Preterm Infant (VLBW) Enteral Nutrition

VLBW: Guideline Recommendations and Supporting Evidence (2020)

Guideline recommendations are the essense of evidence-based guidelines and provide a course of action for the practioiner based on the evidence. Below, you will find a list of the **VLBW Preterm Infant (2020)** Recommendations.

The Academy categorizes Recommendations in terms of either **Imperative** or **Conditional** statements. Conditional statements clearly define a specific situation or specific sub-population with the larger guideline population. Imperative statements are broadly applicable to the target population without restraints on their application. Each recommendation receives a rating, using the scale **Strong, Fair, Weak, Consensus, or Insufficient Evidence.** The rating for the recommendation is primarily based on the strenght of the supporting evidence but also the balance between benefits or harms anticipated and the clinial practice implications when the statment is follows. **Learn more**

Resources Available with Each Recommendation

In addition to the recommendation statement and strength rating, you will find on each recommendation page:

- A brief narrative summary of the evidence analyzed to reach the recommendation
- A statement of justification, or reason for the strength of the recommendation
- Detailed information on the evidence supporting the recommendations and background narrative (available in the Supporting Evidence section toward the bottom of each recommendation page)
- A reference list at the end of each recommendation page that includes all the sources used in the evidence analysis for the particular recommendation (each reference is hyperlinked to a summary of the article analyzed in the evidence analysis).

Guideline Recommendations

Download the **Recommendation Rationale Table** (**PDF**). Click on the **blue** recommendation title below to view each recommendation and supporting information.

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- Preterm Infant (VLBW) Enteral Nutrition Guideline (2017-2020)

Quick Links

Recommendations Summary

VLBW: Protein Amount (2020)

Click here to see the explanation of recommendation ratings (Strong, Fair, Weak, Consensus, Insufficient Evidence) and labels (Imperative or Conditional). To see more detail on the evidence from which the following recommendations were drawn, use the hyperlinks in the Supporting Evidence Section below.

- Recommendation(s)

  VLBW: Protein Amount

  Healthcare practitioners should provide 3.5g to 4.0g of protein per kg bodyweight via enteral nutrition to very low birthweight (less than or equal to 1, 500g) preterm infants. Protein intake at 3.5g to 4.0g per kg bodyweight supports superior growth and protein accretion compared to protein intake of less than 3.5g per kg bodyweight.

  Rating: Fair
  Imperative

  - Risks/Harms of Implementing This Recommendation

    No undesirable effects of the higher protein intake were provided in included studies. Evidence was not located to support or discourage protein intakes greater than 4g per kg per day in infants with birthweights less than or equal to 1, 500g.

  - Conditions of Application

Providing adequate protein intake is feasible in most clinical situations. One barrier is the lack of information about the specific composition of human milk. Most clinicians do not have access to real-time, specific analysis of the human milk fed to patients. This results in the use of estimated, rather than actual, intake values.

- Potential Costs Associated with Application

  The cost of providing adequate nutrition, including adequate protein intake, is relatively small compared to the overall cost of caring for very low birthweight (VLBW) infants. One potential cost that could be considerable, is the purchase of human milk analysis equipment. Multi-component human milk fortifiers are a common method to provide additional protein to human milk-fed VLBW preterm infants.

  Implementation Considerations

  - Consider the protein composition of donor milk if provided by the vendor and of mothersâ€™ own milk if an FDA-approved human milk analyzer is available. If protein composition cannot be obtained, use published average values for breastmilk composition (Gidrewicz DA, Fenton TR; Nakano, etal, 2017).
  - Encourage the development of a feeding protocol that is accepted and used by key stakeholders in the NICU and that specifies when a protein modular is indicated, how it is started and advanced and when it is stopped.
  - Evaluate commercially available protein modulars and consider stocking one or more to add to fortified human milk and/or infant formula.
  - Provide a suitable area and staff education for safe handling and preparation of enteral feedings (Pediatric Nutrition, Steele, Collins et al 2018).

- Recommendation Narrative

  Very low birthweight (VLBW) preterm infants have the highest per kilogram protein requirements of any humans. Health practitioners are concerned that VLBW preterm infants are not growing well and one reason can be inadequate nutrition, especially protein. Human milk is the preferred feeding for nearly all newborns but it requires fortification to meet the nutritional needs of VLBW infants. Specifically, for VLBW infants, human milk is known to provide inadequate amounts of protein. However, human milk is one of the few evidence-informed strategies associated with decreased necrotizing enterocolitis in preterm infants. Providing adequate protein intake to VLBW preterm infants could help reduce health inequities because VLBW infants are disproportionately born to families of low socio-economic status.

