

There are three studies of which 2 used high dose and one used low dose (subgroup analysis). There was no difference between sepsis, NEC, and mortality rates among the erythromycin versus the placebo group (low to moderate quality).

In summary, there is very low-quality evidence that high dose erythromycin (> 12 mg/kg/day) in infants less than 32 weeks, helps in reaching full enteral feeds earlier by 6.82 days (95 % CI 5.37- 8.28). There is no impact on any other outcome.

RECOMMENDATION 13

Erythromycin is not to be used routinely for the management of feed intolerance in preterm LBW infants.

Weak recommendation, based on very-low quality evidence

Practice Question 14: Should Human milk fortification vs. No fortification be used for supplementing feeding in LBW infants?[103–112]

Table 3: Summary of previous guidelines

Association / Professional body	Recommendation	Remarks
WHO Optimal feeding of LBW in low and middle income countries 2011[7]	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 adequate breastmilk feeding should be given human-milk fortifiers, preferably those that are human milk based.	Weak situational recommendation relevant to resource-limited settings, based on low to very low quality evidence for no benefits in critical outcomes and higher costs)
Commentary from ESPGHAN 2010[8]	The Committee advocates the use of human milk for preterm infants as standard practice, provided it is fortified with added nutrients where necessary to meet requirements.	Recommended Energy intake 110–135 kcal/kg/day and Protein 3.5–4.5 g/kg/day
European Milk Bank Association (EMBA) Working Group(WG) on HM Fortification 2019[106]	Recommends fortification of HM for preterm infants with BW<1800g when volume reaches 50-80 ml/kg/day	Individualized fortification (Targeted or Adjusted) is desirable.
AAP; ESPGHAN :Milan Consensus 2015[113]	All preterm infants with a birth weight <1800 grams should be fed fortified HM	HM fortification should start with standard fortification.

Summary of Evidence

Evidence indicates that human milk (HM) is the best form of nutrition. However, HM does not provide sufficient nutrition for the very low birth weight (VLBW) infant when fed at the usual feeding volumes leading to slow growth with the risk of neurocognitive impairment and other poor health outcomes. The objective of fortification is to increase the concentration of nutrients to try to the meet the high requirements of this group.

The recent Cochrane systematic review [103] identified 14 randomized trials in which a total of 1071 infants participated. It concluded that individual trials were generally small and had weak methodology. Nevertheless, meta-analyses led to low-quality evidence that multi-nutrient fortification of breast milk increases in-hospital rates of growth by a mean daily weight gain of 1.81 g/kg (with a 95% confidence interval [CI] 1.23–2.40), by a mean weekly length gain of 0.12 cm (95% CI 0.07–0.17), and by a mean weekly head circumference gain of 0.08 cm/wk (95% CI 0.04–0.12). The meta-analyses did not show a positive effect of fortification on developmental outcomes. There was also low-quality evidence that fortification did not

increase the risk of NEC in preterm infants with a typical relative risk (RR) 1.57 (95% CI 0.76–3.23). In conclusion, multi-nutrient fortified breast milk compared with unfortified breast milk does not significantly affect important outcomes, but that it leads to a slight increase of in-hospital growth rates.

With regards to timing of commencement of fortification, recent systematic review[107] looking into comparing early and delayed fortification included 2 studies[108,109] did not report differences between groups including anthropometry, NEC or sepsis. In conclusion, current data are limited and do not provide evidence on the optimal time to start fortification. Early fortification was at 20 ml/kg/day in one group, first feeding in other group and in study by Sullivan et al [110](which was not designed to compare EF with DF) showed that fortification with human-milk-based fortifier was tolerated at 40 mL/kg/day. The EMBA panel recommends Human milk fortification can be started safely with multi-nutrient fortifiers when the milk volume reaches 50–80 ml/kg/d.[106]

With regards to exclusive Human milk based fortifiers, there is limited efficacy data and high costs prevents its implementation in low resource settings. The OptiMoM study[112], is the first trial comparing the efficacy of HM-based fortifier to bovine-based fortifier in the absence of formula. There was no difference in feeding tolerance, postnatal growth and morbidity, including NEC ≥ grade 2 ((4.7 vs. 4.9%). In one more study[110] HM-based fortifier was never directly compared with the bovine based fortifier and many of the babies who developed NEC on the bovine fortifier were also on the bovine formula, though this study showed a significant reduction in NEC rates from 16 to 6% and cost-effectiveness.

