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Enteral Nutrition in Preterm Infants (2022): A Position Paper from the ESPGHAN Committee on Nutrition and invited experts

Short title: Enteral Nutrition in Preterm Infants: ESPGHAN Position Paper 2022

1. Nicholas David **Embleton**, Newcastle Hospitals NHS Trust and Newcastle University, Newcastle upon Tyne, UK
2. Sissel Jennifer **Moltu**, Department of Neonatal Intensive Care, Oslo University Hospital, Norway
3. Alexandre **Lapillonne**, Paris University, APHP Necker-Enfants Malades hospital, Paris, France and CNRC, Baylor College of Medicine, Houston, Texas
4. Chris H.P. **van den Akker**, Department of Pediatrics – Neonatology, Amsterdam UMC – Emma Children's Hospital. University of Amsterdam, Vrije Universiteit Amsterdam, The Netherlands
5. Virgilio **Carnielli,** Polytechnic University of Marche and Division of Neonatology, Ospedali Riuniti, Ancona, Ancona, Italy.
6. Christoph **Fusch**, Department of Pediatrics, Nuremberg General Hospital, Paracelsus Medical School, Nuremberg, Germany; Division of Neonatology, Department of Pediatrics, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada
7. Konstantinos **Gerasimidis**, Human Nutrition, School of Medicine, Dentistry and Nursing, University of Glasgow, New Lister Building, Glasgow Royal Infirmary, Glasgow, UK

8. Johannes B. **van Goudoever**, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Emma Children's Hospital, Amsterdam, The Netherlands. ORCID 0000-0003-3960-1703
9. Nadja **Haiden**, Medical University of Vienna, Department of Clinical Pharmacology, Austria
10. Silvia **Iacobelli**, Réanimation Néonatale et Pédiatrique, Néonatologie – CHU La Réunion, Saint-Pierre, France
11. Mark J. **Johnson**, Department of Neonatal Medicine, University Hospital Southampton NHS Trust, Southampton, UK, and National Institute for Health Research Biomedical Research Centre Southampton, University Hospital Southampton NHS Trust and University of Southampton, Southampton, UK
12. Sascha **Meyer**, University Hospital of Saarland, Department of General Paediatrics and Neonatology, Homburg, Germany
13. Walter **Mihatsch**, Department of Pediatrics, Ulm University, 89075 Ulm, Germany and Department of Health Management, Neu-Ulm University of Applied Sciences, 89231 Neu-Ulm, Germany
14. Miguel Saenz de **Pipaon,** La Paz University Hospital, Autonoma University of Madrid, Department of Pediatrics-Neonatology, Madrid, Spain
15. Jacques **Rigo,** Neonatal Unit, University of Liège, CHR Citadelle, Blvd du 12e de Ligne 1, 4000 Liège, Belgium
16. Gitte **Zachariassen**, H.C. Andersen Children's Hospital, Odense University Hospital and University of Southern Denmark, Odense, Denmark
17. Jiri **Bronsky**, Department of Paediatrics, University Hospital Motol, Prague, Czech Republic

18. Flavia **Indrio**, Department of Medical and Surgical Sciences, University of Foggia, Italy
19. Jutta **Köglmeier**, Department of paediatric Gastroenterology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
20. Barbara **de Koning**, Paediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherland
21. Lorenzo **Norsa**, Paediatric Hepatology Gastroenterology and Transplantation, ASST Papa Giovanni XXIIII, Bergamo, Italy
22. Elvira **Verduci**, Department of Health Sciences, University of Milan; Department of Paediatrics, Ospedale dei Bambini Vittore Buzzi Milan, Italy
23. Magnus **Domellöf**, Department of Clinical Sciences, Paediatrics, Umeå University, Umeå, Sweden

* ***Correspondence***: Prof Nicholas D Embleton, Ward 35 Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK nicholas.embleton@ncl.ac.uk +44 191 2825034

Chair of CoN: Magnus Domellöf; Secretary of CoN: Jiri Bronsky

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Abbreviations

AGA	Appropriate for gestational age
ALA	Alpha-linolenic acid
ARA	Arachidonic acid
BMC	Bone mineral content
BMDP	Bone mineral deficiency of prematurity
BPD	Bronchopulmonary dysplasia
Ca	Calcium
CA	Corrected age
Cl	Chloride
CMV	Cytomegalovirus
CPAP	Continuous positive airways pressure
DHA	Docosahexaenoic acid
DHM	Donor human milk
EFSA	European Food Safety Authority
EN	Enteral nutrition
FGR	Fetal growth restriction
FM	Fat mass
FFM	Fat-free mass
GF	Growth faltering

GPP	Good practice point
GOR	Grade of Recommendation (A-C)
GR	Gastric residual
HC	Head circumference
HM	Human milk
HMOs	Human milk oligosaccharides
IU	International units
IUGR	In-utero growth restriction
K	Potassium
LA	Linoleic acid
LOE	Level of evidence (1-4)
MEF	Minimum enteral feeding
Mg	Magnesium
MOM	Mother's own milk
N	Nitrogen
Na	Sodium
NEC	Necrotizing enterocolitis
NG	Nasogastric
OG	Orogastric
PER	Protein:energy ratio
P	Phosphorus
PN	Parenteral Nutrition
PUFA	Polyunsaturated fatty acid
RCT	Randomised controlled trial
REE	Resting energy expenditure

ROP	Retinopathy of prematurity
SD	Standard deviation
SGA	Small for gestational age
VLBW	Very low birthweight
WHO	World Health Organisation

Abstract

Objectives

To review the current literature and develop consensus conclusions and recommendations on nutrient intakes and nutritional practice in preterm infants with birthweight <1800g.

Methods

The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee of Nutrition (CoN) led a process that included CoN members and invited experts. Invited experts with specific expertise were chosen to represent as broad a geographical spread as possible. A list of topics was developed, and individual leads were assigned to topics along with other members, who reviewed the current literature. A single face-to-face meeting was held in February 2020. Provisional conclusions and recommendations were developed between 2020-2021, and these were voted on electronically by all members of the working group between 2021-2022. Where >90% consensus was not achieved, online discussion meetings were held, along with further voting until agreement was reached.

Results

In general, there is a lack of strong evidence for most nutrients and topics. The summary paper is supported by additional supplementary digital content that provide a fuller explanation of the literature and relevant physiology: Introduction and overview; human milk reference data; intakes of water, protein, energy, lipid, carbohydrate, electrolytes, minerals, trace elements, water soluble vitamins, and fat soluble vitamins; feeding mode including mineral enteral feeding, feed advancement, management of gastric residuals, gastric tube placement and bolus or continuous feeding; growth; breast milk buccal colostrum, donor human milk, and risks of cytomegalovirus infection; hydrolysed protein and osmolality; supplemental bionutrients; and use of breastmilk fortifier.

Conclusions

We provide updated ESPGHAN CoN consensus-based conclusions and recommendations on nutrient intakes and nutritional management for preterm infants

What is known

- Nutrient intakes and nutritional practices have a major impact on short-term morbidities and long-term outcomes
- The available literature has expanded dramatically in the 12 years since the previous The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) position paper was developed

What is new

- We provide an expert consensus on conclusions and recommendations for nutrient intakes and nutritional practices for preterm infants with a birthweight of <1800g
- We provide recommendations that can be used in clinical practice, but highlight the lack of strong evidence in several topic areas and the need for further high-quality research especially studies that assess long-term functional outcomes

Introduction

The Committee of Nutrition (CoN) of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recognised the need to provide an update of the previous position paper on enteral nutrition for preterm infants and this was approved by the ESPGHAN council in 2019. The working group was coordinated by members of CoN but recognised the benefit of including additional experts. An initial planning meeting was held as in Oslo in March 2019, at which potential topics were discussed and a provisional list of sections were developed. A lead writer was assigned to each chapter to initiate literature reviews and write the first drafts. We met in Amsterdam in February 2020 at which broad consensus was achieved for most topics. Literature searching and review commenced in 2019 and continued until December 2020. Conclusions and recommendations were graded according to level of evidence (LOE) and grade of recommendation (GOR), and all received >90% consensus (1, 2) *(see supplementary digital content, SDC no.1, http://links.lww.com/MPG/C974* for further details on methods*).*

This paper provides evidenced informed conclusions and recommendations for clinicians, and EPSGHAN CoN consider this to be a position paper derived by expert consensus. The lack of strong and robust data in many areas imply we do not consider it to be a robust guideline to be adopted without consideration for local contexts and individual infants. We recognise multiple situations where variation in clinical practice is likely to be appropriate and strongly support the need for further research that might reasonably test or study nutrient intakes or nutritional strategies that differ from our current position. We strongly support the use of human milk and recognise that the variation in nutrient density and absorption make precise recommendations for supplements or fortifiers challenging. We also recognise the need to provide lactation support and hospital policies, guidelines and environments that enable the provision of mother's own milk. We provide justification for our assumptions of the average content of

human breastmilk in *SDC no.2*. Neonatal nutrition research is extremely active, and it is likely that alternative approaches and recommendations may be preferable as our knowledge expands over the next 10 years. ESPGHAN is not responsible for the practices of physicians or other healthcare professionals and provides position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of the healthcare provider.

Water *(see supplementary digital content no.3, http://links.lww.com/MPG/C974)*

Water is the major constituent of the human body and a key component of enteral nutrition, as an essential carrier for nutrients and metabolites. Preterm infants have high fluid requirements due to immature renal function, high water losses, higher surface area to body volume ratio, and because fluid needs are proportional to growth rates.

Determining water requirements is difficult, since a certain volume of water is needed both to maintain body homeostasis, cardiovascular and kidney function, and to provide adequate nutritional intake. These volumes may not be equal, depending on the individual clinical situations and dietary needs. The optimal water intake may also differ depending on macronutrient intakes as higher intakes of protein likely requiring higher fluid intakes. Furthermore, the composition of milk feeds (fortification/formula) affects milk osmolality and the renal load, the latter may be a further factor in determining fluid intakes in preterm infants with limited renal concentration ability and excretory capacity (3). Although prospective studies have demonstrated improved growth with feed volumes up to 200 mL/kg/d (4, 5) caution should be taken in high intake volumes, especially in infants with chronic lung disease or large patent arterial duct. Very few studies have explored outcomes in infancy.

Conclusions, Recommendations

C1: Water requirements show considerable inter- and intra-individual variation, especially in preterm infants **LOE 2++**

C2: Water volume needed to maintain body homeostasis, cardiovascular and kidney function may be different from the volume needed to provide adequate nutrient intakes **LOE 3**

C3: In fully enterally fed preterm infants, water balance, hydration status and renal function should be regularly assessed and considered for the administration of fluid intake **LOE 2++**

R1: Most stable growing infants will require fluid intakes of 150-180 mL/kg/d to achieve appropriate nutrient intakes. **GOR B**

R2: If nutrition needs can be met, fluid intake as low as 135 ml/kg/d may be considered safe to maintain body homeostasis and avoid renal compromise. **GPP**

R3: In individual preterm infants, enteral fluid intakes up to 200 ml/kg/d may be appropriate and safe depending on current clinical status. **GPP**

Energy *(see supplementary digital content no.4, http://links.lww.com/MPG/C974)*

Energy is required by all cells of the body. Energy supply needs to meet resting energy expenditure (REE), plus the requirements of any physical activity, diet induced thermogenesis, and importantly for preterm infants, tissue deposition (growth) (6). Since REE measurements in healthy growing preterm infants also include 1-1.2 kcal/kg weight gain (7), REE is directly related to growth rate. Accumulating evidence suggest that REE in preterm infants is around 35-60kcal/kg/day when full enteral feeds are reached at around 2-4 weeks of age, rising with postnatal age up to 55-70kcal/kg/day (8-13). Meta-analysis of these data suggests a range for REE of 60-70kcal/kg/day, depending on growth rate.