  Two separate systematic reviews were conducted on protein intake: Protein amount with isocaloric comparison groups; and protein-energy, in which comparison groups varied in both protein and energy. There was heterogeneity among studies in regard to amount of protein provided to formula-fed and human milk-fed VLBW preterm infants. There is moderate certainty about the positive impact of adequate protein intake (3.5g to 4g per kg per day compared with lower protein intakes) on weight gain; there is less certainty about the effect of adequate protein intake on length, head circumference, mid-arm circumference gain, necrotizing enterocolitis, gastrointestinal health, or bone mineral content. One small RCT found some improvement in behavior development with protein intakes within the range of 3.5g to 4g per kg per day, compared with less. No studies were identified that evaluated mortality, and no undesirable effects were found with higher protein intake (4.7g per kg per day) within included studies.

  No studies were identified that evaluated less than instead of greater than 4g per kg per day of isocaloric protein intake by VLBW preterm infants. Studies were identified that evaluated less than vs greater 4g per k per day of protein intake by VLBW preterm infants with concurrent changes in energy intakes, however, with both protein and energy varied, it was not possible to attribute noted difference in growth or other outcomes to the differences in protein intake.

- Recommendation Strength Rationale

  Protein Amount

  - Moderate certainty evidence (grade II): Weight
  - Low certainty evidence (grade III): Development, lenght, head circumference, skinfold thickness, mid-arm circumference, bone mineral content

  Protein-Energy

  - Moderate certainty evidence (grade II): Weight
  - Low certainty evidence (grade III): NEC, anemia, length, head circumference, skinfold measurement, fat mass, gastrointestinal health.

- Minority Opinions

  Consensus reached.

- Supporting Evidence

  The recommendations were created from the evidence analysis on the following questions. To see detail of the evidence analysis, click the blue hyperlinks below (recommendations rated consensus will not have supporting evidence linked).

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on NEC?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on anemia?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on weight gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on length?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on head circumference?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on skinfold measurements?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on fat mass or fat-free mass?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein-energy amount via enteral nutrition on

gastrointestinal health?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on weight?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on length, head circumference, skinfold measurements and mid-arm circumference?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on development?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on bone mineral content or density?

- References

  Bhatia J, Rassin D, Cerreto M, Bee D. Effect of protein-energy ratio on growth and behavior of premature infants: preliminary findings. *The Journal of Pediatrics* 1991; 119:103-10

  Hillman L, Salmons S, Erickson M, Hansen J, Hillman R, Chesney R. Calciuria and aminoaciduria in very low birth weight infants fed a high-mineral premature formula with varying levels of protein. *The Journal of Pediatrics* 1994; 125:288-94

  Maas C, Mathes M, Bleeker C, Vek J, Bernhard W, Wiechers C, Peter A, Poets C, Franz A. Effect of Increased Enteral Protein Intake on Growth in Human Milk-Fed Preterm Infants: A Randomized Clinical Trial. *JAMA Pedatrics* 2017; 171:16-22

  Rönnholm K, Siimes M. Haemoglobin concentration depends on protein intake in small preterm infants fed human milk. *Archives of Disease in Childhood* 1985; 60:99-104

  Costa-Orvay J, Figueras-Aloy J, Romera G, Closa-Monasterolo R, Carbonell-Estrany X. The effects of varying protein and energy intakes on the growth and body composition of very low birth weight infants. *Nutrition Journal* 2011; 10:140

  Ditzenberger G, Wallen L, Phelan L, Escoe S, Collins S. Supplemental protein and postnatal growth of very low birth weight infants: a randomized trial. *Journal of Neonatal-Perinatal Medicine* 2013; 6:285-94

  Polberger S, Axelsson I, Räihä N. Growth of very low birth weight infants on varying amounts of human milk protein. *Pediatric Research* 1989; 25:414-9

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  - Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. *BMC Pediatr*. 2014;14:216.
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  - Pediatric Nutrition Practice Group, Steele C, Collins E. Infant and Pediatric Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities. Chicago 2018.

- Preterm Infant (VLBW) Enteral Nutrition
- Preterm Infant (VLBW) Enteral Nutrition Guideline (2017-2020)

Quick Links

Recommendations Summary

VLBW: Type of Fat (2020)

Click here to see the explanation of recommendation ratings (Strong, Fair, Weak, Consensus, Insufficient Evidence) and labels (Imperative or Conditional). To see more detail on the evidence from which the following recommendations were drawn, use the hyperlinks in the Supporting Evidence Section below.

- Recommendation(s)

  VLBW: Type of Fat

  Health care practitioners should not routinely supplement additional enteral long chain fatty acids [docosahexaenoic acid (DHA), eicosapantaenoic acid (EPA), and arachidonic acid (AA)] for very low birthweight (less than or equal to 1, 500g at birth) preterm infants. If health care practitioners choose to supplement additional omega-3, then AA should also be provided. Current evidence does not suggest consistent benefits with enteral long chain fatty acid supplementation.

  Rating: Fair
  Imperative

  - Risks/Harms of Implementing This Recommendation

    Routine supplementation of long chain omega-3 fatty acids (i.e. DHA and EPA) via enteral nutrition without supplementation of arachidonic acid may impair growth in exclusively formula-fed very low birth weight preterm infants.