RECOMMENDATION 14

- Multi-nutrient fortification of breast milk can be initiated in preterm LBW infants with birthweight <1800 g and receiving enteral feeds of at least 50-80 mL/kg/day. *For resource limited settings, fortification may be commenced only for those infants who fail to gain weight despite adequate breast milk feeding.*
- There is limited efficacy and safety data to recommend Human milk based fortifiers. In addition, there are ethical and cost concerns.

Weak Recommendation based on Low to moderate quality evidence

Practice Question 15: Should DHA/LCPUFA supplementation vs. No DHA supplementation be used in LBW feeding?[114–125][126,127]

Summary of Evidence

Data from Cochrane Database of Systematic Reviews 2017[116] which included 17 RCTs (2260 preterm infants) does not indicate a long-term benefit of LCPUFA supplementation of formula on visual development, neurodevelopment or physical growth of preterm infants.

Visual Acuity

Visual acuity was measured by Teller and Lea acuity cards in eight studies, by visual evoked potential (VEP) in six studies and by electroretinography in two studies. Most studies found no differences in visual outcomes between supplemented and control infants. A GRADE analysis for this outcome indicated that the overall quality of evidence was low and meta-analysis could not be performed.

Neurodevelopment

Meta-analysis of four studies evaluating Bayley Scales of Infant Development at 12 months (N = 364) showed no significant effect of supplementation (Mental Development Index (MDI): MD 0.96, 95%CI −1.42 to 3.34; P = 0.43; I^2 = 71% - Psychomotor Development Index (PDI): MD 0.23, 95%CI −2.77 to 3.22; P = 0.88; I^2 = 81%). Furthermore, three studies at 18 months (N = 494) also revealed no significant effect of LCPUFA on neurodevelopment.

Growth

Meta-analysis of four studies at a corrected age of 12 months (N = 271) showed no significant effect of supplementation on growth outcomes (Weight: MD−0.10, 95% CI −0.31 to 0.12; P = 0.34; Length: MD 0.25; 95% CI −0.33 to 0.84; P = 0.40; Head circumference: MD −0.15, 95% CI −0.53 to 0.23; P = 0.45).

Overall, the quality of evidence was considered low, given the small sample sizes high or unclear risk of bias in some of the included studies and high statistical heterogeneity.

Qawasmi [126]2012 conducted a meta-analysis of 19 RCTs (12 term and 7 preterm RCTs) and concluded that LCPUFA supplementation improves visual acuity up to 12 months of age. However, the benefits were not statistically significant for the subgroup of preterm infant RCTs. Beyerlein[127] 2010 conducted an individual patient data (IPD) meta- analysis of 870 infants from four large RCTs (two preterm RCTs and two term RCTS) of LCPUFA supplementation in formula. For preterm infants, they reported no significant differences in BSID scores at 18 months of age between the LCPUFA and control groups (N = 341, mean difference for MDI scores 1.9, 95% CI −1.3 to 5.0; mean difference for PDI scores −0.2, 95% CI −3.2 to 2.7). There is good evidence that supplementing DHA in formula milk at 0.32 in term babies has statistically significant results in Visual acuity and neurodevelopment (DIAMOND study)[117]. Effect of DHA supplementation for role in decrease in BPD in preterm infants is not very clear. In the recent study by Collins et al[128] Enteral DHA supplementation at a dose of 60 mg per kilogram per day did not result in a lower risk of physiological bronchopulmonary dysplasia than a control emulsion among preterm infants born before 29 weeks of gestation and may have resulted in a greater risk. A total of 1205 infants survived to the primary outcome assessment. Of the 592 infants assigned to the DHA group, 291 (49.1% by multiple imputation) were classified as having physiological bronchopulmonary dysplasia, as compared with 269 (43.9%) of the 613 infants assigned to the control group (relative risk 1.13; 95% confidence interval [CI], 1.02 to 1.25; P = 0.02).