Energy for growth represents energy deposition, and this will vary according to the composition of weight gain, with protein and fat deposition representing 5.65 and 9.25kcal respectively per gram of tissue. The estimated average energy requirements for growth are ~3.6-4.7 kcal/g (14, 15), plus REE. Therefore, to achieve 17-20g/kg/day weight gain, and assuming the composition of that weight gain is 13% protein and 20-30% fat, the metabolizable energy needed for growth based on an REE of 60-70kcal/kg/day would be 106-138kcal/kg/day. Allowing for energy lost in stool (5-10%) (16, 17), this equates to a total

energy intake of approximately 115-160kcal/kg/day, regardless of feed type. The upper limit is slightly higher than the 110-135kcal/kg/day recommended in 2010 (18), though is extrapolated from higher rates of growth and fat deposition. A range of 115-140kcal/kg/day is sufficient for adequate growth, and fits with data from RCTs of formula milk or fortifiers (19-25) and cohort studies aimed at implementing the previous recommendations in clinical practice (5, 26-35).

A key challenge in determining energy requirements is the interdependence of the energy fractions provided by the respective macronutrients. Delivery of a protein:energy ratio (PER) which enables accretion of fat free mass (FFM) and fat mass (FM) in the appropriate proportions might have implications for long-term health (36, 37). Studies suggest that the optimal enteral PER for preterm infants is 2.8 - 3.6g/100kcal (19, 38), with PERs at the higher end of this range associated with improved weight gain and FFM accretion. The use of this ratio is however only meaningful if energy and protein intakes are within the recommended ranges. At equal protein and energy intakes, carbohydrate may result in higher nitrogen retention compared with fat (39, 40) although this may be due to differences in absorption rates. Hence, the relative proportion of the macronutrients in the diet also need to be considered.

Since recommendations for energy intake depend on growth targets, we base our recommendations on the aim of supporting growth, body composition and nutrient retention like the in-utero fetus (18), whilst acknowledging that nutritional needs are different in the ex-utero environment. It is important to underline that these recommendations do not consider changes in energy needs related to acute illness or chronic disease states.

Conclusions, Recommendations

C1: The REE for healthy, growing very preterm infants is approximately 60-70 kcal/kg/day

LOE 1+

C2: Metabolizable energy intake needs to meet REE plus the energy needed for growth, adjusted for energy lost in stool. **LOE 1-**

C3: To promote optimal quality of growth and longer-term outcomes, energy intake recommendations also require consideration of the energy fractions provided by the respective macronutrients **LOE 1**

R1: A reasonable range of total energy intake for most healthy growing preterm infants is 115-140kcal/kg/day. **GOR A**

R2: Energy intakes >140kcal/kg/day may be needed where growth is below the recommended range but should not be provided until protein and other nutrient sufficiency has been ensured and should not exceed 160kcal/kg/day. **GOR B**

R3: Provided that energy and protein intakes are within the recommended ranges, a protein to energy ratio of 2.8-3.6g/100kcal is recommended **GOR B**

Protein *(see supplementary digital content no.5, http://links.lww.com/MPG/C974)*

Amino acids are the building blocks for proteins, and selected amino acids have specific functions and are precursors for other metabolites (41, 42). Amino acids that are in excess for protein synthesis capacity are irreversibly oxidised to CO_2 and ammonia, which is detoxified into urea. Protein intake is the main driver of lean body mass growth provided sufficient energy intake. Protein quality is important (43). Human milk contains approximately 25% non-protein nitrogen, but its nutritional role remains unclear.

With the factorial approach it is estimated that protein accretion is ~2.5 g/kg/day in infants weighing 500 g and ~2.2 g/kg/day at a body weight of 1800 g (44). Preterm infants have obligatory nitrogen losses of ~1 g protein/kg/d, and intestinal utilisation of amino acids and suboptimal dietary protein absorption require an additional 0.5 g/kg/d. An extremely preterm neonate requires ~4 g/kg/d of enteral protein of optimal quality to achieve the intrauterine accretion rate (45). The protein content of human milk is variable with ~1 g/100 mL in

mature breastmilk and 1.5-2.0 g/100 mL in colostrum (46-48). This means that a typical intake of 150 to 180 mL/kg/d of unfortified human milk in stable preterm infants will not meet protein requirements.

Several studies have explored optimal protein intakes showing higher growth rates (weight, length and head circumference) with increased protein intakes; however, most are under-powered and, in most studies, actual protein intakes are often estimated rather than directly measured. There is no effect of protein intake on key neonatal morbidities or growth outcomes in infancy, and variation in study designs and reporting make meta-analyses challenging.

There are no easy methods to determine optimal protein intakes for individual infants. Whilst there is a strong correlation between protein intake and plasma urea it is unclear whether plasma urea concentration provides information on protein synthesis.

In addition to being important for growth, individual amino acids may have selective functions. These include glutamine (immune function), arginine (gut health), and taurine (brain development), although extra administration of these individual amino acids has not been shown to result in clinical benefits.

Conclusions, Recommendations

C1: Protein content of human milk decreases rapidly over time, from around 1.5-2.0 g/dL before two weeks of age to around 1.0-1.5 g/dL during the weeks thereafter. Donor milk contains around 0.9-1.0 g/dL of protein or less. **LOE 1++**

C2: Based on a factorial approach, an extremely preterm neonate would require around 4.0 g/kg/d of enteral protein of optimal quality to grow at a comparable rate as intrauterine. **LOE 2+**

C3: Several recent RCTs have been performed comparing higher versus more moderate protein intakes, however most of these studies are underpowered and protein intake is

measured imprecisely meaning it is difficult to draw firm conclusions. It seems that enteral protein intakes ranging from 3.5 up to 4.5 g/kg/d are justified to support somatic growth (including head growth), although data on functional outcomes are extremely limited. **LOE 1-**

C4: The evidence for cut-off values of plasma urea concentrations to guide protein intake is very limited and concentrations may be affected by immature glomerular filtration rate as well. Yet, elevated urea concentrations in the absence of fluid or renal derangements indicate that proteins are not fully used for protein synthesis but are oxidised instead. This thus hints at either optimising concomitant nutritional intakes or decreasing protein intake. **LOE 1-**

C5: Separate supplementation of certain extra amino acids (e.g., glutamine, arginine, or taurine) may reduce several neonatal morbidities but data are limited. Whilst arginine appears promising in reducing NEC rates, the number of infants studied remains limited. **LOE 1-**

R1: We strongly recommend very preterm infants are given at least 3.5 to 4.0 g protein/kg/d together with sufficient other macro- and micronutrients. Protein intake may be further increased up to 4.5 g/kg/d where growth is slow, provided protein quality is good, concomitant energy and other micronutrient intakes are optimal, and there are no other causes for suboptimal growth. **GOR A**

R2: We conditionally recommend monitoring plasma urea at regular intervals. Low urea concentrations after the first few weeks of life may indicate enteral protein intakes can be increased up to 4.5 g/kg/d. If urea concentrations are above 5.7 mmol/L (34 mg/dL; or 16 mg N/dL) in the absence of fluid or renal derangements, while providing sufficient concomitant energy, lowering of protein intake should be considered. **GOR C**

R3: No recommendation can be made regarding the use of additional supplementation with glutamine, arginine, or taurine to decrease neonatal morbidities. **GOR B**

Lipids *(see supplementary digital content no.6, http://links.lww.com/MPG/C974)*

Dietary fats provide about 50% of the energy needs of preterm infants as well as essential polyunsaturated fatty acids (PUFAs), lipid soluble vitamins, and complex lipids. Human milk (HM) is a suspension of fat globules with a variable fat concentration of about 3.2-4 g/100mL. The core of the milk fat globule (MFG) consists of 98-99% triglycerides surrounded by a membrane of phospholipids, cholesterol and other highly active bioactive components (49). About 15-20% of FAs in HM are PUFAs (50, 51). The balance of the essential and conditionally essential PUFAs to each other is important because these FAs compete for desaturases and elongases in the PUFA conversion pathways.

Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are actively transferred through the placenta during the 3rd trimester of pregnancy and brain accumulation is considerable (52, 53). Many studies show a decrease in ARA and DHA levels in preterm infants after birth suggesting insufficient endogenous synthesis from the essential FAs linoleic acid (LA) and α-linolenic acid (ALA) (54, 55). ARA and DHA are thus considered conditionally essential in preterm infants. Reduced concentrations of both ARA and DHA are associated with increased risk of retinopathy of prematurity, septicemia and severe bronchopulmonary dysplasia (49). Data from meta-analysis and RCTs on the effect of DHA supplementation (with or without ARA) on neurodevelopmental and other clinical outcomes show inconsistent results but this may reflect variation in study design and methodology (see SDC 6 for further detail and references). Estimates for lipid needs based on fetal lipid accretion, losses due to fat malabsorption, unavoidable oxidation, and conversion of absorbed to tissue deposited triglyceride are 3.8-4.8 g/kg/d (18). Aiming for dietary fat to provide 45-55% of the energy intake, a minimum supply of 4.8 g/kg/d is required to assure 96 kcal/kg/d of non-protein calories. Mature breast milk fed at 160–180 mL/kg/day will provide a mean fat intake of up to 7 g/kg/d (46, 56) with an upper interquartile range of ~8.1 g/kg/d. These intakes appear safe even in extremely low-birth weight infants (57).

Adding ARA and DHA to enteral feeds are thought to be a reliable way of ensuring adequate supplies of these PUFAs, but both the composition and the mode of administration (enteral or buccal) need to be considered. Providing > 50 mg/kg/d of DHA seems sufficient to obtain DHA concentrations like fetal blood *in utero.* Determining appropriate ARA intakes are demanding because ARA requirements

are less studied than that of DHA, and the endogenous synthesis of ARA is more efficient. Intakes based on the average value observed in human milk of 0.5% of FAs would equal 30 mg/kg/d ARA. Considering a range of DHA intake of 30 to 65 mg/kg/d, and an ARA:/DHA ratio ranging from 0.5 to 2, an ARA intake up to 100 mg/kg/d appears safe. Limited data are available to determine if there is any benefit for dietary eicosapentaenoic acid and because of concerns around toxicity.

