Clinical Practice Guidelines

Breastmilk for Preterm Neonates

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Guideline Development Group (Alphabetical)

J P Dadhich (Chairperson)
Sankalp Dudeja
M M A Faridi
Jayashree Mondkar
Subhash Chandra Shaw

Reviewers (Alphabetical)

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G Guruprasad
Nishad Plakkal

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Executive Summary

Mother's milk is of particular importance for preterm and sick babies in the neonatal unit. Preterm babies fed mothers milk are less likely to suffer from NEC, late onset sepsis, and mortality rates are lower compared to formula fed babies. Preterm infants fed breastmilk have better cognitive outcomes.

All interventions leading to better initiation of breastfeeds, continuation of any breastfeeding and exclusive breastfeeding as long as possible, are very important. These guidelines evaluate evidence for various interventions to enhance breastmilk supply and establish and sustain breastfeeding in mothers with preterm infants and provide recommendations for care providers in the neonatal units, policy-makers, administrators and mothers whose preterm infants are admitted in the neonatal unit.

These guidelines evaluate evidence for the interventions to enhance breastmilk supply and establish and sustain breastfeeding in mothers with preterm infants such as methods of breastmilk expression, use of Kangaroo Mother Care, use of galactagogues, provision of skilled professional support, provision of peer support, use of methods like non-nutritive sucking (NNS), breast massage, breast warming, music therapy etc. The guidelines do not provide information and evidence about interventions like protection of breastfeeding from commercial influence by implementation of the Infant Milk Substitute(IMS) Act; keeping mother and baby together in the hospital to facilitate getting breastmilk from mothers, methods of feeding the preterm infants and fortification on breastmilk etc. Using the assembled list of priority questions and critical outcomes from the scoping exercise, the guidelines development group, identified systematic reviews that were either relevant or potentially relevant and assessed whether they needed to be updated. If any relevant review was found to be out of date, it was updated. Cochrane systematic reviews were the primary source of evidence for the recommendations included in these guidelines.

These guidelines provide recommendations for pediatricians, obstetricians, medical officers, nurses, policy-makers, hospital administrators, health-care providers in the neonatal units and lactating mothers of preterm infants. Table 1 lists the key recommendations of the guideline.

Table 1: Summary of Recommendations for supporting breastmilk feeding in preterm Neonates

S.No.	Recommendations	Strength of recommendations	Quality of Evidence
1.	Mothers whose preterm infants are admitted in the neonatal unit may use either electric or manual breast pumps in the first week after delivery to get higher volume of expressed breastmilk; they may use manual breast pumps to do sequential expression (i.e. expression from one breast followed by that from the other) in the second week after delivery. *Comment*: In resource constrained settings, manual milk pumps and manual expression of milk may be used in place of electric milk pumps.	Weak	Low
2.	KMC should be routinely used for all low birth weight infants.	Strong	Moderate
3a.	Domperidone may be used to enhance the volume of expressed breastmilk in mothers with preterm infants who are expressing insufficient amounts of breastmilk. *Comment :* Domperidone should not be used in women at risk for arrythmias.	Weak, conditional	Moderate
3b.	Metoclopramide should not be used to enhance the volume of expressed breastmilk in mothers of preterm infants.	Strong	Moderate
4.	Skilled professional support should be provided to lactating mothers whose babies are admitted in neonatal units to establish and sustain breastfeeding.	Strong	Moderate
5a.	Low-cost interventions like breast massage, breast warming, and relaxation techniques should be used to enhance breastmilk supply in mothers whose preterm infants are admitted in the neonatal unit.	Strong	High
5b.	Non-nutritive sucking should be encouraged in preterm very low birth weight infants admitted in neonatal unit	Strong	Moderate
6.	Peer support should be provided to the mothers to help in initiating and sustaining breastfeeding.	Strong	High

Introduction

Preterm birth is defined as birth before 37 completed weeks of gestation. Breastmilk feeding in preterm infants is crucial not only in providing optimal nutrition, but also in preventing morbidities like necrotising enterocolitis, retinopathy of prematurity and neonatal sepsis. The cognitive outcomes of such babies have shown to be better and incidence of obesity, childhood diabetes, asthma etc. is lower. (1)

Preterm babies due to immaturity and associated problems are unable to feed directly at the breast. In such situations mothers of preterm infants require skilled support to express sufficient milk for feeding their babies per oral, generally by gavage, as well as to maintain their milk output till the baby is in a position to feed directly at the breast. (2)