RECOMMENDATION 15

Routine supplementation of docosahexaenoic acid (DHA) / long chain polyunsaturated fatty acid (LC-PUFA) is NOT recommended in preterm LBW infants.

Weak recommendation based on Low quality evidence

Practice Question 16: Should vitamin A supplementation vs. No vitamin A supplementation be used for LBW infants?[7,129–133]

Table 4: Summary of previous guideline

Association / Professional body	Recommendation	Remarks
WHO Optimal feeding of LBW in low and middle income countries 2011[7]	Daily oral vitamin A supplementation for LBW infants who are fed mother's own milk or donor human milk is not recommended.	Weak recommendation based on low quality evidence

Summary of Evidence

Table 5: Vitamin A supplementation compared to No vitamin A supplementation for LBW infants

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No vitamin A supplementation	Risk difference with Vitamin A supplementation
Mortality before 1 month (Intramuscular + Oral route) follow up: mean 1 months	1165 (6 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 0.86** (0.66 to 1.11)	168 per 1,000	**23 fewer per 1,000** (57 fewer to 18 more)
Mortality before 1 month - Supplementation by oral route follow up: mean 1 months	154 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 0.86** (0.56 to 1.33)	377 per 1,000	**53 fewer per 1,000** (166 fewer to 124 more)
Chronic lung disease (oxygen use at 28 days in survivors) follow up: mean 1 months	1070 (7 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 0.93** (0.86 to 1.01)	725 per 1,000	**51 fewer per 1,000** (101 fewer to 7 more)
Death or chronic lung disease (oxygen use at 28 days)	1165 (6 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 0.93** (0.88 to 0.99)	798 per 1,000	**56 fewer per 1,000** (96 fewer to 8 fewer)

Table 5: Vitamin A supplementation compared to No vitamin A supplementation for LBW infants

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No vitamin A supplementation	Risk difference with Vitamin A supplementation
Death before 36 weeks' postmenstrual age.	1089 (4 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 1.00** (0.77 to 1.29)	168 per 1,000	**0 fewer per 1,000** (39 fewer to 49 more)
Chronic lung disease (oxygen use at 36 weeks' postmenstrual age in survivors).	986 (5 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 0.87** (0.77 to 0.99)	530 per 1,000	**69 fewer per 1,000** (122 fewer to 5 fewer)
Neurodevelopmental impairment at 18 to 24 months follow up: mean 2 years	538 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	**RR 0.89** (0.74 to 1.08)	481 per 1,000	**53 fewer per 1,000** (125 fewer to 38 more)

Cochrane review assessed the benefits and risks of vitamin A supplementation in VLBW infants (<1500g &<32 weeks). The meta-analysis of the eight eligible trials suggested a beneficial effect in reducing death or oxygen requirement at 1 month of age (RR 0.93, 95% CI 0.88 to 0.99) and oxygen requirement at 36 weeks postmenstrual age (RR 0.87, 95% CI 0.77 to 0.98).[131]However, of the eight studies, only one trial used the oral route for vitamin A supplementation. (Wardle et al 2001)[134].This study did not find any significant effect on either mortality until discharge (RR 0.86, 95% CI 0.56 to 1.33) or chronic lung disease (RR 1.0, 95% CI 0.8 to 1.24) following daily oral vitamin A supplements of 5000 IU/kg in ELBW infants. The quality of evidence for both the outcomes was graded as low.