Conclusions, Recommendations

C1: There is not enough new data to support a significant modification of previous recommendations for linoleic and linolenic acids nor medium chain triglycerides **LOE 2+**

C2: DHA supplementation has modest and transient effects on neurodevelopment outcomes but may help achieve intakes close to intrauterine accretion rate **LOE 1+**

C3: With a DHA intake range of 30 to 65 mg/kg/d and aiming for an ARA/DHA ratio ranging from 0.5 to 2, 15 to 100 mg/kg/d of ARA appear to be safe **LOE 1-**

C4: Limited data are available to define if there is any benefit for including EPA in the diet of preterm infants **LOE 3**

R1: A total fat intake of 4.8 to 8.1 g/kg/d is recommended although higher intakes may be safe **GOR B**

R2: Amounts of medium chain triglycerides exceeding 40 % of total fat are not recommended **GOR B**

R3: A Linoleic acid intake of 385 to 1540 mg/kg/d, a minimum linolenic acid intake of 55 mg/kg/d, and a linoleic acid to linolenic acid ratio of 5-15:1 (wt/wt) are considered acceptable **GOR B**

R4: A DHA intake of 30 to 65 mg/kg/d is recommended assuming sufficient intake of ARA **GOR A**

R5: An ARA intake of 30 to 100 mg/kg/d is recommended **GOR B**

R6: EPA intake should be < 20 mg/kg/d **GPP**

Carbohydrates *(see supplementary digital content no.7, http://links.lww.com/MPG/C974)*

The carbohydrate concentration of human milk (HM) is quite stable and increases from ~6.2 g/100mL to 7.1 g/100mL during the first month of life (47, 58). The predominant digestible carbohydrate is the disaccharide lactose (48, 59) but free glucose, galactose and human milk oligosaccharides (HMOs) comprise about 15-30% (48). Incomplete digestion of lactose (HM) or lactose/glucose polymers (preterm formula) may limit the availability of energy from carbohydrate, however lactose feeding increases intestinal lactase activity (60). Undigested lactose and glucose polymers are salvaged by colonic bacteria (59, 61). Concerns that carbohydrate malabsorption increases the risk of necrotizing enterocolitis (NEC) have been explored in studies, but replacing lactose with more readily digestible glucose polymers show inconsistent results in regard to feeding tolerance, weight gain and calcium absorption (62-66).

The low glycogen reserves and limited fat stores put preterm infants at risk of hypoglycaemia (67), but they are also at risk of hyperglycemia due to immature glucose regulatory mechanisms including persistent hepatic gluconeogenesis, decreased pancreatic beta-cell activation and partial insulin resistance (67-69). Hyperglycemia is associated with increased mortality, morbidity, and longer-term brain outcomes (69, 70).

Carbohydrates constitute 45%-50% of non-protein calories in HM and standard preterm formulas. The relative contribution of carbohydrate to total non-protein energy might be of importance (71). At equal protein and energy intakes, carbohydrate improves nitrogen retention compared with fat (39, 40). However, high-energy, high-carbohydrate intakes increase fat deposition (39, 40), and higher postnatal carbohydrate intakes and hyperglycemia have been associated with higher blood pressure at 6.5 years of age (72). The balance of benefits and risks needs consideration when determining carbohydrate intake recommendations. Supplementation of human milk exclusively by digestible carbohydrates (e.g. lactose, glucose, or glucose polymers) has not been studied in RCTs (73). Therefore, the optimum enteral carbohydrate still is unknown but observational studies suggest that increasing energy together with protein by providing either fortified or non-fortified high HM volume regimens are safe and

improve in-hospital growth (4, 74, 75) and possibly language scores at 2 years of age (74). Assuming energy needs of 115-140 kcal/kg/d, enteral protein intakes of 3.5-4.0 g/kg/d, and a carbohydrate composition contributing to 40-50% of non-protein energy intakes, a carbohydrate intake in the range of 11-15 g/kg/d seems reasonable.

Conclusions, Recommendations

C1**:** There are no new data from randomized controlled trials (RCTs) on the effects of exclusively increasing carbohydrate intakes on short- and long-term outcomes in preterm infants, therefore the optimal intake range is uncertain **LOE 2**

C2: Observational data suggest that carbohydrate given as fortified human milk at upper intake ranges is safe and improves in-hospital weight, length and head circumference growth **LOE 2++**

C3: Preterm infants fed formula may need lower carbohydrate intakes than infants fed fortified HM, due to higher absorption rates of glucose polymers compared to lactose **LOE 2**

C4: The optimal lactose to total carbohydrate ratio in human milk fortifiers or in preterm formulas is unknown **LOE 3**

R1: In preterm infants, a carbohydrate intake of 11-15 g/kg/d is recommended **GOR B**

R2: Higher carbohydrate supplies as part of higher multicomponent supplementation or higher human milk intakes may be considered during a short period of time to cover cumulative deficits and facilitate catch-up growth if tolerated (euglycemia), but should also be tapered accordingly to avoid overnutrition **GPP**

Sodium, Chloride and Potassium *(see supplementary digital content no.8, http://links.lww.com/MPG/C974)*

Sodium

Sodium (Na) is the principal cation in extracellular fluid and concentrations influence intravascular and interstitial volumes, and blood pressure. Na also has a role in bone mineralization, nerve conduction, nitrogen retention and growth. Fetal accretion rates of Na are estimated at 1.6-2.1 mmol/kg/d at 27-34 weeks of gestation (76). Gastrointestinal Na absorption is effective in preterm

infants with typical faecal Na excretion rates <10% of intake, but is higher in early postnatal life and those born more preterm (77). Preterm infants have limited renal capacity both to conserve Na when challenged by Na restriction and excrete Na when challenged by a Na load. Tubular Na loss is inversely associated with gestational age (78), and it is increased during critical illness and by certain medications (79). Urinary Na losses as high as 7 mmol/kg/d have been reported in preterm infants (80). The Na concentration of human milk (HM) declines rapidly over the first few postnatal days (81), and is also influenced by expression methods and maternal serum concentration (82, 83).

Few high quality RCTs of Na supplementation exist, although some show that higher Na intakes of 4-6 mmol/kg/d versus 3-4 mmol/kg/d increase weight gain. Furthermore, the addition of concentrated sodium chloride or sodium phosphate to expressed fortified HM may increase milk osmolality (84).

Conclusions, Recommendations

C1: Na requirements show considerable inter- and intra-individual variation, especially in VLBW infants. **LOE 2**

C2: Breastmilk with added fortifiers may be insufficient to meet Na needs in preterm infants **LOE 2++**

C3: The enteral administration of Na additives exposes the infant gut to higher osmolality **LOE 3**

R1: A Na intake of 3 to 8 mmol/kg/day is recommended. The upper range of Na intake is slightly higher than in previous recommendations and should be considered in infants receiving high energy and protein intakes or with important sodium loss. **GPP**

R2: Na additives should be diluted with milk and divided between different feeds over 24 hours to maintain osmolality as low as possible **GOR C**

Chloride

Chloride (Cl) is the most abundant anion in extracellular fluid and along with Na, helps maintain osmotic pressure and hydration. Cl is also involved in maintaining ionic neutrality. The difference between Na and Cl plasma concentration affects hydrogen and bicarbonate ion concentrations. The daily turnover of Cl is high, and renal tubular reabsorption rate is 60-70%. Chloride content in HM is

similar at different gestations (85). Low Cl intakes may result in failure to thrive, slower growth and delayed neurological development (86, 87).

In enterally fed preterm infants receiving oral salt supplementation, Cl intake parallels that of Na or K, so, where there are high intakes of Na or K there will also be high Cl intakes (88). Cl losses and excretion can occur independently from Na. Medications may also be a source of additional Cl intake. Studies in infants receiving parenteral nutrition suggest that Cl intake should be slightly lower than the sum of Na and K intakes to avoid severe metabolic acidosis (89).

Conclusions and Recommendations

C1: Cl intakes parallel that of Na where oral salt supplementation is used **LOE 2++**

C2: High Cl intakes from additives and human milk fortifiers with low strong ion difference may induce metabolic acidosis **LOE2++**

R1: A Cl intake of 3 to 8 mmol/kg/d is recommended. **GOR C**

R2: Cl intake from HM fortifiers and preterm formula should be slightly lower than the sum of Na + K intakes to avoid metabolic acidosis. HM fortifiers should provide buffers to compensate for high renal acid load. **GOR B**

Potassium

Potassium (K) is the most abundant cation in the human body and the major intracellular ion. The K concentration gradient across cell membranes is crucial for maintaining contractility and neuronal function and is maintained by the tight balance of the influx or efflux of K from intra- to extracellular spaces. K is needed for somatic growth and the K pool correlates well with lean body mass. A growth rate of 15 g/kg/d results in a net storage of about 1.0-1.5 K mmol/kg/d (77). The total body K content depends on the balance of K intake and excretion and is mainly dependent on renal regulation. After an enteral feed, 80% of the absorbed K enters the cells due to increased insulin concentrations stimulated by the contemporary absorption of glucose and amino acids (90). Renal K excretion is increased by diuretics, and several factors increase gastrointestinal K losses including vomiting and diarrhea, changes in aldosterone, epinephrine, and prostaglandins (90).

Several studies in parenterally fed preterm infants show an increased incidence of hypokalaemia with higher protein and energy intakes (91-93). In infants receiving amino acid intakes of 3 g/kg/d, the K balance remains positive with K intakes ≥ 2 mmol/kg/d. It seems likely that similar amounts are needed when enterally fed but the optimal K intake in infants receiving higher protein intakes (<4.5g/kg/d) is not clear. K concentrations in extracellular fluid are tightly regulated, implying that intracellular K deficiency may still occur in the presence of a normal plasma K concentration.

Conclusions, Recommendations

C1: In enterally fed preterm infants there is a linear association between K needs and protein retention

LOE 3

R1: A K intake of 2.3 to 4.6 mmol/kg/d is recommended. The upper range of K intake should be considered in growing infants receiving the upper ranges of energy and protein intakes. **GOR B**

Mineral intakes Ca, P, Mg *(see supplementary digital content no.9, http://links.lww.com/MPG/C974)*

Bone mineral metabolism in early neonatal life is complex and determining optimal intakes is challenging. Ca accretion in the bone accounts for ~ 98% of total Ca-stores, whereas P stored in bone only represents ~ 80% of the total P accretion. The remaining P, about 20%, is involved in lean mass accretion, incorporated in nucleic acids and cell membranes, or used in the intra-cellular energy metabolism. This means that P intakes must be greater than that needed simply for bone mineral accretion (94-96). Estimates of the fetal mineral accretion rate and estimates of the the rate of mineral absorption by the preterm intestine (18, 95, 97-99) suggest fetal accretion rates of calcium (Ca), phosphorus (P) and magnesium (Mg) of approximately 2.5-3.0mmol/kg/d, 1.6-2.1mmol/kg/d, and 0.12-0.21mmol/kg/d respectively (76, 100, 101). Dietary mineral provision to achieve the estimated retention rates may be quite variable, as Ca and P absorption rates range between 30-70% and 70-90%, respectively (102, 103). Bioavailability is also dependent on the type and composition of the milk, the fatty acid components (e.g., presence of beta-palmitate) and the form of mineral given (102-110). Accretion rates in preterm infants are lower than in-utero estimates, resulting in a lower bone mineral content (BMC) at term corrected age compared to term-born peers.