  - Conditions of Application

    This recommendation applies to very low birth weight (less than or equal to 1, 500g birth weight) preterm infants. Healthcare practitioners should use professional expertise and individual assessment prior to prescribing enteral long chain omega-3 supplementation. Formula-fed preterm infants receiving docosahexaenoic acid (DHA) supplementation should also be supplemented with arachidonic acid (AA).

  - Potential Costs Associated with Application

Enteral supplementation of long chain omega-3 fatty acids or formula fortified with long chain omega-3 fatty acids may increase formulary cost.

Implementation Considerations

When considering a DHA supplement, clinicians should also consider the AA content and the presence of other ingredients, such as vitamin A and vitamin D. Avoid use of cod liver oil as a source of DHA, as it is prone to heavy metal and environmental toxin contamination.

- Recommendation Narrative

  Clinicians and parents question the type and amount of fat a preterm infant should receive. Observational research indicates that changes in the fatty acid profile of preterm infants from fetal or birth levels have been associated with neonatal morbidity and subsequent negative cardiometabolic and neurodevelopmental outcomes (Martin et al., 2011; Panagos et al., 2016) . It is accepted by most clinicians and parents that preterm infants would benefit from enteral fat sources that are rich in long chain omega-3 fatty acids.

  A systematic review was conducted to determine the effect of type of fat intake on preterm infant outcomes. A total of 14 randomized controlled trials were included in the review. All included studies evaluated the impact of DHA and EPA intake amongst human milk-fed and formula-fed infants. There is high-certainty evidence that the long chain omega-3 fatty acid intake does not have an effect on mortality, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, or gastrointestinal health. There is moderate certainty that long chain omega-3 fatty acids does not have an effect on mental development or IQ by seven years of age. There is low certainty that long chain omega-3 fatty acids does not have an effect on anthropometrics, visual acuity, or adverse events. There was low-certainty evidence that long chain omega-3 supplementation in formula -fed infants for four months to five months may have lower weight compared to usual care. These infants were formula fed and not supplemented with arachidonic acid.

  Results of the systematic review failed to demonstrate substantial health benefits for supplementation of long chain omega-3 fatty acids. Lack of effect may be due to ineffective delivery strategies rather than the importance of the type of fat. Studies were heterogenous and spanned a long period of time, during which health care interventions changed.

- Recommendation Strength Rationale

  - High certainty evidence (Grade I) for mortality, necrotizing enterocolities, retinopathy of prematurity, feeding tolerance and sepsis.
  - Moderate certainty evidence (Grade II) for bronchopulmonary disease and neurodevelopment.
  - Low certainty evidence (Grade III) for atopy (hay fever), visual acuity, weight gain, lenght gain, head circumference and adverse effects.

- Minority Opinions

  Consensus reached.

- Supporting Evidence

  The recommendations were created from the evidence analysis on the following questions. To see detail of the evidence analysis, click the blue hyperlinks below (recommendations rated consensus will not have supporting evidence linked).

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on mortality?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on necrotizing enterocolitis?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on bronchopulmonary disease?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on retinopathy of prematurity?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on atopy (hay fever)?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on neurodevelopment?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on visual acuity?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on feeding tolerance?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on weight gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on length gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on head circumference?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on sepsis?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of fat via enteral nutrition on adverse effects?

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Makrides M, Gibson R, McPhee A, Collins C, Davis P, Doyle L, Simmer K, Colditz P, Morris S, Smithers L, Willson K, Ryan P. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. *The Journal of the American Medical Association* 2009; 301:175-82

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- Preterm Infant (VLBW) Enteral Nutrition
- Preterm Infant (VLBW) Enteral Nutrition Guideline (2017-2020)

Quick Links

Recommendations Summary

VLBW: Human Milk Fortification (2020)

Click here to see the explanation of recommendation ratings (Strong, Fair, Weak, Consensus, Insufficient Evidence) and labels (Imperative or Conditional). To see more detail on the evidence from which the following recommendations were drawn, use the hyperlinks in the Supporting Evidence Section below.

- Recommendation(s)

  VLBW: Human Milk Fortification

  Healthcare practitioners should fortify human milk fed to very low birth weight preterm infants because fortification increases weight gain and head circumference growth compared to human milk alone.

  Rating: Weak
  Imperative

  - Risks/Harms of Implementing This Recommendation

    Very low birth weight (VLBW) preterm infants receiving human milk fortification in comparison to human milk alone experienced improved growth in hospital (weight gain and head circumference) and post discharge (weight, length, and head circumference). No potential risks or harms (including necrotizing enterocolitis) were identified with human milk fortification.