With regards to outcome of retinopathy of prematurity, there was a small trend to reduced incidence of retinopathy of prematurity in the vitamin A group (typical RR 0.81, 95% CI 0.65 to 1.01). There was a marginal reduction of the combined outcome of death or chronic lung disease (moderate-quality evidence). Although there is a statistical reduction in chronic lung disease, these findings are consistent with either a meaningful impact on chronic lung disease or a negligible impact. One trial that investigated neurodevelopmental status at 18 to 22 months of age correcting for prematurity found no evidence of benefit or harm associated with vitamin A supplementation compared to control (RR 0.89, 95% CI 0.74 to 1.08) (low-quality evidence).[132] No adverse effects of vitamin A supplementation were reported, but it was noted that intramuscular injections of vitamin A were painful.

Evidence provided in the review by Haider et al [129] does not indicate a potential beneficial effect of vitamin A supplementation among term neonates at birth in reducing mortality during the first six months or 12 months of life. High-quality evidence indicates that vitamin A supplementation in children aged between 6 and 59 months decreases all-cause childhood mortality by 12% (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.79 to 0.98)[130] There is low quality evidence for no benefits or harm in any of the critical outcomes with daily oral vitamin

A supplementation. In VLBW infants (less than 1000 grams birth weight), repeat intramuscular doses of vitamin A to prevent chronic lung disease may depend upon the local incidence of this outcome and the value attached to achieving a modest reduction in the outcome balanced against the lack of other proven benefits and the acceptability of the treatment to be considered. The optimal dose appears to be 5000 IU three times weekly for four weeks.

RECOMMENDATION 16

Routine oral or intramuscular supplementation of vitamin A is not recommended in LBW infants.

Weak recommendation, based on Low quality evidence

Practice Question 17: Should iron supplementation vs. no iron supplementation be used for supplementing LBW infants?[7,135–142]

Table 6 : Summary of previous guidelines

Association / Professional body	Recommendation	Remarks
WHO Optimal feeding of LBW in low and middle income countries 2011[7]	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	Weak recommendation based on low quality evidence
Commentary from ESPGHAN 2010[8]	Prophylactic enteral iron supplementation should be started at 2 to 6 weeks of age in dose range of 2-3 mg/kg/day at least until 6-12 months of age	
Nutrition Committee, Canadian Pediatric Society[143]	Recommends Iron supplementation Birthweight >1 kg – 2-3 mg/kg/day <1 kg 3-4 mg/kg/day to start at 6-8 weeks of age till 12 months of age	

Summary of Evidence

Additional iron is necessary to meet the needs of erythropoiesis and growth of preterm infants. The iron status of preterm infants receiving non-fortified breast milk starts to deteriorate within 1 to 4 months.

The Cochrane review 2012[142] looked into enteral iron supplementation in preterm and low birth weight infants. Twenty six studies (2726 infants) were included in the analysis. Of thirteen studies reporting at least one growth parameter as an outcome, only one study of poor quality found a significant benefit of iron supplementation. Most studies reported a higher mean

haemoglobin in iron-supplemented infants after 2 months. Limited studies included in the metanalysis. suggested the haemoglobin concentration in iron-supplemented infants was higher by about 6 g/L at six to nine months. The studies comparing high and low doses of iron indicated that there was no discernible haematological benefit in exceeding 'standard' doses of iron (i.e. 2 mg/kg/day to 3 mg/kg/day).

In the more recent systematic review which included recent studies McCarthy et al[135] reported on 27 articles, and most articles (23/27) reported iron status indices. Supplementation for more than 8 weeks resulted in increased hemoglobin and ferritin concentrations and a reduction in iron deficiency and anemia. No article reported on iron overload. Growth-related parameters reported in 12 articles were not affected by supplementation. Among the 7 articles on neurological development, a positive effect on behavior at 3.5 and 7years was observed[144,145] No association was found between supplementation and adverse clinical outcomes in the 9 articles included. Further study follow up at 12 months[146] showed Iron supplements with 2 mg/kg/day until 6 months of life effectively reduces the risk of Iron deficiency during the first 12 months of life.