The low mineral content of HM does not meet the needs of preterm infants, and studies show that current breastmilk fortifiers and preterm milk formula result in Ca and P retention rates of 2.3-2.8 and 2.2-2.6 mmol/kg/d, respectively, close to fetal accretion rates. Insufficient provision of Ca and/or P may lead to osteopenia and fractures. Improvements in nutritional care, including more appropriate use of breastmilk fortifiers, changes in milk formula composition, and better positioning of infants inside incubators, have resulted in a reduction in fractures, albeit osteopenic changes on X-ray are still common (111, 112). Unfortunately, there are no useful clinical techniques that directly measure or estimate BMC to guide clinical practice.

Whilst adequate mineral intakes are clearly important, the only RCT with long-term outcomes showed no effect of different postnatal calcium and phosphorus intakes on adult BMC (113). Based on an intestinal absorption rate of 60% for Ca and 80-90% for P, we estimate that healthy growing preterm infants will need approximately 4-4.5 mmol/kg/d of Ca and 3-3.5 mmol/kg/d of P when fed fortified HM. However, intakes up to 5 mmol/kg/d of Ca and 3.7 mmol/kg/d of P (or higher) may be needed if milk formulas with poor mineral absorption are provided.

Mg accretion during the last trimester of gestation is around 0.12-0.21mmol/kg/day with around half being accreted in the bone, and the remainder in muscle and soft tissue. Mg absorption rates change depending on Mg intakes but are typically around 40-50% (102, 114), and in preterm infants serum concentrations are higher than older infants with a range of 0.6-1.25mmol/L (115). Studies in preterm infants on fortified HM providing 0.2-0.3 mmol/kg/d showed absorption rates of around 45-50 % leading to a Mg retention of 0.1mmol/kg/d. In preterm infants fed formula, Mg intakes are approximately 0.4-0.5 mmol/kg*/d which appears to be adequate. No RCTs determining effects on bone accretion have been conducted.

Conclusions, Recommendations

C1: The lack of a strong evidence base for determining mineral intakes that will optimise functional bone or other outcomes means that recommended reference ranges are wide. **LOE 2+**

C2: Inadequate mineral intakes postnatally result in osteopenia which increases the risks for bone fractures in preterm infants. However, there is no consensus regarding how best to assess BMC in clinical practice and there are few well-designed RCTs to determine optimal mineral intakes. **LOE 3**

C3: Targeting a Ca *retention* of 2.2-2.8mmol (90-110mg)/kg/d is appropriate to minimise mineral bone deficiency and the risk of fractures in preterm infants. The target for P *retention* is 2.2-2.6 mmol (70-80 mg)/kg/d and includes both the functional P requirements as well as the P requirement for bone- and soft tissue accretion. **LOE 3**

C4: Adequate phosphorus intakes are essential to accrete lean tissue (each gram of protein requires approximately 0.35mmol of phosphorus). The provision of PN with low phosphate and unfortified HM increase the risk of both early and late hypophosphatemia. **LOE 2+**

R1: It is recommended to fortify HM early with phosphate followed by early introduction of multi-component breastmilk fortifiers to optimise bone mineral outcomes **GOR C**

R2: A Ca *intake* of 3.0-5.0 mmol (120-200 mg)/kg/d and a P intake of 2.2-3.7 mmol (70-115 mg P)/kg/d of P are recommended. **GOR C**

R3: The recommended molar calcium to phosphate ratio to ensure adequate Ca retention is ≤1.4 (≤1.8 in mass) **GOR C**

R4: Preterm infants fed artificial milk formula may require higher mineral intakes than those fed human milk. **GPP**

R5: Regular monitoring of P and Ca status is recommended. We do not recommend the routine use of bone imaging or other direct assessments of BMC in clinical practice. **GOR C**

R6: In preterm infants fed fortified human milk or preterm milk formula, a Mg intake of 0.4-0.5 mmol (9 to 12.5 mg)/kg/d is recommended. **GOR C**

Trace elements *(see supplementary digital content no.10, http://links.lww.com/MPG/C974)*

Trace elements are essential for many functions in different organ systems, as well as for normal growth and development. Whilst adequate dietary intakes are important for preterm infants to prevent deficiencies, important adverse effects of excessive intakes exist.

Iron

Systematic reviews clearly show that iron supplements effectively prevent iron deficiency anemia in preterm infants but there is no benefit in exceeding standard doses of iron (i.e. 2-3 mg/kg/day) in VLBW infants (116). Overall, there is a lack of RCTs with long term neuro-developmental outcomes,

but RCTs in late preterm infants have shown improved developmental outcomes in iron supplemented infants. Furthermore, starting at ~2-3 weeks vs later ~4-8 weeks of age is associated with a lower need for blood transfusions in VLBW infants (117). Delayed umbilical cord clamping increases neonatal iron stores and is associated with a lower mortality, lower risk of intraventricular haemorrhage and lower need for red cell transfusions in preterm infants (118). Erythropoietin may reduce the need for red blood cell transfusions but requires much higher iron intakes.

Ferritin is a useful biomarker of iron status, but reference intervals differ from older infants and children. Ferritin concentrations <35-40 µg/L indicate iron deficiency while concentrations >300-350 µg/L indicate iron overload (119-121). Ferritin is not useful as a biomarker of iron status in patients with ongoing inflammation or liver disease.

Recommendations:

- A daily iron intake of 2-3 mg/kg/day starting at 2 weeks of age is recommended for very low birth weight infants. **LOE 1+, GOR A**
- Infants who receive erythropoietin treatment need a higher dose (up to 6 mg/kg/day). **LOE 1-, GOR B**
- Since individual iron status in VLBW infants is highly variable, depending on the number of received blood transfusions and blood losses from phlebotomy, it is recommended to follow these infants with repeated measurements of serum ferritin. **LOE 4, GOR GPP**
- If ferritin is <35-70 µg/L, the iron dose may be increased up to 3-4 (or maximum 6) mg/kg/day for a limited period. **LOE 4, GOR GPP**
- Prolonged dietary iron intakes of >3 mg/kg/day should be avoided in most cases because of possible adverse effects. **LOE 1-, GOR B**
- If ferritin is >300 µg/L, which in the absence of ongoing inflammation and liver disease usually is the result of multiple blood transfusions, iron supplementation and fortification should be discontinued until serum ferritin falls below this level. **LOE 4, GOR GPP**
- Iron supplements or intake of iron-fortified formula in the recommended doses should be continued until 6-12 months of corrected age. **LOE 4, GPP**

- Like all infants, preterm infants should receive iron-rich complementary foods from 6 months of age. **LOE 1+, GOR A**
- Delayed umbilical cord clamping, whenever feasible, is recommended for all preterm infants. **LOE 1++, GOR A**

Zinc

Zinc is an essential trace element involved in growth and tissue differentiation. Zinc deficiency in preterm infants is associated with stunted growth, increased risk for infections, skin rash, and possibly poor neurodevelopment (122). In contrast to iron and copper, zinc does not have a pro-oxidant effect and adverse effects of excess zinc intakes are rarely reported, except for a negative effect on copper absorption with high zinc intakes.

The factorial method combined with data from metabolic balance studies suggest enteral zinc intakes of at least 2.0-2.25 mg/kg/d are required (123) and up to 3 mg/kg/d in extremely preterm infants due to faster growth rates (88, 124). A small number of studies suggest an intake of at least 1.4-2 mg/kg/d is needed to achieve optimal growth in preterm infants (125, 126) but higher enteral intakes appear safe and may be beneficial. Two recent meta-analyses suggests that zinc supplementation improves weight gain and linear growth in preterm infants and may decrease mortality (127, 128). Very preterm infants can develop symptomatic zinc deficiency with acrodermatitis enterohepatica and/or poor growth, especially those infants who have an enterostomy after NEC surgery (129).

Recommendations

- We recommend an enteral zinc intake of 2-3mg/kg/d, based on the most recent randomized controlled trial as well as on factorial calculations. **LOE 2, GOR C**
- Measurement of serum zinc should be considered in preterm infants with poor growth and low alkaline phosphatase level, especially if they have excessive GI fluid losses. **LOE 4, GOR GPP**

Other trace elements

Recommendations for copper, selenium, manganese, iodine, chromium, and molybdenum are covered only very briefly here, while the full background is reported in the supplementary material. The recommended copper intake has been increased to 120-230 µg/kg/d to compensate for the higher

recommended zinc intake (see above), since these two ions compete for intestinal absorption. We recommend an enteral selenium intake of 7-10 µg/kg/d, which has been shown to result in Se status like term infants and possibly a reduced risk of sepsis. Based on the average HM manganese content and the lower range of manganese in current preterm formulas, an enteral manganese intake of 1-15 µg/kg/d can be recommended. Despite a recent RCT, there is not enough conclusive evidence to change the previous recommendation, so an iodine intake of 11-55 µg/kg/d is recommended. The recommendations for chromium (0.03-2.25 µg/kg/d) and molybdenum (0.3-5 µg/kg/d) are unchanged.

Water soluble vitamins *(see supplementary digital content no.11, http://links.lww.com/MPG/C974)*

Water soluble vitamins are essential for whole body function and homeostasis. There is a major lack of studies to determine requirements for preterm infants. We used European Food Safety Authority (EFSA) recommendations for infants <6 months to calculate weight-based estimates, human breastmilk concentrations to estimate intakes in healthy infants, clinical studies where they exist and considered the amount provided by preterm infant formulas when fed at a minimum energy intake of 115kcal/kg/d, acknowledging that this last approach may significantly overestimate needs and noting that excess intakes are unlikely to be beneficial. Wide ranges in intake recommendations for preterm infants do not represent the distribution of intakes in a population, and in the absence of robust evidence dietary recommendations may be inflated to ensure adequacy well in excess.

Our approach is described in the supplementary materials. We acknowledge that estimates solely derived from EFSA recommendations or the concentration in breastmilk may underestimate the increased requirements of the rapidly growing preterm infant. However, it is likely that total daily recommendations from EFSA for term infants will be adequate for preterm infants as the weight difference results in an approximate 3-5 fold higher intake per kg body weight. The recommendations, which are largely similar (but not identical) to the previous ESPGHAN recommendations, are only briefly reported here and we refer to the full text in the supplementary documents.

Thiamine: Considering the available evidence we propose an intake of 140-290 µg/kg/d based on the content of infant formula milk **LOE 3, GPP**. The B1 content in breastmilk or the EFSA daily recommendations for B1 (42 µg/100 kcal or 46 µg/kg) might also be adequate (130).

Pantothenic acid: Considering the available evidence we propose an intake of 0.6 to 2.2 mg/kg based on the content of infant formula milk **LOE 3, GPP**.

Biotin: We recommend using the lowest concentration of biotin that would be provided using preterm formula and the upper level in the previous recommendations by ESPGHAN (18). We propose an intake of 3.5 to 15 µg/kg based on the content of infant formula milk **LOE 3, GPP**

Niacin: Considering the available evidence we propose an intake of 1100 to 5700 µg/kg based on the content of infant formula milk **LOE 3, GPP**

Ascorbic acid (vitamin C): Considering the available evidence we propose an intake of 17 to 43 mg/kg based on the content of infant formula milk **LOE 3, GPP**

Riboflavin (B2): We recommend an intake of riboflavin of 200 to 430 µg/kg/d [LOE 3, GOR GPP]. The daily recommendations made by the EFSA Panel may also be adequate considering the lack of evidence of differences in requirements between preterm and full-term infants.