Any intervention helping in increasing quantity of expressed milk, weight gain, transition from gavage to full oral feeding, full breastfeeding at discharge, start oral feeding to full oral feeding (days) etc. are important considerations. Various methods of milk expression, Kangaroo Mother Care (KMC), support of skilled professional, peer support (3), and techniques like non-nutritive sucking, breast warming, breast massage, music relaxation therapy etc., are some easy interventions that can be applied. Sometimes, medications, known as galactagogues (4) are also suggested to enhance the breastmilk supply. Kangaroo Mother Care has been reported to have a positive effect on breastfeeding in preterm infants. (5) Different studies have shown a variety of methods used to obtain milk like hand expression, use of manual pumps, battery operated or electric pumps. Quantity of milk output, and acceptability of expression/ pumping method by the mother may vary among methods of expression. (6) Mothers feel physiologically and emotionally connected to their preterm infants admitted in the neonatal unit by providing expressed breastmilk. (7)

These guidelines evaluate evidence for the interventions to enhance breastmilk supply and establish and sustain breastfeeding in mothers with preterm infants such as methods of breastmilk expression, use of Kangaroo Mother Care, use of galactagogues, provision of skilled professional support, provision of peer support, use of methods like non-nutritive sucking (NNS), breast massage, breast warming, music therapy etc.

The guidelines do not provide information and evidence about interventions like protection of breastfeeding from commercial influence by implementation of the IMS Act (8); keeping mother and baby together in the hospital to facilitate getting breastmilk from mothers, methods of feeding the preterm infants and fortification on breastmilk etc.

Scope of the guidelines

Aim

The objective of these guidelines is to provide global evidence-based recommendations on interventions to ensure and improve optimal breastmilk feeding of preterm Infants in neonatal units and at home. While breastfeeding has a positive impact on infant and child health and survival (1), enhancing use of breastmilk and breastfeeding rates with appropriate actions is also important to achieve the Sustainable Development Goals for reducing neonatal mortality to 12/1000 live births by the year 2030 (9) and objectives of the

India Newborn Action Plan. (10) Recommendations of the guidelines will help in developing relevant policies for enhanced breastmilk procurement in neonatal units by the concerned agencies and the health facilities.

Target population

Primary beneficiary of these guidelines will be the Mother- Preterm Infant dyad when preterm babies are admitted in the neonatal units, particularly in Level 2 and Level 3 Neonatal Units and at home after discharge from the hospital.

These guidelines will also help clinical decision makers in the neonatal units; care providers in the community settings, policy makers and administrators in hospitals and lactating mothers of preterm infants to make evidence-based decisions to enhance breastmilk supply.

Relevant existing guidelines and tools on use of breastmilk in neonatal units

There are several guidelines and policy documents are available on use of breastmilk in neonatal units. Some of the relevant documents are -AAFP recommendations on breastfeeding (11), Turkish neonatal society guideline on enteral feeding of the preterm infants (12), National Institute of Health and Care Excellence (NICE) guidelines on donor milk banks (13), WHO guidelines on optimal feeding of low birth-weight infants in low- and middle-income countries (14) and NNF Clinical Practice Guidelines (2011) (15).

Outcomes of interest

The guidelines development group (GDG) considered following *critical* outcomes for different interventions studied: Volume of the breastmilk, transfer to feeding at breast, breastfeeding at discharge, mortality at discharge, initiation of breastfeeding and breastfeeding duration. *Important* outcomes like adverse effects were also studied in some interventions.

Questions relevant to clinical practice

The GDG in consultation with a wider group of NNF members identified 6 questions to be of the highest priority for development of recommendations. A list of potential outcomes of interest for each question was circulated to all members of the GDG, who scored the importance of each outcome on a scale of 1 to 9 . A score of 1-3 was considered *not important*; 4 – 6 as *important* and 7-9 *critical*. The average of the scores for each outcome was used to prioritize the outcomes and to select the most important outcomes for each PICO question. (16):

1. Should milk pumps vs. manual expression be used by the mothers of preterm infants admitted in the neonatal units, to sustain breastmilk output?
2. Should KMC compared to no KMC be used for establishing and sustaining breastmilk supply by the mothers of preterm infants admitted in the neonatal units for optimal nutrition, optimum growth and survival?
3. Should medications like domperidone or metoclopramide be used by the mothers of preterm infants admitted in the neonatal units for enhancing breastmilk supply?