  - Conditions of Application

    Health care practitioners should use professional expertise and individual assessment to select an appropriate human milk fortifier (Ganapathy et al 2012, Guest et al 2017, Knake et al 2019, WHO 2011)

    Implementation Considerations

    - Consider offering human milk fortification to VLBW; preterm infants to improve growth.
    - Evaluate commercially available human milk fortifiers and consider stocking one or more to add to expressed human milk.
    - Provide a suitable area and staff education for safe handling and preparation of enteral feedings (Pediatric Nutrition, Steele, Collins et al 2018)
    - Encourage the development of a feeding protocol that is accepted and used by key stakeholders in the NICU and that specifies when human milk fortification is started, how it is advanced and when it is stopped.

  - Potential Costs Associated with Application

    There is variability in the cost of available human milk fortifiers.

  - Recommendation Narrative

Human milk is the preferred food for nearly all infants, however, fortification is often necessary for VLBW infants (Guest et al 2015, Ramaswamy 2019, Johnston et al 2012). Improved medical care and technology have resulted in improved survival for VLBW preterm infants and an urgency to improve nutrition care for this population. Healthcare practitioners need unbiased guidance on the use of fortifiers, and type of fortifiers for human milk-fed VLBW preterm infants.

Two separate analyses were conducted to evaluate effect of human milk fortification on identified health outcomes. Only studies that evaluated fortifiers with both macronutrients and micronutrients were included in this review.

The first analysis compared infants receiving human milk and fortification vs. human milk alone. No studies were identified that met these criteria and evaluated fortification vs. none and impact on mortality, morbidities, development, gastrointestinal health, bone mineral content, or protein utilization. With regard to growth, evidence with low certainty found that VLBW preterm infants receiving fortification had improved growth in hospital (weight gain and head circumference) and post discharge (weight, length, and head circumference).

The second analysis compared different types of fortifiers (liquid vs. powdered, and varying nutrient content) among VLBW preterm infants. Low-certainty evidence indicated no significant difference between type of fortifier on mortality, necrotizing enterocolitis, sepsis, weight gain or gastrointestinal health. Moderate-certainty evidence indicated that a fortifier with added protein, iron and essential fatty acids decreased the odds of blood transfusions, compared to a standard powdered fortifier. However there was no effect on hematocrit or ferritin levels. Moderate-certainty evidence also indicated that fortifiers with increased protein and micronutrient levels may result in higher blood urea nitrogen (BUN) levels compared to BUN levels when a standard fortifier was fed. Effect of type of fortifier was unable to be analyzed on length and head circumference growth due to heterogeneity and on bone mineral content due to lack of reported data. In summary there was insufficient evidence to recommend one fortifier over another.

Results of the human milk fortification analyses have limitations due to heterogeneity amongst studies, lack of reported data, and lack of information regarding the nutrition composition of the human milk received by study population.

- Recommendation Strength Rationale

  Fortification versus None

  - Limited/weak certainty evidence for weight gain, lenght, gain, and head circumference.

  Type of Fortifier

  - Limited/weak certainty evidence for mortality.
  - Moderate certainty evidence for anemia.
  - Limited/weak certainty evidence for mortality, necrotizing enterocolities and sepsis, weight gain, lenght gain, head circumference, gastrointestinal health, bone mineral content, protein utilization, and adverse events.

- Minority Opinions

  Consensus reached.

- Supporting Evidence

  The recommendations were created from the evidence analysis on the following questions. To see detail of the evidence analysis, click the blue hyperlinks below (recommendations rated consensus will not have supporting evidence linked).

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on morbidities and mortality?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on weight gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on weight gain post discharge?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on length gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on length gain post discharge?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on head circumference?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on head circumference post discharge?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortification vs. none via enteral nutrition on development, gastrointestinal health, bone mineral content, protein utilization or adverse events?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of human milk fortifier type via enteral nutrition on mortality?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on blood transfusions and anemia indices?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on necrotizing enterocolitis or sepsis?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on weight gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on length gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition head circumference gain?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on development?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on gastrointestinal health?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on bone mineral content?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on protein utilization?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of type of human milk fortifier via enteral nutrition on adverse events?

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- Preterm Infant (VLBW) Enteral Nutrition
- Preterm Infant (VLBW) Enteral Nutrition Guideline (2017-2020)

Quick Links

Recommendations Summary

VLBW: Formula Enrichment (2020)

Click here to see the explanation of recommendation ratings (Strong, Fair, Weak, Consensus, Insufficient Evidence) and labels (Imperative or Conditional). To see more detail on the evidence from which the following recommendations were drawn, use the hyperlinks in the Supporting Evidence Section below.

- Recommendation(s)

  VLBW: Formula Enrichment

  When human milk is not available, healthcare practitioners should provide very low birthweight (less than or equal to 1, 500g) preterm infants with preterm infant formulas that provide higher nutrient density than standard infant formula. Nutrient-dense preterm formulas appear to more closely match the nutritional needs of very low birthweight preterm infants and long clinical experience with preterm formulas suggests that they support good growth, and both functional, and biochemical measures of nutritional adequacy.