Pyridoxine: We suggest a recommended intake in keeping with the concentration range that would be provided by commercially available preterm milk formula (70-290 µg/kg/d) [LOE 3, GOR GPP]. This is close to the previous guidelines of ESPGHAN (18), the EFSA daily recommendations and the available evidence discussed above.

Folate: Considering the range of folic acid content in preterm infant formula (20 to 45 µg/100 kcal, or 23 to 52 µg/kg) we propose an intake of 23-100 µg/kg/d **LOE 3, GPP**. Based on the evidence available, a folate intake at the maximum of the recommended range may improve patients' outcomes.

Cobalamin (B12): We propose dietary recommendations of 0.10 to 0.60 µg/kg based on the cobalamin content in preterm infant formulas **LOE 3, GPP**. An intake >0.6 µg might be associated with excessively elevated B12 levels in blood.

Fat soluble vitamins ADEK *(see supplementary digital content no.12, http://links.lww.com/MPG/C974)*

Vitamin A

Vitamin A is essential for growth and tissue differentiation (131, 132), and especially important in lung maturation (133). Preterm infants often have lower plasma concentrations of both retinol and retinol binding protein (RBP) at birth compared with term infants reflecting low hepatic stores (134). A plasma retinol concentration of ≥ 200 ng/mL is generally considered adequate (135), but due to the complexity of vitamin A metabolism and organ immaturity in preterm infants, vitamin A supplementation may still not result in adequate concentrations in blood. The beneficial role of high dose intramuscular vitamin A for prevention of BPD in preterm infants has been demonstrated (136). However, due to discomfort,

this form of supplementation is not common practice. Studies of higher enteral doses (5000 IU/day) produced inconsistent effects on BPD (137-140).

Conclusions, Recommendations

C1: There are insufficient data to change the previous recommendation of daily vitamin A intake in preterm infants (18), but infants with hepatic impairment may need higher intakes, and those with renal impairment may require lower doses **LOE 2++**

R1: Based on best current available data, we recommend a daily total intake of vitamin A of 1.333-3.300 IU/kg body weight (400-1000µg retinol ester/kg/d) **GOR B**

Vitamin D

Vitamin D plays a critical role in multiple cellular processes especially bone metabolism and the immune system (141). Pathways of vitamin D absorption and metabolism are fully operative in babies <28 weeks GA (142-144). Mineral bone deficiency in preterm infants is common and is primarily caused by suboptimal intakes of calcium and phosphate, but this can be compounded by Vitamin D deficiency (145). Even though there is no consensus regarding the definition of vitamin D deficiency in infants, the ESPGHAN Committee on Nutrition has previously recommended the pragmatic use of a serum 25-hydroxy vitamin D concentration >50 nmol/L to indicate sufficiency and a serum concentration <25 nmol/L to indicate severe deficiency, whilst noting that excessive vitamin D intakes resulting in concentrations >120nmol/L should also be avoided (146, 147).

Several studies have assessed the effect of vitamin D3 intake on circulating of 25(OH)D concentrations, but few studies assess the impact on bone mineral density (BMD) after the immediate neonatal period and results are inconsistent (145, 148-150). Vitamin D intakes of 400-670 IU/kg/day in infants weighing 1500-2000g and 500-1000 IU/kg/day for those weighing 100-1500g reduces the risk of deficiency (148-150), but studies suggest that lower doses (200-300 IU/kg/day) may also be sufficient (148, 151). Conversely, another study suggested a daily vitamin D supplementation of 800 IU/d in extremely premature infants with a gestational age < 28 weeks (152). Based on this, we recommend a daily vitamin D intake of 400-700 IU/kg/d (10-17.5µg/kg/d) for stable preterm infants. This corresponds to 300-525 IU/kg/d at 750 g body weight, 400-700 IU/kg/d at 1000 g body weight, and 600-1000 IU/kg/d at 1500 g body weight. The maximum recommended routine intake is 1000 IU/d, but preterm infants who are

vitamin D deficient due to maternal vitamin D deficiency or cholestasis may temporarily need higher doses. Adequate vitamin D supplementation could be monitored by measuring serum 25(OH)D at 3-4 weeks of life and then every month until discharge to adapt vitamin D supplementation to each individual's needs.

Conclusions, Recommendations

C1: Ensuring adequate vitamin D intakes in preterm infants is essential for bone health and may possibly have positive effects on immune function, even though this is not conclusively shown. **LOE 2+**

C2: There are few adequately powered controlled trials on which to base firm recommendations in preterm infants, and even fewer trials provide clinically relevant outcomes beyond vitamin D concentrations, e.g., markers of bone health. **LOE 4**

R1: Based on currently available data, we recommend a daily vitamin D intake of 400 to 700 IU/kg/d (10 µg-17.5 µg/kg/d) during the first months of life with a maximum dose of 1000 IU/day (25 µg/d) **LOE 2++, GOR B**

Vitamin E

Vitamin E comprises a group of eight biologically active tocopherols which act as antioxidants to scavenge free radicals, potentially limiting lipid peroxidation which can lead to bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and hemolytic anemia (153, 154).

Low concentrations of vitamin E were found at birth and at discharge in preterm infants (155) but serum concentrations may not reflect tissue concentrations (156).

Clinical studies of supplementation are inconsistent, and although there may be benefits (157, 158) there are some data suggesting high intakes may increase risk of sepsis and NEC (159).

Studies of routine enteral vitamin E supplementation in preterm infants, suggest it may be prudent to maintain plasma vitamin E concentrations of 10 - 35 mg/L, and a ratio of serum-α-tocopherol of at least 1 mg to 1 g total lipids, which would suggest a minimum dose of 3.8 mg/kg/d. However, no clinical benefits have been seen, and the recommended daily intake of vitamin E in preterm infants is 2.2-11 mg/kg/d (18, 159, 160). Infants with prolonged cholestasis may require higher intakes.

Conclusions, Recommendation

R1: Based on the current available data, we recommend a daily dose for vitamin E supplementation in preterm infants of 2.2-11 mg/kg/d **LOE 2++, GOR B**

Vitamin K

Vitamin K is a group of lipophilic, hydrophobic vitamins necessary for the synthesis of coagulation factors (factors II (prothrombin), VII, IX, and X, and the anticoagulation proteins C and S in the liver. Maternal transfer of vitamin K across the placenta is very low with cord blood concentrations of vitamin K often below the detection limit of 0.02 ng/mL in healthy newborns (161) and breastmilk also has very low levels of vitamin K (162, 163). Late onset vitamin K deficiency bleeding is primarily seen in exclusively breast-fed infants or in those with cholestatic disease (164).

Whilst preterm infants are at high-risk of Vitamin-K deficiency bleeding most receive prophylactic vitamin K at birth, and additional intakes from parenteral nutrition, infant formula, and breast milk fortifiers. Vitamin K can be administered intramuscularly, intravenously, and orally with different recommended dosing regimen (165). Thus, serum concentrations in preterm infants are usually higher than those found in term formula-fed infants (166). There are no RCTs in preterm infants, and nutritional recommendations vary from 4.4-28 µg/kg/d, to up to 100 µg/kg/day (18, 163, 167) although higher intakes may be needed where there is prolonged cholestasis.

Conclusions, Recommendation

R1: Based on the current based available data, we recommend a daily dose for vitamin K of 4.4-28 µg/kg **LOE 2++, GOR B**

Feeding mode: minimal enteral feeds, feed advancement, gastric residuals and timeline of parenteral and enteral nutrition *(see supplementary digital content no.13, http://links.lww.com/MPG/C974)*

Minimal enteral feedings and enteral fasting during the first days of life

Minimal enteral feeding (MEF) is synonymous with gut priming, minimal enteral nutrition, trophic feeding or hypocaloric feeding and defined as small volumes of milk (typically 12-24 ml/kg/day) without advancement in feed volumes during the first 3-7 days (168, 169). Numerous studies and systematic reviews exist comparing MEF with no feeds, or earlier advancement, but many studies

were conducted more than 20 years ago. Overall there are no consistent effects on NEC or all-cause mortality (170, 171) and this is supported by more recent studies (172-174).

Conclusions, Recommendations

C1: Minimal enteral feedings are defined as nutritional insignificant small volumes of milk (typically 12-24 ml/kg/day) without advancing the feed volumes for a period of 3-7 days. **LOE 1+**

C2: There is no clear beneficial effect of enteral fasting or MEF of any duration compared to advancing feeds immediately after birth. **LOE 1+**

R1: Start small volume enteral feeds as soon as possible after birth in most preterm infants and advance feeds as clinically tolerated. **GOR B**

Advancement of enteral feeds

Systematic review of 10 RCTs including a total of 3753 infants show no impact of speed of advancement (175) on NEC or sepsis supported by findings of the large Speed of Increasing milk Feeds Trial (SIFT) (176) which compared daily increments of 18 mL/kg/day to 30 mL/kg/day. The median enrolment age of 4 days in the SIFT trial may not adequately inform the relative safety of these increments at an earlier age. In addition, the actual daily increment was slower than targeted in both groups and other factors such as the approach and definition of feeding tolerance or gastric residuals might have influenced practice.

Conclusions, Recommendations

C1: After 4 days of life, faster feeding progression (30mL/kg/day) of enteral feed volumes does not significantly increase the incidence of NEC or all-cause mortality compared to slower (15-20 mL/kg/day) feeding advancement **LOE 1+**

C2: Meta-analysis showed that faster increment of enteral feed volumes positively reduces the time to full enteral feeding and the length of hospital stay as well as possibly the incidence of invasive infections **LOE 1+**

R1: In stable preterm infants where the clinician considers that feed volume can be increased, a routine daily increment of 18-30mL/kg/day is recommended, especially in breastmilk-fed infants.

GOR A

Gastric residuals

Gastric residuals (GR) are commonly used to define feeding tolerance although there are few high-quality data and no adequately powered RCTs to determine the relationship with NEC. Gastric emptying is influenced by positioning of the infant and the type of enteral feed, with breastmilk emptied almost twice as fast as formula (177, 178) although this may differ following pasteurization (179) or fortification (180). There is no consistent, agreed definition of feeding intolerance, clinical practice varies widely and RCTs have used different volume definitions. Evidence from relatively small studies suggest that routine monitoring of GR increases the risk of feed interruption episodes, the time taken to reach full enteral feeds and to regain birth weight, and PN days, but does not have an impact on NEC incidence (181, 182). There is no consensus on whether to re-feed or discard the aspirated GR.