4. Should skilled professional support vs. self-care/ no skilled support be provided to the mothers of preterm infants admitted in the neonatal units to enhance breastmilk supply and practice breastfeeding?
5. Should care techniques like non-nutritive sucking (NNS), breast massage, breast warming, music therapy etc. be used by the mothers of preterm infants admitted in the neonatal units for increasing breastmilk production?
6. Should peer support be provided to the mothers of preterm infants admitted in the neonatal units for establishing and sustaining breastmilk supply, optimal nutrition, growth, reduced morbidity and survival?

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 tables of individual studies

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

Pooled effects

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

Quality assessment

Quality assessment of the body of evidence for each outcome was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE approach was used for all the critical outcomes identified in the PICOs, and a GRADE profile was prepared for each quantitative outcome within each PICO. Accordingly, the quality of evidence for each outcome was rated as “high," “moderate," “low," or “very low” based on a set of criteria. As a baseline, RCTs provided “high-quality” evidence, while non-randomized trials and observational studies provided “low-quality” evidence. This baseline quality rating was then downgraded based on consideration of risk of bias, inconsistency, imprecision, indirectness and publication bias. For observational

studies, other considerations, such as magnitude of effect, could lead to upgrading of the rating if there were no limitations that indicated a need for downgrading.

Risk of bias

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

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

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

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

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

Document review

The GDG met face to face on two occasions and prepared a draft of the full guideline document with revisions to accurately reflect the deliberations and decisions of the GDG participants. 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 summary and Recommendations

Practice Question 1: Should milk pumps vs. manual expression be used by the mothers of preterm infants admitted in the neonatal units, to sustain breastmilk output?

Summary of evidence (17)

The quantity of milk expressed was examined in 6 studies. The volume of milk expressed was measured on different days in different studies. There was a clinically significant increase in volume of milk pumped over first six days with use of electric pump in comparison to hand expression. There was no difference in milk output over first six days between electric pump expression and manual pump expression. The time taken for pumping reduced with specific instructions and support provided.

There was no difference in the contamination rate (at least one expressed milk sample contaminated) using milk pump or hand expression.

Table 2: Summary of evidence- Method of expression of breastmilk

Outcomes	Effects (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)
Manual pump vs hand expression: Quantity of milk expressed - Mean volume on day 4-5 (ml) assessed with: Milk volume in ml	MD 73.94 ml higher (64.11 lower to 211.99 higher)	28 (1 RCT)	⊕⊕◯◯ LOW [a,b]
Large electric pump versus hand expression - Quantity of milk expressed over 6 days of pumping (mL)	MD 373.1 ml higher (161.09 higher to 585.11 higher)	43 (1 RCT)	⊕⊕◯◯ LOW [a,c]
Electric Pump vs Manual Pump. Quantity of milk expressed - Mean volume per day pumped (mL)	MD 5.07 higher (56.59 lower to 66.73 higher)	145 (1 RCT)	⊕⊕◯◯ LOW [a,b]
Any Large Electric Pump vs Manual Pump. Time taken to express milk - Mean time per day spent pumping (min)	MD 20.27 lower (28.3 lower to 12.24 lower)	145 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Any method plus specific instructions or support provided Vs no support. Quantity of milk expressed - Volume of milk (mL) pumped each time while in NICU	MD 6 higher (16.35 lower to 28.35 higher)	128 (1 RCT)	⊕⊕◯◯ LOW [a,b]
Any method plus specific instructions or support provided Vs no support. Quantity of milk expressed - Volume mL/day, Week 6	MD 42.47 higher (274.99 lower to 359.93 higher)	33 (1 RCT)	⊕⊕◯◯ LOW [a,b]
Any pump vs manual expression. Adverse effects for mother or infant - At least 1 expressed milk sample contaminated	RR 1.13 (0.79 to 1.61)	28 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,d]

Explanations a. Only one study b. 95% CI crosses the null value of 0 c. because of the small sample size – the optimal information size is not met. d. randomization sequence generation, blinding of participants and outcome are unclear

RECOMMENDATION 1

- **Mothers whose preterm infants are admitted in the neonatal unit may use either electric or manual breast pumps in the first week after delivery to get higher volume of expressed breastmilk; they may use manual breast pumps to do sequential expression (i.e. expression from one breast followed by that from the other) in the second week after delivery.**
- Specific instructions and support for pumping should be provided to mothers for enhancing milk supply.
- In resource constrained settings, manual milk pumps and manual expression of milk may be used in place of electric milk pumps.