  Rating: Consensus
  Conditional

  - Risks/Harms of Implementing This Recommendation

    No undesirable effects were found which could be due to limited evidence.

  - Conditions of Application

    This recommendation is limited to scenarios when human milk is not available in sufficient supply. This recommendation is in reference to preterm infant formulas that generally provide 68 kcal to 100 kcal per 100 ml, protein-enriched (2.0g to 3.0g per 100 ml) (2.9 to 3.3 /100 kcal) and enriched with minerals, vitamins, electrolytes, and trace elements (Young et al, 2012).

    Implementation Considerations

    Practitioners should work with the multidisciplinary care team to ensure that preterm infant formulas within the hospitalâ€™s formulary meet Life Sciences Research Office (LSRO) criteria for protein, calcium and phosphorus content (Klein 2002; Klen 2005).

    When motherâ€™s own milk is not available health care practitioners should provide preterm formula to very low birthweight preterm infants until hospital discharge. The multidisciplinary care team should evaluate the infantâ€™s gestational age, growth, nutritional status and overall nutrient intake prior to recommending continuation of preterm formula post-discharge. Infants on preterm infant formula with extended stays in the hospital who approach term age or size (more than three kilograms) should have an evaluation by the multidisciplinary care team to assure that nutrient intakes are not exceeding tolerable upper levels.

  - Potential Costs Associated with Application

    Costs of preterm formula will vary upon location and health care policies.

  - Recommendation Narrative

    Formula enrichment comparisons were evaluated in the very low birthweight (VLBW) preterm infant systematic reviews process. No randomized control trials that compared standard formulas to preterm infant formulas (as defined by organizations such as the Life Science Research Organization for preterm and standard term formulas) were identifed in the VLBW preterm infant formula enrichment systematic review.

    The workgroup examined and compared reliable resources for nutrient recommendations for preterm infant formulas. The 2002 Life Sciences Research Office (LSRO), 2020 American Academy of Pediatricts (AAP), Nutritonal Care of Preterm Infants (Koletzko 2014), 2010 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommendations were evaluated. The nutrient recommendations for these resources were also compared to the VLBW Peterm Infant Protein Systematic Review. Calcium and phosphorus were not included in the Pre-B VLBW Preterm Infants Systematic Reviews since no studies were identified from the scoping review that met the VLBW preterm infant inclusion criteria.

    Calcium and Phosphorus

    - Recommended calcium content for preterm formulas had the following range:109mg to 185mg per 100 kcal.
    - Recommended phosphorus content for preterm formulas had the following range: 55mg to 109mg per 100 kcal.

    Protein

    - VLBW Preterm Infant systematic review recommends 3.5g to 4.0g per kg per day
    - The LSRO protein recommendations for preterm formula is 2.5g to 3.6g per 100 kcal which at 120kcal per kg would provide a daily intake of 3.0g to 4.3g per kg per day. However, if infants are provided with the lower end of the AAP (110kcal to 130kcal per kg per day) and ESPGHAN (110kcal to 135kcal per day) ranges for energy, LSROâ€™s lower end of their protein recommendation is not likely to provide sufficient protein (110 x 2.5 = 2.8g per kg per day).
    - Protein recommendations for preterm infants from AAP 2020 (3.2g to 4.1g per 100kcal; 4.1g per /100kcal, at 120kcal per kg would provide up to 4.9g per kg) exceed the Pre-B Preterm Recommendations.

    Based on the above assessment, preterm formulas should contain 3.2g to 3.3g of protein per 100kcal.

  - Recommendation Strength Rationale

    Formula enrichment systematic reviews conducted by the preterm team did not identify literature that compared standard vs. preterm formulas for VLBW preterm infants. The consensus statement is based on credible resources and experience from the preterm team.

  - Minority Opinions

    Consensus reached.

- Supporting Evidence

  The recommendations were created from the evidence analysis on the following questions. To see detail of the evidence analysis, click the blue hyperlinks below (recommendations rated consensus will not have supporting evidence linked).

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on weight?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on length, head circumference, skinfold measurements and mid-arm circumference?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on development?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of protein amount via enteral nutrition on bone mineral content or density?

- References
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- Preterm Infant (VLBW) Enteral Nutrition
- Preterm Infant (VLBW) Enteral Nutrition Guideline (2017-2020)

Quick Links

Recommendations Summary

VLBW: Mothers' Milk (2020)

Click here to see the explanation of recommendation ratings (Strong, Fair, Weak, Consensus, Insufficient Evidence) and labels (Imperative or Conditional). To see more detail on the evidence from which the following recommendations were drawn, use the hyperlinks in the Supporting Evidence Section below.

- Recommendation(s)

VLBW: Mother's Milk

Health care practitioners should provide fortified mother's milk, when available, to VLBW (less than or equal to 1, 500g) preterm infants. Mother's own milk intake is associated with lower odds of retinopathy of prematurity when compared to exclusive formula, and there is evidence of a negative dose-response relationship with sepsis and a positive dose-response relationship with Bailey development scores.