Early versus Late supplementation (2 weeks versus 6 weeks) [136,138]
Early treatment was associated with significantly smaller decreases in serum ferritin and haemoglobin levels (P <.001). In addition, the rate of blood transfusions was lower with early compared with late iron supplementation (P = .022). There was no difference between early and late supplementation in the number of patients with necrotizing enterocolitis (P = .646). Sensitivity analysis indicated no one study overly influenced the findings and that the data was reliable.[138]

Cumulative iron intake with early supplementation was calculated to be > 3 times of late supplementation. A follow-up study demonstrated a lower incidence of mild motor signs and a trend towards better cognitive function at 5 years of age in those supplemented from 2 weeks, suggesting potential long-term benefits with early supplementation.[147]The lack of long-term neurological morbidity also supports the safety of early iron supplementation

RECOMMENDATION 17

Oral iron supplement in a daily dose of 2–4 mg/kg of elemental iron is recommended in LBW infants from 2-4 weeks of life to 12 months of age.

Weak recommendation based on Low quality evidence

Practice Question 18: Should Probiotics vs. No probiotics be used to supplement feeding in LBW infants?[148–159]

Summary of Evidence

Table 7: Probiotics compared to No Probiotics for feeding in LBW infants

Patient or population: feeding in LBW infants
Setting: NICU
Intervention: Probiotics
Comparison: No Probiotics

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Probiotics	Risk difference with Probiotics
Severe NEC (NEC) follow up: median 2 years	8535 (29 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 0.57** (0.47 to 0.70)	60 per 1,000	**26 fewer per 1,000** (32 fewer to 18 fewer)
Sepsis (LOS)	7987 (28 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 0.88** (0.80 to 0.97)	168 per 1,000	**20 fewer per 1,000** (34 fewer to 5 fewer)
Mortality	8186 (27 RCTs)	⊕⊕⊕⊕ HIGH [b]	**RR 0.77** (0.65 to 0.92)	66 per 1,000	**15 fewer per 1,000** (23 fewer to 5 fewer)

In a systematic review[149] for benefits of probiotics in Low and Middle income countries looked into NEC, Late onset sepsis and All -cause mortality outcomes

Table 8 : Systematic review of probiotics in LMIC

Outcome	Absolute risk Control	Absolute risk Probiotics	Number of participants	Relative effect (RR) 95% CI	Quality of evidence
Late-onset sepsis	358/1986 (18%)	308/1986 (14.5%)	3902	0.80 (0.71 to 0.91); P=0.0009, I2=25%	High
Mortality	176/2048 (8.6%)	137/2148 (6.4%)	4196	0.73 (0.59 to 0.9); P=0.003, I2=0%	High
NEC	135/1957 (6.9%)	65/2065 (3.1%)	4022	0.46 (0.34 to 0.61); P<0.00001, I2=19%	High

The evidence was deemed high in view of the large sample size, low risk of bias in majority (14/20) of the included studies, narrow CIs around the effect size estimate, very low P Value for effect size estimate and mild statistical heterogeneity. Further meta-analysis[151] comparing single strain probiotic versus multi-strain probiotics included a total of 25 trials (*n* = 7345 infants).Multiple strains probiotics were associated with a marked reduction in the incidence of NEC, with a pooled OR of 0.36 (95% CI, 0.24–0.53; *P* < .00001). Single strain probiotic using Lactobacillus species had a borderline effect in reducing NEC (OR of 0.60; 95% CI 0.36–1.0; *P* = .05), but not mortality. Multiple strains probiotics had a greater effectiveness in reducing mortality and were associated with a pooled OR of 0.58 (95% CI, 0.43–0.79; *P* = .0006. One more meta-analysis[150] showed probiotics prevented NEC in preterm infants (RR 0.47 [95 % CI 0.36-0.60], p < 0.00001). Strain-specific sub-meta-analyses showed a significant effect for *Bifidobacteria* (RR 0.24 [95 % CI 0.10-0.54], p = 0.0006) and for probiotic mixtures (RR 0.39 [95 % CI 0.27-0.56], p < 0.00001).