Weak recommendation, Low quality of evidence

Practice Question 2 : Should Kangaroo Mother Care (KMC) compared to no KMC be used for establishing and sustaining breastmilk supply by the mothers of preterm infants admitted in the neonatal units for optimal nutrition, optimum growth and survival?

Summary of evidence (18)

We found one Cochrane systematic review that examined the effect of Kangaroo mother care on breastfeeding in low birth weight infants. No subsequently published trials were found.

KMC improves the chances of any breastfeeding at discharge or at 40 weeks postmenstrual age by an RR of 1.20 (95% CI 1.07 to 1.34). It also reduces mortality at discharge or 40 weeks post menstrual age with an RR of 0.60 (95% CI 0.39-0.92). KMC, however, has no significant effect on mortality at 6 months or 12 months of corrected age. KMC being a potentially harmless intervention, no harmful effects are anticipated.

Table 3 : KMC compared to no KMC be used for establishing and sustaining breastmilk supply by the mothers of preterm infants admitted in the neonatal units for optimal nutrition, optimum growth and survival

Patient or population: preterm neonates
Setting: NICU
Intervention: KMC
Comparison: No KMC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with No KMC	Risk with KMC			
Any breastfeeding at discharge/40 weeks PMA	762 per 1,000	914 per 1,000 (815 to 1,000)	RR 1.20 (1.07 to 1.34)	1696 (10 RCTs)	⊕⊕⊕⊕ HIGH
Mortality at discharge or 40 weeks post menstrual age	53 per 1,000	32 per 1,000 (21 to 49)	RR 0.60 (0.39 to 0.92)	1736 (8 RCTs)	⊕⊕⊕⊕ HIGH
Mortality at 6 months of age or 06 months follow up	80 per 1,000	79 per 1,000 (38 to 161)	RR 0.99 (0.48 to 2.02)	354 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Mortality at 12 mo corrected age	55 per 1,000	32 per 1,000 (15 to 65)	RR 0.57 (0.27 to 1.17)	693 (1 RCT)	⊕⊕◯◯ LOW [b,c]

Explanations
a. Confidence Interval too wide b. Only single study c. 95% CI crossing null value

RECOMMENDATION 2

Kangaroo Mother Care should be practiced routinely for all low birth weight infants.

Strong recommendation, Moderate quality evidence

Practice Question 3 : Should medications like domperidone or metoclopramide compared to no medications or placebo be used by the mothers of preterm infants admitted in the neonatal units for enhancing breastmilk supply?

Summary of evidence (19-23)

A systematic review and meta-analysis on the effect of domperidone use on breastmilk supply published in 2019. It included 5 RCTs with 237 subjects randomly assigned to receive domperidone or a placebo. In the same publication, we found sub-group analysis of effect of duration of domperidone use, < 7 days (2 studies) and > 7 days (3 studies). For the comparison of use of metoclopramide and domperidone as galactagogues, we found a single RCT published in 2012, which included 80 mothers. For the effect of metoclopramide on breastfeeding duration, we found a single RCT published in 2005 with 57 mothers randomly assigned to metoclopramide and control groups. For the effect of metoclopramide on breastmilk volume, we found two RCTs published in 2005 and 2011 with 76 mothers assigned to intervention and control arms randomly.

There was significant increase in the volume of expressed breastmilk with the use of domperidone (MD 94.23 ml higher MD 95% CI 71.31 to 117.16), N=237, 5 RCTs (HIGH). This effect was noted when domperidone was given for < 7 days (MD 93.51 ml higher 95% CI 52.45 to 134.57), N=59 (2 RCTs) (HIGH) as well as when it was given for > 7 days (MD 94.56 ML higher, 95% CI 66.93 to 122.19), N= 178, (3 RCTs) (HIGH). The mean enhanced breastmilk supply with Metoclopramide was not significant (P 0.8 higher, 95% CI 0.26 to 0.98), N=76, (2 RCTs), (LOW). The mean duration of breastfeeding was also not significantly higher with metoclopramide (median 0.2 week higher), N=57, (1 RCT), (HIGH). The mean unadjusted milk volumes was significantly higher in mothers (N= 31) who received domperidone 284.7 ml (SD 158.0) in comparison to those (N= 34) who received metoclopramide 211.5 ml (SD 154.3) with a Mean difference (domperidone – metoclopramide) (95% CI) of 74.1 (−3.4 to 151.7), (1 RCT), Moderate.