Rating: Fair
Conditional

- Risks/Harms of Implementing This Recommendation

  No undesirable effects were found which could be due to limited evidence.

- Conditions of Application

  This recommendation is limited to scenarios in which mother's own milk is available. In addition, this review compared formula to mother's milk that was fortified.

- Potential Costs Associated with Application

  The costs of supporting motherâ€™s provision of their own milk to their infants, will be balanced against the costs of pasteurized donor human milk or formula. The balance between these costs is not clear and has not been addressed systematically in the literature.

- Recommendation Narrative

  Many studies, as well as international health organizations, agree that mother's milk is associated with improved infant health outcomes. Two systematic reviews were conducted to evaluate available evidence for mothersâ€™ milk intake for VLBW preterm infants in developed nations.

  The first systematic review evaluated a minimum of 75% intake from m mother's milk in comparison to exclusive formula and association with identified outcomes among VLBW preterm infants. All systematic reviews outcomes had Grade III evidence (limited or weak) and were based on observational non-randomized studies. No significant differences were found between groups for mortality, necrotizing enterocolitis (NEC), sepsis, bronchopulmonary dysplasia, anthropometrics (weight, length, head circumference, fat free mass, or skinfold measurements), protein utilization, or visual acuity. No studies were identified that evaluated association with gastrointestinal health or bone mineral content. Infants fed mother's milk, however, were associated with lower incidence of retinopathy of prematurity (ROP), in comparison to those fed formula.

  The second systematic review evaluated dose-response of higher vs. lower mother's milk and association with identified health outcomes among VLBW preterm infants. Remaining intake was supplemented with formula in the study populations. The majority of reviews for identified outcomes also resulted in Grade III evidence (limited or weak) and were based on observational non-randomized studies. One study was identified that evaluated mortality, however, it was within a composite score that combined mortality, NEC, and sepsis. Infants who received more than 50% of intake from mother's milk the first and second five days of life had a decreased

hazard of the composite of mortality, NEC, and sepsis by 60 days, and a weaker effect was seen for mother's milk intake of 50% or less vs. none. No significant differences between groups were found for total infection, ROP, NEC (outside composite score), or anthropometrics, all Grade III evidence. A negative dose-response association was found for sepsis [Grade II evidence (fair)], and positive dose-response association was found for Bailey development scores (Grade III evidence).

The benefits associated with mothersâ€™ milk intake may be attributed to confounding factors or social determinants of health. Three specific associated benefits for mothersâ€™ milk were found (decreased ROP and sepsis, and increased Bailey scores), however, these findings were from studies where mothersâ€™ milk was fortified, and each study had risks of bias. Practitioners must exercise caution when making recommendations for mother's milk, in order to prevent promotion of mother's milk as the only option, increased pressure on mothers, or internet milk sharing. Ultimately, healthcare practitioners need to support parents to create healthy environments.

- Recommendation Strength Rationale

  Mothers' Milk vs. Formula

  - Limited/weak certainty evidence (Grade III) for mortality, necrotizing enterocolitis, sepsis, bronchopulmonary disease, retinopathy of prematurity, weight gain, fat free mass, head circumference, protein utilization, skinfold measurment, visual acuity, lenght gain, and BUN.

  Mother's Milk Dose Response.

  - Moderate certainty evidence (Grade II) for sepsis.
  - Limited/Weak certainty evidence (Grade III) for mortality, total infections, retinopathy of prematurity, sepsis, necrotizing enterocolitis, bronchopulmonary dysplagia, anthropometrics, neurodevelopment, gastrointestional function.

- Minority Opinions

  Consensus reached.

- Supporting Evidence

  The recommendations were created from the evidence analysis on the following questions. To see detail of the evidence analysis, click the blue hyperlinks below (recommendations rated consensus will not have supporting evidence linked).

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula intake and mortality?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mothers' milk intake vs. exclusive formula and necrotizing enterocolitis?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula and sepsis?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula and bronchopulmonary disease??

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula and retinopathy of prematurity?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula and weight gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula intake and fat mass and fat free mass?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula intake on head circumference?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula intake and gastrointestinal health or bone mineral content?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mothers' milk intake vs. exclusive formula intake and protein utilization?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula intake and skinfold measurement?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula intake and visual acuity?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mother's milk intake vs. exclusive formula intake on length gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% mothers' milk intake vs. exclusive formula intake and BUN?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mothers' milk dose response and mortality?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mother's milk dose-response and total infections?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mother's milk dose-response and retinopathy of prematurity?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mother's milk dose-response and sepsis?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mothers' milk dose response and necrotizing

enterocolitis?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mothers' milk dose response and bronchopulmonary dysplasia?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mothers' milk dose response and anthropometric measurement?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mothers' milk dose response and neurodevelopment?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between mothers' milk dose response and time to full enteral feeding?