Conclusions, Recommendations

C1: Positioning of the infant has an impact on gastric emptying with the prone position for the first half hour post feeding being quickest. **LOE 2+**

C2: The GR alone is neither a sensitive nor a specific indicator for bowel injury of the premature gut **LOE 2+**

C3: Routine monitoring of GR increases the time taken to reach full enteral feeds and to regain birth weight and increases the number of PN days but does not have an impact on NEC incidence. **LOE 2+**

C4: There is no consensus on whether to re-feed or discard the gastric aspirate **LOE 3**

R1: Routine monitoring of GR in the clinically stable infant is not recommended **GOR B**

R2: Assessment of GR should be performed only when other clinical signs associated with feeding intolerance or NEC are present such as extreme abdominal distension, tenderness, emesis, bloody stools, apnea, temperature instability **GOR B**

Timeline of parenteral and enteral nutrition

Most preterm infants receive parenteral nutrition (PN), enteral nutrition (EN), and a transitional period in between influenced by local feeding practices, feeding intolerance and metabolic intolerance (183-185). The transition phase is a critical time period for poor growth (184) although early progressive

PN and EN strategies may lead to reductions in the cumulative energy and protein deficits that occur during the first weeks of life (186, 187). Standardized feeding guidelines and protocols, designed to maintain targeted intake throughout the transition phase (188, 189) can help to achieve nutritional goals (190). Data from multiple observational studies suggest that the use of standardized feeding protocols allow preterm infants to achieve full enteral feeds faster, shorten the time on PN and hospital stay, decrease the rates of NEC, and improve growth and neurodevelopment (5, 191-198). A key challenge during the transition phase is to determine optimal intakes when both parenteral and enteral nutrition is provided. The use of computerised software able to adapt to changing reference values may be helpful.

C1: Early progressive parenteral and enteral nutrition strategies may reduce cumulative energy and protein deficits **LOE 2+**

C2: The transition phase between parenteral and exclusive enteral nutrition is a critical time period for cumulative nutrient deficits and for poor growth **LOE 2+**

R1: To avoid nutrient deficits we recommend establishing a standardized feeding protocol in every NICU that defines the following parameters: duration of minimal enteral feedings, daily advancement of milk feeds, definition and management of gastric residuals, definition, and approach to feeding intolerance, breast milk fortification strategy and the definition of full enteral feedings. **GOR B**

Feeding Mode: gastric tube and bolus or continuous feeding *(see supplementary digital content no.14, http://links.lww.com/MPG/C974)*

Nasogastric versus orogastric feeding tubes

Orogastric (OG) and nasogastric (NG) feeding tubes are both used. NG tubes may increase nasal airway resistance especially in the smallest infants (199) which may accelerate work of breathing and cause pharyngeal airway collapse (200, 201); although systematic reviews show no consistent effects on feed tolerance, incidence or frequency of apneas, desaturation episodes or bradycardia (202). OG tubes may be more prone to vagal stimulation which may provoke bradycardia (203, 204) due to tube

movements in the hypopharynx. Adverse effects of both NG and OG tube placement have been described, including tube misplacement (205, 206), nasal damage (207) and oesophageal perforation.

Bolus versus continuous feeding

Bolus feeds promote cyclical release of gastrointestinal tract hormones to stimulate gut maturation and motility (208) but marked variations in practice exist and many use continuous feeds (183). Low-quality evidence suggests feeding 3-hourly is comparable to 2-hourly feeding although extremely low-birth-weight infants may reach full enteral feeds earlier when fed 2-hourly compared with 3-hourly (209). Bolus feeding increases splanchnic perfusion more than continuous feeding (210). Energy expenditure may increase upon bolus feeding as compared to continuous feeding (211). Systematic reviews show longer time to reach full enteral feeding using continuous rather than intermittent feeding infants (212) and fat loss may also be greater (213, 214) although there were no significant effects on growth (212). Data on apnea are inconsistent (215-219).

When to start oral (breast)feeding and stop tube feeding

Infant oral feeding requires coordination of sucking, swallowing, breathing and esophageal transport, but factors such as milk availability, NICU environment, and caregiver feeding approach are also important (220). Establishing oral feeding may be more challenging in high-risk infants e.g. those with BPD (221) where micro-aspirations may compromise respiratory capacity further. Introducing oral feeds to infants on CPAP seems clinically safe based on two small studies and may decrease time to full oral feeds (222, 223), and studies also suggest feeding infants receiving high flow nasal cannula is possible (224) although swallowing dysfunction and risk of aspiration is important (225). There is no consistent evidence that early introduction and advancement of oral feeds based on the infant's individualized cues, state, and behaviour, rather than a predetermined feeding schedule, affects important outcomes for preterm infants or their families. Low quality evidence suggests preterm infants fed in response to feeding and satiation cues may achieve full oral feeding earlier (226). Meta-analyses provided evidence of low to moderate quality indicating that avoiding bottles increases breast feeding on discharge home.

Meta-analysis suggests that non-nutritive sucking reduces time to full oral feeding (227), and sensorimotor interventions may improve the sucking process (228, 229). Nipple shields may affect breastfeeding success, but reviews are contradictory (230, 231) and most do not advocate routine use (232).

Conclusions, Recommendations

C1: No preferential method to use either nasogastric or orogastric feeding tubes for preterm neonates can be determined. **LOE 2**

C2: Bolus feeding (2-3 hourly) might be slightly more preferential than continuous feeding in preterm infants, but more well-designed studies are needed for definitive advice. **LOE 2+**

C3: Establishment of non-nutritive sucking prior to the introduction of oral feeding may reduce time to reach full oral feeding and length of hospital stay. **LOE 3**

R1: Introducing oral feeding should be guided by the competence and stability of the preterm infant and may be started from 32 weeks postmenstrual age. **GOR GPP**

Growth *(see supplementary digital content no.15, http://links.lww.com/MPG/C974)*

Growth is evaluated by measuring gain in weight, length, and head circumference (HC) but also using measures of body composition. Plotting on a growth chart enables clinicians to compare the growth trajectory of each infant to a reference group throughout infancy and childhood and is essential. Growth must be considered in the context of improving short- and long-term functional outcomes rather than simply promoting an increase in anthropometric values.

Growth standards for preterm infants are challenging to develop and many growth references are simply based on cross-sectional birth weight data. Using postnatal growth data is however challenging because many sick infants show altered growth and there are uncertainties of how best to define 'healthy' preterm infants that might act as a standard. Growth velocity based on foetal ultrasound estimations can also be challenging, but foetal estimates can guide clinician's evaluating growth in a stable preterm infant. Using e.g., WHO in-utero data, an average foetal weight gain of 20-23 g/kg/d during 23-25 weeks of gestation, decreasing to 17-20 g/kg/d during weeks 26-29, 13-17 g/kg/d during weeks 30-34 and 10-13 g/kg/d during weeks 35-37 can be guiding.

Growth faltering (GF) describes an infant whose growth slows and does not grow parallel to a centile during the period of established growth. GF is more common in sick infants and associations with poor neurodevelopmental outcomes may be confounded (233). Catch-up growth refers to accelerated rates of growth following a period of GF. However, there are concerns that rapid catch-up growth may increase the risk of cardiovascular and metabolic disease in later life especially when it is due to catch-up in weight without contemporaneous linear or head growth (234). There are no data that allow clinicians to determine the optimal degree or duration of catch-up growth in an individual infant. During the first 3-4 days after birth, in AGA infants, a weight loss is expected (7-10%), mainly due to a one-time irreversible contraction of extracellular water space (235, 236). Studies show small for gestational age (SGA) infants often lose less (4-7%) (237, 238). A variety of approaches have been suggested to determine the optimal growth trajectory or target percentile for preterm born infants, for instance the pragmatic aim of not losing more than 1 SDS in weight and HC from birth to discharge (239). However, calculating changes in SDS from birth to discharge is confounded by skewed reference data (240), and even more so for the most immature infants growing on lower centiles. It is not clear whether infants should regain their actual centile at birth, or whether a target centile should be based on weight at 1-3 weeks of age. Growth expectations of each infant have to be individualized since infant growth vary depending on genetic potential, intra uterine environment (e.g. pre-eclampsia or poorly controlled diabetes) and morbidity in the NICU.

One concept is to avoid a large weight loss after birth, stabilise growth, avoid GF, approximately grow along a target centile and adjust nutrient intakes gradually so that the preterm and term growth trajectories merge at around 44 weeks (236). Growth patterns in preterm SGA infants may differ (241), and the optimal time frame and/or speed of catch-up growth are not known.

Conclusions, Recommendations

C1: Based on current evidence, the optimal growth velocity that optimises outcomes in preterm infants remains unclear. **LOE 2+**

C2: According to WHO in-utero growth fetal weight gain decreases from slightly above 20 g/kg/d at 23-25 weeks of gestation to about 10 g/kg/d at term age **LOE2++**

R1: Regular monitoring of weight, length and HC growth is strongly recommended. Ideally, weight should be measured at least once or twice daily during the first 1-2 weeks, followed by measurements 2-3 times weekly in the stable growing phase. Length and HC should be measured once weekly unless clinical conditions (e.g., hydrocephalus) indicate more frequent monitoring **GPP**

R2: After a typical acceptable initial weight loss of 7-10%, reaching a nadir at day 3-4, nutritional strategies should aim to regain birth weight by 7-10 days of age, followed by growth along a target centile and a gradual transition to the corresponding birth percentile on the WHO postnatal growth chart within the first weeks or months post term **GPP**

R3: Nutritional management and growth assessment for infants born IUGR and/or SGA should be the same as those born AGA, although initial weight loss is often less and acceptable up to 4-7% of birth weight. **GOR B**

R4: Postnatal growth trajectories (weight, length and head circumference) of each infant must be followed and evaluated to ensure nutrition is adequate; ideally using a growth chart based on a large robust dataset **GPP**

R5: In infants experiencing postnatal growth faltering, some catch-up growth should be allowed but rapid catch-up growth should be avoided. If catch-up growth is perceived as too rapid, ensure that nutrients are within recommended intake ranges and not excessive **GPP**

R6: NICUs should adopt a standardised approach to the management of postnatal growth faltering. If growth faltering is recognized, ensure that nutrition is within recommended intake ranges. Careful consideration must be used in balancing the well-documented neurocognitive risks of nutrient deficiencies and slow growth in early life, against the theoretical risks from rapid catch-up growth and adverse metabolic programming in later life **GPP**

Breast milk (Buccal colostrum, donor human milk, and pasteurisation of mother's own milk to reduce Cytomegalovirus transmission) *(see supplementary digital content no.16, http://links.lww.com/MPG/C974)*

Administration of buccal colostrum to preterm infants appears safe and theoretically attractive from both an emotional as well as immunological point of view, but no clear clinical benefits have

consistently been proven in high-resource settings. There is therefore no current data to recommend routine administration of buccal colostrum to reduce morbidity or mortality, although there may be wider behavioural effects and other benefits (242, 243).

Fresh mother's own milk (MOM) contains higher amounts of macronutrients, and immunoactive and trophic factors than pasteurised MOM or donor human milk (DHM). Nevertheless, fortified pasteurised DHM instead of preterm formula may reduce NEC rates in preterm infants, whereas other neonatal morbidity and mortality rates are unaltered (244, 245). We strongly recommend MOM as the first choice of feeding in both preterm as well as term infants. In case of insufficient MOM availability, fortified DHM is conditionally recommended over preterm formula in preterm infants born <32 weeks' gestation or with a birth weight <1500 g. When providing DHM, health care providers must continue to increase awareness of the benefits of MOM over both DHM and preterm formula and recognise the variable nutrient density of DHM.