Table 4: Domperidone or metoclopramide compared to no medications or placebo be used by the mothers of preterm infants admitted in the neonatal units for enhancing breastmilk supply

Patient or population: mothers of preterm neonates
Setting: NICU
Intervention: Medications
Comparison: No Medications

Outcomes	**Effects (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)
Use of Domperidone and difference in volume of EBM per day (Breastmilk volume) assessed with: ml per day follow up: range 3 days to 14 days	MD 94.23 ml higher (71.31-11.16)	237 (5 RCTs)	⊕⊕⊕◯ MODERATE [a]
Difference in volume of EBM per day Domperidone duration < 7 days (EBM Volume) assessed with: ml per day follow up: range 3 days to 7 days	MD 93.51 ml higher (52.45-134.57)	59 (2 RCTs)	⊕⊕⊕⊕ HIGH
Difference in volume of EBM per day Domperidone duration > 7 days (EBM Volume) assessed with: ml per day follow up: range 10 days to 14 days	MD 94.56 ml (66.93-122.19)	178 (3 RCTs)	⊕⊕⊕◯ MODERATE [b]
Enhanced Breastmilk Supply with Metoclopromide assessed with: ml/day	Mean 0.8 higher (0.26-0.98)	57 (1 RCT)	⊕⊕⊕◯ MODERATE [c]
Metoclopramide and duration of breastfeeding (duration of breastfeeding) assessed with: weeks	Median 0.2 week higher	57 (1 RCT)	⊕⊕⊕⊕ HIGH

Table 4: Domperidone or metoclopramide compared to no medications or placebo be used by the mothers of preterm infants admitted in the neonatal units for enhancing breastmilk supply

Patient or population: mothers of preterm neonates
Setting: NICU
Intervention: Medications
Comparison: No Medications

Outcomes	**Effects (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)
Domperidone versus Metoclopramide for increased breastmilk volume assessed as mL follow up: range 30 days to 30 days	Mean unadjusted milk volumes (ml per 24 h) in the medication phase of the trial and mean differences with 95% CIs for 65 mothers (31 received Domperidone and 34 received Metoclopramide) was 284.7 ml (SD 158.0) and 211.5 ml (SD 154.3) respectively with a Mean difference (domperidone – metoclopramide) (95% CI) of 74.1 (−3.4 to 151.7).	65 (1 RCT)	⊕⊕⊕◯ MODERATE [1,d]

a. Two out of five studies did not provide sufficient details to allow for replication of randomization and blinding methods. In one of the study, an unclear description of any adjustment for covariates in the analysis was provided. Weightage of these studies is > 50% in the pooled analysis
b. The major limitation of the existing evidence lies in the small number of women included in clinical trials, limiting the potential to comprehensively evaluate both the efficacy and safety of the medication
c. 95% CI crosses null value d. 95% CI crosses null value

RECOMMENDATION 3

3a. Domperidone may be used to enhance the volume of expressed breastmilk in mothers with preterm infants who are expressing insufficient amounts of breastmilk.

Weak conditional recommendation, Moderate quality of evidence

3b. Metoclopramide should not be used to enhance the volume of expressed breastmilk in mothers with preterm infants.

Strong recommendation, Moderate quality of evidence

Comment: Domperidone should not be used in women at risk for arrhythmias.

Practice Question 4: **Should skilled professional support vs. self-care/ no skilled support be provided to the mothers of preterm infants admitted in the neonatal units to enhance breastmilk supply and practice breastfeeding?**

Summary of evidence

We found one Cochrane systematic review that examined the effect of various techniques for providing support to healthy breastfeeding mothers with healthy term babies. (24) The review was last updated in February 2016. No subsequent trails were found. We could not find good quality studies for preterm infants. Therefore, we included this Cochrane review on term infants. We downgraded the quality of evidence by increasing the indirectness to 'serious' because of this.