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- Preterm Infant (VLBW) Enteral Nutrition
- Preterm Infant (VLBW) Enteral Nutrition Guideline (2017-2020)

Quick Links

Recommendations Summary

VLBW: Human Milk (Mother's and Donor) (2020)

Click here to see the explanation of recommendation ratings (Strong, Fair, Weak, Consensus, Insufficient Evidence) and labels (Imperative or Conditional). To see more detail on the evidence from which the following recommendations were drawn, use the hyperlinks in the Supporting Evidence Section below.

- Recommendation(s)

VLBW: Human Milk (Mother's and Donor)

Health care practitioners should provide fortified human milk regardless of source (mother's or donor) to very low birth weight (less than or equal to 1, 500g) infants when available. Growth should be monitored by practitioners and the nutrition care plan should be adjusted as appropriate.

Rating: Weak
Conditional

- Risks/Harms of Implementing This Recommendation

  Results of the systematic review indicate that VLBW preterm infants who received at least 75% human milk had less weight gain compared to infants who received formula exclusively. Results of the review also indicate that infants receiving human milk had less absolute nitrogen retention.

- Conditions of Application

  This recommendation is limited to scenarios in which motherâ€™s own milk or donor milk is available.

- Potential Costs Associated with Application

  Some studies have shown no difference in total cost between donor milk and formula. However, cost comparison likely differs by institution, region, country, cost of donor milk, rate of necrotizing enterocolities (NEC), and the cost of NEC for a specific institution (Treng et al 2018, Fengler et al 2019, Buckle and Taylor 2017).

  Implementation

  Practitioners should use a multidisciplinary approach when implementing donor human milk programs in Neonatal Intensive Care Units. Implementation teams should consider development of policies and protocols, and a process for tracking human milk. The Food and Drug Administration (FDA) recommend against feeding infants donor milk obtained directly from individuals or the internet. Donor milk should only be obtained from a source that has screened its milk donors and taken other precautions to ensure safety such as the Human Milk Banking Association of North America (FDA, 2018).

- Recommendation Narrative

  Many studies and international and national organizations promote motherâ€™s own milk, or donor milk when motherâ€™s milk is not available for VLBW preterm infants (WHO 2011, ESPGHAN 2013, Committee on Nutrition 2017). Two systematic reviews were conducted to evaluate available evidence for human milk (motherâ€™s own or donor) intake for VLBW preterm infants in developed nations.

  The first systematic review evaluated 75% intake or more from human milk, in comparison to exclusive formula and association with identified outcomes. Each of the conducted systematic reviews resulted in Grade III evidence (limited or weak). No evidence was found for mortality, gastrointestinal health, bone mineral content or development. The systematic review on morbidities identified one prospective multicenter cohort study, which found that infants who received infant formula, compared to infants who received human milk exclusively, had higher risk of bronchopulmonary disease, retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC). The systematic review on weight found that human milk-fed infants had less weight gain than formula-fed infants. Human milk-fed infants were also found to have less nitrogen retention than formula fed infants. The remaining reviews did not find a significant difference in length, head circumference, or skin-fold measurements.

The second systematic review evaluated dose-response of higher vs. lower human milk intake and association with identified health outcomes. No evidence was found meeting systematic review criteria except for weight gain. Higher portions of fortified human milk resulted in greater decreases in weight *Z*-scores from birth to discharge.

- Recommendation Strength Rationale

  Low certainty evidence (grade III): ROP, NEC, and BPD; Anthropometrics; Protein Utilization

- Minority Opinions

  Consensus reached.

- Supporting Evidence

  The recommendations were created from the evidence analysis on the following questions. To see detail of the evidence analysis, click the blue hyperlinks below (recommendations rated consensus will not have supporting evidence linked).

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% human milk (mothers' and donor) intake vs. exclusive formula intake and ROP, NEC, and BPD ?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% human milk (mothers' and donor) intake vs. exclusive formula intake and weight?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% human milk (mothers' and donor) intake vs. exclusive formula intake and length, head circumference and skin-fold measurements?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between greater than or equal to 75% human milk (mothers' and donor) intake vs. exclusive formula intake and protein utilization?

  In VLBW preterm infants (less than or equal to 1.500g at birth), what is the association between greater than or equal to 75% human milk (mothers' and donor) intake vs. exclusive formula intake and mortality, GI health, bone mineral content, and development?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between human milk (mothers' and donor) dose response and weight gain?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the association between human milk (mothers' and donor) dose response and mortality, morbidities, development, GI health, or protein utilization?

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- Preterm Infant (VLBW) Enteral Nutrition
- Preterm Infant (VLBW) Enteral Nutrition Guideline (2017-2020)

Quick Links

Recommendations Summary

VLBW: Mother's Milk Supplementation (2020)

Click here to see the explanation of recommendation ratings (Strong, Fair, Weak, Consensus, Insufficient Evidence) and labels (Imperative or Conditional). To see more detail on the evidence from which the following recommendations were drawn, use the hyperlinks in the Supporting Evidence Section below.