The above results indicate that probiotics are effective in significantly reducing the risk of all-cause mortality, LOS and NEC in preterm VLBW neonates. Things which needs to be considered before the local unit decides for blanket probiotic supplementation for all preterm infants :

1) Have other efforts to reduce NEC been applied in your unit? 2.) What is the baseline incidence of NEC within your unit? 3) Is the target population in your unit similar to the population studied in trials and implementation cohort studies? 4.) Which probiotic products are available to your unit?

RECOMMENDATION 18

Multi-strain probiotics may be initiated in preterm low birth weight infants from as early as day 1 of life and continued until 36-37 weeks post-menstrual age or discharge (whichever is earlier) in neonatal units with high baseline incidence of necrotizing enterocolitis.

Weak recommendation based on Moderate quality evidence

Practice Question 19: Should Vitamin D supplementation vs. no Vitamin D supplementation be used for supplementing LBW infants

Table 9: Summary of previous guidelines

Association / Professional body	Recommendation	Remarks	Recommended Vit D Serum level
WHO Optimal feeding of LBW in low and middle income countries 2011[7]	VLBW infants should be given vitamin D supplements at a dose ranging from400 i.u to 1000 i.u. per day until 6 months of age.	Weak recommendation based on very low quality evidence	
Commentary from ESPGHAN 2010[8]	Recommends 800-1000 IU/ day	Preterm infants	>80 nmol/l
AAP Committee on Nutrition 2013[160]	Vitamin D should be provided at 200 to 400 IU/day both during hospitalization and after discharge from the hospital	Preterm Infants VLBW	>50 nmol/l
AAP Committee on Nutrition 2013[160]	400 IU-1000 IU / day	Preterm infants >1500g, tolerating full enteral feeds	>50 nmol/l

Summary of evidence

Several studies have demonstrated that preterm infants born <32 weeks (and especially those <28 weeks) are at greater risk of developing vitamin D deficiency compared to more mature infants.[161,162]Approximately 10% to 20% of extremely low-birth weight infants have radiological evidence of rickets with metaphyseal changes despite current nutritional practices.[163]. Level of less than 20 ng/ml (50 nmol/liter) is considered as Vitamin D deficient by professional bodies[164] Vitamin D deficiency (serum 25-hydroxyvitamin D < 15 ng/mL) in low birth weight infants was 87.3% in a study from India (Agarwal 2012)[165]

From the metanalysis of 12 RCT's by Yang et al[166], there are no differences between high-dose (800–1000 IU/d) and low-dose (400 IU/d) groups on calcium, phosphorus, and 25(OH)D concentrations (p>.05). However, length gain and head circumference gain are significantly increased in the high-dose group (p< .05)

In a study by Mathur et al[167] comparing 400 IU vs 1000 IU , Vitamin D supplementation in a dose of 1000 IU/day is more effective in maintaining serum calcium, phosphate, ALP, 25-OHD and parathormone levels with lower incidence of skeletal hypomineralization and better growth. The mean serum 25 OHD levels increased significantly in both the groups after 6 weeks, but were significantly higher in 1000 IU (50.91 6 11.14 ng/ml) compared with 400 IU (29.37 6 11.03 ng/ml) (p < 0.001).Another Indian trial also reported supplementation at 800 IU better than 400 IU[168]