For outcomes stopping any breastfeeding by 4-6 weeks and stopping exclusive breastfeeding by 4-6 weeks, there were 23 and 22 trials, respectively. (24) We found one observational study with 350 subjects, which looked into effect of lactation support services on use of mother's own milk. (25)

Professional support helps in initiation of breastfeeding with RR of 1.43 (95% CI 1.07-1.92), reduces stopping any breastfeeding before last study assessment up to 6 months with RR of 0.92 (95% CI 0.89-0.96), reduces stopping any breastfeeding by 4-6 weeks with RR of 0.81 (95% CI 0.72-0.91), and reduces stopping exclusive breastfeeding by 4-6 weeks with RR of 0.84 (95% CI 0.75-0.95) in healthy term infants. An observational study concluded that availability of lactation support service in the neonatal units enhances chances of receiving Own Mother's Milk (OMM) by the admitted infants 0R -2.0 (95% CI 1.3-3.0).

Table 5: Skilled professional support vs. self-care/ no skilled support be provided to the mothers of preterm infants admitted in the neonatal units to enhance breastmilk supply and practice breastfeeding

Patient or population: Mothers of preterm infants admitted in the neonatal units
Setting: NICU
Intervention: Skilled professional support
Comparison: No Skilled professional support

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk without Professional support	Risk with professional support			
Stopping exclusive breastfeeding by 4-6 weeks	320 per 1,000	259 per 1,000 (231 to 291)	RR 0.81 (0.72 to 0.91)	8104 (33 RCTs)	⊕⊕⊕⊕ HIGH
Stopping any breastfeeding by 4-6 weeks	592 per 1,000	497 per 1,000 (444 to 503)	RR 0.84 (0.75 to 0.85)	7435 (32 RCTs)	⊕⊕⊕◯ MODERATE

a. direction of results not consistent

RECOMMENDATION 4

Skilled professional support should be provided to lactating mothers whose babies are admitted in neonatal units to establish and sustain breastfeeding.

Strong recommendation, Moderate quality evidence

Practice Question 5: Should care techniques like non-nutritive sucking (NNS), breast massage, breast warming, music therapy etc. be used by the mothers of preterm infants admitted in the neonatal units for increasing breastmilk production?

Summary of evidence

We found one Cochrane review that examined the effect of non-nutritive sucking on breastfeeding in preterm infants. The review was last updated in February 2016. (26) There was one Cochrane review for effect of various other techniques (breast massage, breast warming and music therapy) for providing support to breastfeeding mothers.(17) In the review, there were 2 randomised trials each for the outcome of gavage to full oral feeding and start of oral feeding to full oral feeding. There were one trial each for effect of breast massage, breast warming and music therapy on quantity of milk expressed.(17)

There was significant effect of NNS on transition from gavage to full oral feeding (MD −5.51 days, 95% CI −8.20 to −2.82; N = 87), transition from start of oral feeding to full oral feeding (MD −2.15 days, 95% CI −3.12 to −1.17; N = 100), and the length of hospital stay (MD −4.59 days, 95% CI −8.07 to −1.11; N = 501). There was no significant effect of NNS on weight gain. The quantity of expressed milk obtained was increased, by clinically significant amount, by interventions involving music relaxation therapy, breast warming, and breast massage.

Table 6:Care techniques like non-nutritive sucking (NNS), breast massage, breast warming, music therapy etc. be used by the mothers of preterm infants admitted in the neonatal units for increasing breastmilk production

Patient or population: mothers of preterm neonates **Setting**: NICU
Intervention: Care techniques **Comparison**: None

Outcomes	Effects (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
Gavage to full oral feeding	Mean difference -5.51 (-8.20 to -2.82)	87 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Days from birth to full breastfeeding	Mean Difference -1.00 (-6.71 to 4.71)	303 (1 RCT)	⊕⊕◯◯ LOW [a,b]
Full breastfeeding at discharge	RR 1.08 (0.88 to 1.33)	303 (1 RCT)	⊕⊕⊕◯ MODERATE
Length of hospital stay	Mean Difference -4.59 (-8.07 to -1.11)	501 (6 RCTs)	⊕⊕⊕⊕ HIGH [a]
Weight gain (grams per day)	Mean Difference -1.57 (-3.50 to 0.37)	103 (3 RCTs)	⊕⊕◯◯ LOW [a,c]
Breast Massage: Quantity of milk expressed	Mean difference 4.82 (1.25 to 8.39)	(1 RCT)	⊕⊕⊕◯ MODERATE [a,d]
Music Therapy: Breastmilk volume by Day 14	Mean Difference 503.30 (410.76 to 595.84)	160 (1 RCT)	⊕⊕⊕⊕ HIGH [a]
Breast Warming: Quantity of milk expressed	Mean difference 13.02 (3.81 to 22.23)	(1 RCT)	⊕⊕⊕⊕ HIGH [a,d]

a. The available studies are for term and not preterm babies b. 95% CI crosses null value
c. Inconsistent results d. Wide confidence interval