- Recommendation(s)

  VLBW: Mothers' Milk Supplementation

  When quantity of mothersâ€™ milk is insufficient, health care practitioners should supplement VLBW (less than or equal to 1, 500g) preterm infants with donor milk during the time that the infant is at high risk for necrotizing enterocolitis (NEC). VLBW preterm infants fed mother's own milk supplmented with donor milk had a lower risk of NEC compared to those fed mother's own milk supplemented with formula.

  Rating: Fair
  Conditional

  - Risks/Harms of Implementing This Recommendation

    VLBW preterm infants supplemented with donor milk vs. formula may have a higher risk of cognitive neuroimpairment, according to post-hoc exploratory analysis of data from an RCT conducted by Oâ€™Connor and colleagues (O'Connor et al 2016). However, meta-analysis of this and other studies did not show a significant difference in neurodevelopment (Quigley et al 2018).

    VLBW preterm infants supplemented with donor milk vs. formula may have lower short-term growth rates in weight, length, and head circumference, according to Cochrane analysis (Quigley et al 2018).

  - Conditions of Application

    This recommendation is limited to scenarios in which motherâ€™s milk for VLBW preterm infants is limited, and donor milk is available to supplement.

  - Potential Costs Associated with Application

    Some studies have shown no difference in total cost between donor milk and formula. However, cost comparison likely differs by institution, region, country, cost of donor milk, rate of NEC, and the cost of NEC for a specific institution (FDA 2018, Trang et al 2018, Fengler et al 2019)

    Implementation Considerations

    Practitioners should use a multidisciplinary approach when implementing donor human milk programs in Neonatal Intensive Care Units. Implementation teams should consider development of policies and protocols, and a process for tracking human milk. Furthermore, practitioners should work with the multidisciplinary team to develop an institutional protocol regarding the time period when VLBW preterm infants are at highest risk for NEC and need for donor milk supplementation.

    The Food and Drug Administration (FDA) recommend against feeding infants donor milk obtained directly from individuals or the Internet. Donor milk should only be obtained from a source that has screened its milk donors and taken other precautions to ensure safety such as the Human Milk Banking Association of North America (Buckle and Taylor 2017).

  - Recommendation Narrative

    Many studies, and international health organizations agree that mother's milk is associated with improved infant health outcomes (WHO 2015, Eidelman 2012). However, VLBW preterm infants that receive motherâ€™s milk will potentially require supplementation. Increased awareness of the benefits of human milk has led to increased use of donor milk. The Human Milk Banking Association of North America reported a 12 percent increase in distribution of donor human milk from 2017 to 2018 (Human Milk Banking Association of North America, 2020). A systematic review was conducted to compare supplementation of motherâ€™s milk-fed VLBW preterm infants with donor milk vs. formula. A decreased risk of NEC was found in infants receiving 58% to 89% intake from motherâ€™s own milk supplemented with human milk vs. formula. No difference was found in the remaining evaluated outcomes: Mortality, retinopathy of prematurity, sepsis, bronchopulmonary disease, growth, or body composition. One randomized controlled trial with low risk of bias was identified in the systematic review that compared impact of formula supplementation vs. donor supplementation on neurodevelopment when the motherâ€™s milk supply was not sufficient. No difference was found on Bayley Development scores after 18 months, however, this did result in a higher risk of cognitive neuroimpairment.

  - Recommendation Strength Rationale

    - High certainty evidence for mortality, necrotizing enterocolitis, retinopaty of prematurity, sepsis, weight gain, lenght gain, head circumference.
    - Moderate certainty evidence for bronchopulmonary disease.
    - Low/weak certainty evidence for body composition, neurodevelopment, gastrointestinal health, bone mineral content.

  - Minority Opinions

    Consensus reached.

- Supporting Evidence

  The recommendations were created from the evidence analysis on the following questions. To see detail of the evidence analysis, click the blue hyperlinks below (recommendations rated consensus will not have supporting evidence linked).

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula intake on mortality?

  In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on late onset sepsis, NEC and ROP?

  In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on weight?

  In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on length?

  In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on head circumference?

In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on feeding tolerance?

In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on bone mineral content?

In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on protein utilization?

In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of greater than or equal to 75% donor milk intake vs. exclusive formula on development?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on mortality?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on nectorizing enterocolitis?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on retinopathy of prematurity?

In VLBW preterm infants (less than or equal to 1,500g at birth) what is the effect of supplementation of mothers' milk with donor milk versus formula on sepsis?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on bronchopulmonary disease?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on weight gain?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on length gain?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on head circumference?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on body composition?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on neurodevelopment?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on gastrointestinal health?

In VLBW preterm infants (less than or equal to 1,500g at birth), what is the effect of supplementation of mothers' milk with donor milk vs. formula on bone mineral content?

- References

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