In the RCT[169] comparing 400 IU vs 800IU, concludes that Improvement in 25(OH)D3 levels at 4 weeks, bone density, and trends towards improvement in linear growth support consideration of a daily dose of 800 IU of vitamin D for infants <32 weeks cared for in the NICU. Serum 25(OH)D3 levels at birth were 41.9 and 42.9 nmol/l for infants in the 400 IU group and 800 IU group, respectively (p = 0.86). After 4 weeks of D3 supplementation, median 25(OH)D3 levels increased in both groups (84.6vs. 105.3 nmol/l for 400 vs. 800 IU/day. respectively, with significantly more improvement in the higher dose (p = 0.048). Infants in the 400 IU group were significantly more likely to have dual energy x-ray absorptiometry (DEXA) bone density measurements <10 percentile (56% vs 16%, p = 0.04).

Cho SY et al[170] demonstrated that supplementation during NICU hospitalization with 800 IU in a cohort of infants <1500 grams showed no safety concerns with all infants having levels above 25 nmol/l but 21% of infants still insufficient at 36 weeks CGA[170]. Another trial[171] evaluating placebo, 200 IU and 800 IU daily vitamin D supplement evaluated levels at 36 weeks and days of respiratory support, showing prevention of vitamin D deficiency with the 800 IU dose, and an improvement in serum levels with the 200 IU dose as compared to placebo, but no difference in days alive or in respiratory support.

There is evidence that Preterm infants fed breast milk or formula without supplementation have been shown in previous studies to have decreasing levels over the subsequent weeks (up to 28%) or to maintain their 25(OH)D status at suboptimal levels[172] As studies have confirmed that relation between vitamin D3 intake and the mean circulating concentration of 25(OH)D, additional supplementation of Vitamin D is required to reach a circulating 25(OH)D concentration above 50-75 nmol/L.

RECOMMENDATION 19

VLBW infants should be given vitamin D supplements at a dose ranging from 400 IU to 1000 IU per day from the day of reaching full enteral feeds to 6 months of age.

Weak recommendation based on moderate level of evidence

Abbreviations

AA – Arachidonic acid	AC – Abdominal circumference	ALA – Alpha linolenic acid
BPD – Bronchopulmonary dysplasia	BSID – Bayley's scale of infant development	CI – Confidence interval
CLD – Chronic lung disease	CMV – Cytomegalovirus	DBM – Donor breast milk
DHA – Docosahexaenoic acid	DHM – Donor human milk	EBM – Expressed breast milk
ELBW – Extremely low birth weight	EMPD – Electromagnetic device	FFM – Fat free mass
FT – Feeding tube	GA – Gestational age	GER – Gastro esophageal reflux
GERD - Gastro esophageal reflux disease	GRV – Gastric residual volume	HBF – Human milk based fortifier
HIV – Human immunodeficiency virus	HM – Human milk	HMB – Human milk bank
IUGR – Intrauterine growth restriction	IV – Intravenous	IQR – Interquartile range
KMC – Kangaroo mother care	LA – Linoleic acid	LBW – Low birth weight
LCPUFA – Long chain polyunsaturated fatty acid	LMIC – Low and middle income countries	MD – Mean difference
MDI – Mental developmental index	MMC – Migrating motor complex	MOM – Mother's own milk
NDI – Neurodevelopmental impairment	NEC – Necrotizing enterocolitis	NEMU – Nose ear midway to umbilicus
NG – Nasogastric	NNT – Number needed to treat	NPV – Negative predictive value
OG – Orogastric	PDI – Psychomotor developmental index	PN – Parenteral nutrition
PPV – Positive predictive value	PVL – Periventricular leukomalacia	RCT – Randomized controlled trial
RD – Risk difference	ROP – Retinopathy of prematurity	RR – Relative risk
SCBU – Special care baby unit	SGA – Small for gestational age	SNCU – Sick newborn care unit
TPN – Total parenteral nutrition	USG - Ultrasonography	VLBW – Very low birth weight

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