The vast majority of Cytomegalovirus (CMV) seropositive women undergo CMV reactivation during lactation and excrete CMV in their breast milk (246, 247). This leads to (sub)-clinical CMV transmission in approximately 15-20% of very preterm infants, although rates may be higher in extremely preterm infants (248, 249). Symptomatic postnatal CMV infection, presenting as thrombocytopenia, cholestasis, or sepsis-like illness occurs in less than 5 to 10% of infected infants (248, 249), whereas associations with BPD, NEC and adverse neurological sequelae are less clear (250-252). Whilst pasteurisation will effectively eliminate CMV from breast milk, it also reduces or inactivates important bioactive factors. There is insufficient evidence to determine whether potential sequelae of postnatal CMV transmission are more harmful than potential adverse effects arising from providing pasteurised MOM instead of fresh MOM (253). Thus, while we acknowledge the potential adverse consequences of postnatally acquired CMV, especially in the most immature infants, we do not recommend routinely pasteurising MOM from CMV-positive women as this may reduce the beneficial effects of fresh MOM.

Conclusions, Recommendations

C1: While the administration of buccal colostrum to premature infants appears safe and theoretically attractive from both an emotional as well as immunological point of view, no clear clinical benefits for the infant have consistently been proven in high-resource settings **LOE 1-**

C2: Fresh MOM contains higher amounts of macronutrients, and immunoactive and trophic factors than Holder-pasteurised DHM **LOE 1++**

C3: Fortified pasteurised DHM instead of preterm formula milk reduces NEC rates in preterm infants, whereas other neonatal morbidity and mortality rates are similar **LOE 1+**

C4: Most CMV-seropositive women undergo CMV reactivation in breast tissue during lactation and excrete CMV in their breast milk, which may cause (sub)-clinical CMV transmission in approximately 15-20% of very preterm infants, although rates may be higher in extremely preterm infants **LOE 1+**

C5: Symptomatic postnatal CMV infection, presenting as thrombocytopenia, cholestasis, or sepsis-like illness occurs in a minority of infected infants although associations with BPD, NEC, and adverse long-term neurological sequelae are less clear **LOE 1-**

C6: Whilst Holder-pasteurisation will effectively eliminate CMV from breast milk, it also reduces or destroys many beneficial and important bioactive factors **LOE 1++**

C7: There is insufficient data to determine whether the potential sequelae of postnatal CMV transmission are more harmful than potential adverse effects arising from providing pasteurised instead of fresh MOM **LOE 2+**

R1: No recommendation can be made either for or against the use of buccal colostrum in preterm infants in order to reduce neonatal morbidities or mortality so parent preferences must be considered.

R2: We strongly recommend MOM as the first choice of feeding in both preterm as well as term infants **GOR A**

R3: In case of insufficient MOM availability, fortified DHM is conditionally recommended over preterm formula milk in preterm infants born <32 weeks' gestation or with a birth weight <1500 g **GOR B**

R4: When providing DHM, health care providers must continue to increase awareness of the benefits of MOM over both DHM and preterm formula. Health care providers must support and facilitate mothers in order to promote higher rates and volumes of MOM provision (e.g. through lactation consultants) **GOR A**

R5: While we acknowledge the potential adverse consequences of postnatally acquired CMV, especially in the most immature infants, there is insufficient evidence to recommend routine pasteurisation of MOM from CMV-positive women as pasteurisation simultaneously reduces the activity of many bioactive factors **GOR B**

Osmolarity and hydrolyzed protein *(see supplementary digital content no.17, http://links.lww.com/MPG/C974)*

Osmolality

More than 40 years ago an association between hypertonic infant formula and an increased incidence of NEC was noted (254) and the American Academy of Pediatrics (AAP) recommended that the osmolarity of infant formula should not exceed 400 mOsm/l (approximately equivalent to an osmolality of 450 mOsm/kg) (255). However, recent systematic reviews have not found any consistent evidence that differences in feed osmolality in the range 300–500 mOsm/kg are associated with adverse gastrointestinal symptoms although study interpretation is challenging (256, 257). Breast milk fortification increases the osmolality of the milk immediately after addition (up to more than 50%), followed by additional smaller increases in osmolality (up to 10%) after storage at 4°C for up to 24 h (254, 258-262). Routine additives and medications can also significantly increase osmolality to levels that exceed guidelines from other professional bodies (84, 260, 263). However, drugs as well as vitamin supplements often contain carrier molecules that can diffuse across membranes without increasing tonicity, and therefore are not likely to present a risk from their osmolar load. We consider it prudent to dilute additives in the largest possible volume of feed, to use multi component breast milk fortifiers in preference to multiple individual supplements, and to avoid simultaneous addition of multivitamins, electrolyte solutions, or other high osmolar substances where possible.

Hydrolyzed protein

Hydrolyzed protein has increasingly been used in preterm infant milk formula and fortifiers. Protein hydrolysis alters amino acid kinetic, utilization by the gut, and may reduce nutrient utilization especially for nitrogen (108) but these formulas are generally regarded as safe and no adverse effects on growth or development have been demonstrated in term infants. In preterm infants, RCTs show faster gastrointestinal transit with hydrolyzed protein formulas (264-267) and improved nitrogen and mineral retention can be achieved with higher protein concentrations or due to other changes in formulation or production (268). Effects on growth (269), NEC and feeding advancement vary in more recent studies (270-272). Relatively high levels of "advanced glycation end-products" in most hydrolyzed formulas have been associated in other settings with development of chronic inflammatory, metabolic, or neurodegenerative diseases (273, 274) but the clinical relevance of these theoretical concerns is unknown. Finally, the more complex processing required to create safe hydrolyzed protein products adds substantially to costs.

Conclusions, Recommendations

C1: The available evidence does not allow the definition of an upper safety osmolality threshold for enteral feeding of preterm infants. **LOE 2+**

C2: Commercial ready-to-feed milk formula with an osmolality that is at the upper end of the intake range may create challenges for clinicians who want to use additional supplements (e.g., iron, vitamins, sodium etc.) but avoid excess feed osmolality. **LOE 4**

C3: Commercial milk formula differ in the degree of protein hydrolysis (range of Dalton sizes) which may be associated with differing functional effects. **LOE 3**

C4: In preterm infants hydrolyzed protein formula accelerates gastrointestinal transit and enteral feeding advancement but there are no data to show routine use improves long-term outcome. **LOE 1+**

R1: Where supplements or other feed additives are given, these should be added to the largest possible volume of milk feed **GPP**

R2: Where breastmilk fortification is required, multi component fortifiers should be used in preference to multiple individual nutrient supplements. **GPP**

R3: Hydrolyzed protein may be used for early enteral feeding in preterm infants if human milk is not available. **GOR B**

Supplemental bionutrients *(see supplementary digital content no.18, http://links.lww.com/MPG/C974)* Choline

Choline is a conditionally essential water-soluble nutrient with vitamin-like qualities and is found in a wide variety of foods including breastmilk and infant formula. Choline has multiple physiological functions including structural roles in cell membrane and myelin synthesis, cell signalling, neuro-transmitter functions, and DNA methylation. Adults can produce choline in the liver, but de-novo synthesis in preterm infants may be limited. There are theoretical risks of toxicity as choline is metabolised to trimethylamine oxide, high levels of which may cause liver damage and are associated with cardiovascular disease in adults. EFSA recommends that infant formula contain a minimum choline concentration of 25mg/100kcal (EFSA 2014). No good studies exist, and no deficiency state has been described, but recent studies suggest higher intakes may be beneficial in preterm infants (275-277).

Other suggested food supplements for preterm infants

Lactoferrin, milk fat globule membrane, nucleotides, inositol, human milk oligosaccharides, lutein, zeaxanthin, and bile salt stimulated lipase have all been suggested to have health benefits for preterm infants but there is currently insufficient evidence to support the recommendation of any of these routinely as a food supplement for preterm infants (LOE varies 1++ to 4).

Conclusions, Recommendations

C1: Dietary intakes in preterm infants must include choline because de novo synthesis may be limited or compromised but defining minimum and maximum intakes is challenging due to a lack of RCTs in preterm infants. **LOE 4**

C2: There is no current evidence that preterm infants primarily fed with breastmilk benefit from routine choline supplements. **LOE 4**

R1: There are no data to support any change in the previous recommended daily intake of choline 8-55mg/kg/day, although higher intakes appear safe. **GPP**

R2: Milk formula designed for preterm infants should include choline in a concentration designed to meet recommended intakes, but additional routine choline supplementation in preterm infants is not recommended. **GPP**

Breastmilk fortification *(see supplementary digital content no.19, http://links.lww.com/MPG/C974)*

Human breast milk (HM) is the optimal source of nutrition, but both macro- and micronutrient density is insufficient to support optimal growth for most very preterm infants (see supplementary data for HM nutrient density). Whilst data on nutrient accretion based on factorial methodology strongly support the use of breastmilk fortifiers there is only limited evidence from clinical trials (278). Multiple small studies have explored individual protein, fat or carbohydrate supplements or multi-component fortifier products. Most studies show slightly greater weight, length, and head gain, with no consistent adverse effects on NEC, but also no consistent data showing improvements in long-term neuro-developmental outcomes. Fortifiers will increase the osmolality of the milk feed (see earlier section) and risks bacterial contamination. It is not clear which sub-populations of preterm infants benefit most, or whether all very preterm infants should receive them routinely, and there are few data on the optimal time to commence fortifiers (279). In lower resource settings, a small number of studies have explored using milk formula powder rather than multi-component fortifiers, but no studies are large enough to determine potential adverse effects including sepsis and NEC, and the nutrient composition of the resulting mixture will be sub-optimal.

Most fortifiers provide approximately 1-1.1 g of additional protein per 100ml although some provide more. Because protein content in human milk decreases over the first 2-4 weeks, a standard regime of fortification may not be optimal, and donor human milk (DHM) macronutrient concentrations may be lower than for mother's own milk (MOM). Energy, protein:energy ratios, and the proportion of energy provided as fat or carbohydrate also differ between studies making evidence synthesis challenging. Whilst pooling of DHM will reduce macronutrient variability, this is not practical when using MOM. 'Adjustable' fortification using serum urea concentrations (22) may improve growth although methodological challenges exist and cut-off values for urea lack a robust evidence base.

'Targeted' fortification describes various methods including analysis of macronutrient concentration at the cot-side (280-282) but could also be utilised when donor milk banks provide data on nutrient concentrations of analysed pooled milk. Whilst earlier studies showed inconsistent or no effects on growth, more recent studies using better validated human milk analysers and individualised supplementation with protein, fat and carbohydrate show promise (283).

There are strong observational data to show that the use of MOM is associated with a lower risk of NEC, and this also seems likely for DHM based on meta-analyses of RCTs, although no single adequately powered trial exists (244). It remains unclear whether DHM reduces NEC risk due to the presence of beneficial functional components (e.g. HMOs) or whether protective mechanisms primarily involve decreasing exposure to bovine proteins or other components. Human milk derived fortifiers are now commercially available either as concentrated liquids or lyophilised powders which make an exclusive human milk diet possible. Whilst a small number of studies suggesting benefit exist, no adequately powered trials to conclusively determine a reduction in NEC solely due to a human-milk derived fortifier have been performed, and some studies show slower growth in the human versus bovine derived fortifier groups.