RECOMMENDATION 5

5a. **Low-cost interventions like breast massage, breast warming, and relaxation techniques should be used to enhance breastmilk supply in mothers whose preterm infants are admitted in the neonatal unit.**

Strong recommendation, High quality evidence

5b. **Non- nutritive sucking should be encouraged in preterm very low birth weight infants admitted in neonatal unit.**

Strong recommendation, Moderate quality evidence

Practice Question 6: **Should peer support be provided to the mothers of preterm infants admitted in the neonatal units for establishing and sustaining breastmilk supply, optimal nutrition, growth, reduced morbidity and survival?**

Summary of evidence

We found one Cochrane systematic review that examined the effect of various techniques for providing support to healthy breastfeeding mothers with healthy term babies. (24) The review was last updated in February 2016. There were 9 randomised trials for the outcome of any breastfeeding before last study assessment up to 6 months of age, which included 3109 mothers. Therefore outcomes stopping any breastfeeding by 4-6 weeks and stopping exclusive breastfeeding by 4-6 weeks, there were 8 trials each (24) We also found a RCT, which was not a part of the Cochrane review, looking into the effect of peer counsellors on breastfeeding rates in neonatal care unit. (27)
There is low to moderate grade evidence that peer support is beneficial as compared to no peer support in preventing stoppage of any breastfeeding before 6 moths by RR of 0.85 (0.77 to 0.93), and stoppage of exclusive breastfeeding before 6 weeks by RR of 0.64 (0.46 to 0.89). However there is no statistically significant effect on stopping any breastfeeding before 6 weeks. There is high grade evidence that peer counselling is beneficial in providing any OR - 2.81 (95% CI 1.11- 7.14) or mostly OR - 2.49 (95% CI 0.97 - 6.4) breastfeeding at 12 weeks.

Table 6: Peer support vs no peer support provided to the mothers of preterm infants admitted in the neonatal units for establishing and sustaining breastmilk supply, optimal nutrition, growth, reduced morbidity and survival

Patient or population: Mothers of preterm infants admitted in the neonatal units
Setting: NICU
Intervention: Peer support
Comparison: No Peer support

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk without Peer support	Risk with peer support			
Stoppage of any breastfeeding before 6 months	586 per 1000	498 per 1000 (452 to 545)	RR 0.85 (0.77 to 0.93)	3109 (9 RCTs)	⊕⊕⊕◯ MODERATE
Stoppage of exclusive breastfeeding before 6 weeks	729 per 1000	467 per 1000 (336 to 649)	RR 0.64 (0.46 to 0.89)	2354 (8 RCTs)	⊕⊕⊕◯ MODERATE [a]
Mother giving any breastfeeding at 12 weeks with peer counselling (assessed with: practicing breastfeeding)	515 per 1000	749 per 1000 (541 to 883)	OR 2.81 (1.11 to 7.14)	206 (1 RCT)	⊕⊕⊕◯ MODERATE [b]

Explanations
a. Most studies are for term neonates
b. Single study

RECOMMENDATION 6

Peer suppport should be provided to the mothers to help in initiating and sustaining breastfeeding.

Strong recommendation, High quality evidence

Abbreviations

AAFP - American Academy of Family Physicians	CI - Confidence interval	DARE - Database of abstracts of reviews of effectiveness
GDG - Guideline development group	GRADE - Grading of Recommendations, Assessment, Development and Evaluation	KMC - Kangaroo mother care
LBW - Low birth weight	MD - Mean difference	NICE - National Institute of Health and Care Excellence
NEC - Necrotizing enterocolitis	NNF - National Neonatology Forum	OR Odds ratio
PICO - Population, intervention, comparison, outcome	RCT - Randomized controlled trial	RR - Relative risk
SD - Standard deviation	WHO - World Health Organization	

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