Conclusions, Recommendations

C1: The protein content of some fortifiers might be insufficient to increase protein concentrations to recommended intake levels if the volume of enteral feeds is limited **LOE 2**

C2: The optimal time to start fortification is not clear, but early fortification seems to be as safe as delayed fortification, may reduce cumulative nutrient deficiencies, and positively influence bone metabolism **LOE 2+**

C3: There is variation in the nutrient content of commercially available fortifiers and this may affect growth and health outcomes **LOE 2**

C4: Adjustable and target fortification strategies may be employed to compensate for variation in human milk macronutrient composition, but the optimal strategy is uncertain. DHM may require higher levels of fortification compared to MOM **LOE 2+**

C5: Fortifiers derived from human milk may reduce the risk of NEC but there are insufficient data from adequately powered studies to determine the optimal strategy **LOE 2+**

R1: We recommend the use of multi-component fortifier products to enhance the nutrient content of human milk fed and to promote growth in preterm infants **GOR A**

R2: We recommend starting fortifier when enteral intakes reach 40 – 100 ml/kg/d. **GOR C**

R3: Individualised fortification strategies including adjustable and targeted approaches may be appropriate. **GOR A**

R4: There is insufficient evidence to recommend the routine use of human milk derived fortifiers until further high-quality data is available. **GOR C**

Disclaimer: ESPGHAN is not responsible for the practices of physicians and provides position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of the healthcare provider.

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Supplementary digital content (SDC)

1. Introduction, methods and limitations
2. Human milk nutrient concentrations: evidence base and justification
3. Water
4. Energy
5. Protein
6. Lipids
7. Carbohydrates
8. Sodium, chloride and potassium
9. Minerals: calcium, phosphorus and magnesium
10. Trace elements
11. Water soluble vitamins
12. Fat soluble vitamins
13. Feeding mode: minimal enteral feeding, feed advancement, gastric residuals and timeline of parenteral and enteral nutrition
14. Feeding mode: gastric tube and bolus or continuous feeding
15. Growth
16. Breastmilk: buccal colostrum, donor human milk, and risk of CMV infection
17. Hydrolysed protein and osmolality
18. Supplemental bionutrients: lactoferrin, choline, milk fat globule membrane, human milk oligosaccharides, bile salt stimulated lipase, lutein and nucleotides
19. Breastmilk fortification

References

1. Bischoff SC, Singer P, Koller M, et al. Standard operating procedures for ESPEN guidelines and consensus papers. Clin Nutr. 2015;34(6):1043-1051.

2. Mihatsch W, Shamir R, van Goudoever JB, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Guideline development process for the updated guidelines. Clin Nutr. 2018;37(6 Pt B):2306-2308.

3. Iacobelli S, Guignard JP. Renal aspects of metabolic acid-base disorders in neonates. Pediatr Nephrol. 2020;35(2):221-228.

4. Travers CP, Wang T, Salas AA, et al. Higher- or Usual-Volume Feedings in Infants Born Very Preterm: A Randomized Clinical Trial. J Pediatr. 2020;224:66-71 e1.

5. Rochow N, Fusch G, Muhlinghaus A, et al. A nutritional program to improve outcome of very low birth weight infants. Clinical nutrition (Edinburgh, Scotland). 2012;31(1):124-131.

6. Joosten K, Embleton N, Yan W, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Energy. Clin Nutr. 2018;37(6 Pt B):2309-2314.

7. Towers HM, Schulze KF, Ramakrishnan R, et al. Energy expended by low birth weight infants in the deposition of protein and fat. Pediatr Res. 1997;41(4 Pt 1):584-589.

8. Bauer J, Werner C, Gerss J. Metabolic rate analysis of healthy preterm and full-term infants during the first weeks of life. Am J Clin Nutr. 2009;90(6):1517-24.

9. Bauer J, Maier K, Hellstern G, et al. Longitudinal evaluation of energy expenditure in preterm infants with birth weight less than 1000 g. The British journal of nutrition. 2003;89(4):533-537.

10. Denne SC, Poindexter B. Differences between metabolism and feeding of preterm and term infants, in Neonatal Nutrition and Metabolism. 2nd ed. PJ T, Hay WW J, editors: Cambridge University Press; 2006.

11. Bauer J, Maier K, Linderkamp O, et al. Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnea. Pediatrics. 2001;107(4):660-663.

12. Abranches AD, Soares FVM, Villela LD, et al. Energy expenditure, growth, and nutritional therapy in appropriate and small for gestational age preterm infants. J Pediatr (Rio J). 2018;94(6):652-657.

13. Bell EF, Johnson KJ, Dove EL. Effect of Body Position on Energy Expenditure of Preterm Infants as Determined by Simultaneous Direct and Indirect Calorimetry. Am J Perinatol. 2017;34(5):493-498.

14. Roberts SB, Young VR. Energy costs of fat and protein deposition in the human infant. Am J Clin Nutr. 1988;48(4):951-955.

15. Reichman BL, Chessex P, Putet G, et al. Partition of energy metabolism and energy cost of growth in the very low-birth-weight infant. Pediatrics. 1982;69(4):446-451.

16. Putet G, Senterre J, Rigo J, et al. Nutrient balance, energy utilization, and composition of weight gain in very-low-birth-weight infants fed pooled human milk or a preterm formula. J Pediatr. 1984;105(1):79-85.

17. Romera G, Figueras J, Rodriguez-Miguelez JM, et al. Energy intake, metabolic balance and growth in preterm infants fed formulas with different nonprotein energy supplements. J Pediatr Gastroenterol Nutr. 2004;38(4):407-413.

18. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85-91.

19. Rigo J, Hascoet JM, Billeaud C, et al. Growth and Nutritional Biomarkers of Preterm Infants Fed a New Powdered Human Milk Fortifier: A Randomized Trial. J Pediatr Gastroenterol Nutr. 2017;65(4):e83-e93.

20. Shah SD, Dereddy N, Jones TL, et al. Early versus Delayed Human Milk Fortification in Very Low Birth Weight Infants-A Randomized Controlled Trial. J Pediatr. 2016;174:126-131 e1.

21. Maas C, Mathes M, Bleeker C, et al. Effect of Increased Enteral Protein Intake on Growth in Human Milk-Fed Preterm Infants: A Randomized Clinical Trial. JAMA Pediatr. 2017;171(1):16-22.

22. Arslanoglu S, Moro GE, Ziegler EE. Adjustable fortification of human milk fed to preterm infants: does it make a difference? J Perinatol. 2006;26(10):614-621.

23. Brumberg HL, Kowalski L, Troxell-Dorgan A, et al. Randomized trial of enteral protein and energy supplementation in infants less than or equal to 1250 g at birth. J Perinatol. 2010;30(8):517-521.

24. Bulut O, Coban A, Uzunhan O, et al. Effects of Targeted Versus Adjustable Protein Fortification of Breast Milk on Early Growth in Very Low-Birth-Weight Preterm Infants: A Randomized Clinical Trial. Nutr Clin Pract. 2020;35(2):335-343.

25. McLeod G, Sherriff J, Hartmann PE, et al. Comparing different methods of human breast milk fortification using measured v. assumed macronutrient composition to target reference growth: a randomised controlled trial. Br J Nutr. 2016;115(3):431-439.

26. de Halleux V, Pieltain C, Senterre T, et al. Growth Benefits of Own Mother's Milk in Preterm Infants Fed Daily Individualized Fortified Human Milk. Nutrients. 2019;11(4).

27. Senterre T, Rigo J. Optimizing early nutritional support based on recent recommendations in VLBW infants and postnatal growth restriction. J Pediatr Gastroenterol Nutr. 2011;53(5):536-542.

28. Christmann V, Visser R, Engelkes M, et al. The enigma to achieve normal postnatal growth in preterm infants--using parenteral or enteral nutrition? Acta Paediatr. 2013;102(5):471-479.

29. Hu F, Tang Q, Wang Y, et al. Analysis of Nutrition Support in Very Low-Birth-Weight Infants With Extrauterine Growth Restriction. Nutr Clin Pract. 2019;34(3):436-443.

30. Olsen IE, Harris CL, Lawson ML, et al. Higher protein intake improves length, not weight, z scores in preterm infants. J Pediatr Gastroenterol Nutr. 2014;58(4):409-416.

31. Collins CT, Chua MC, Rajadurai VS, et al. Higher protein and energy intake is associated with increased weight gain in pre-term infants. J Paediatr Child Health. 2010;46(3):96-102.

32. Coviello C, Keunen K, Kersbergen KJ, et al. Effects of early nutrition and growth on brain volumes, white matter microstructure, and neurodevelopmental outcome in preterm newborns. Pediatr Res. 2018;83 (1):102-110.

33. Kadioglu Simsek G, Alyamac Dizdar E, Arayici S, Canpolat FE, et al. Comparison of the Effect of Three Different Fortification Methods on Growth of Very Low Birth Weight Infants. Breastfeed Med. 2019;14(1):63-68.

34. McLeod G, Simmer K, Sherriff J, et al. Feasibility study: Assessing influence of macronutrient intakes on preterm body composition, using air displacement plethysmography. J Paediatr Child Health. 2015;51(9):862-869.

35. Peiler A, Woelfle J, Stutte S, et al. Postnatal nutrition in extremely low birth weight infants and its impact on growth until the age of 6 years. Acta Paediatr. 2014;103(2):e61-68.

36. Johnson MJ, Wootton SA, Leaf AA, et al. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. Pediatrics. 2012;130(3):e640-e649.

37. Hamatschek C, Yousuf EI, Mollers LS, et al. Fat and Fat-Free Mass of Preterm and Term Infants from Birth to Six Months: A Review of Current Evidence. Nutrients. 2020;12(2).

38. Costa-Orvay JA, Figueras-Aloy J, Romera G, et al. The effects of varying protein and energy intakes on the growth and body composition of very low birth weight infants. Nutr J. 2011;10:140.

39. Kashyap S, Ohira-Kist K, Abildskov K, et al. Effects of quality of energy intake on growth and metabolic response of enterally fed low-birth-weight infants. Pediatric research. 2001;50(3):390-397.

40. Kashyap S, Towers HM, Sahni R, et al. Effects of quality of energy on substrate oxidation in enterally fed, low-birth-weight infants. Am J Clin Nutr 2001;74(3):374-380.

41. Wu G. Amino acids: metabolism, functions, and nutrition. Amino Acids. 2009;37(1):1-17.

42. Embleton ND, van den Akker CHP. Protein intakes to optimize outcomes for preterm infants. Semin Perinatol. 2019;43(7):151154.

43. van Goudoever JB, Vlaardingerbroek H, van den Akker CH, et al. Amino acids and proteins. World Rev Nutr Diet. 2014;110:49-63.

44. Ziegler EE, O'Donnell AM, Nelson SE, et al. Body composition of the reference fetus. Growth. 1976;40(4):329-341.

45. Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very low birthweight infant. Clin Perinatol. 2002;29(2):225-244.

46. 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.

47. Mimouni FB, Lubetzky R, Yochpaz S, et al. Preterm Human Milk Macronutrient and Energy Composition: A Systematic Review and Meta-Analysis. Clin Perinatol. 2017;44(1):165-172.

48. Boyce C, Watson M, Lazidis G, et al. Preterm human milk composition: a systematic literature review. Br J Nutr. 2016;116(6):1033-1045.

49. Koletzko B, Lapillonne A. Lipid Requirements of Preterm Infants. World Rev Nutr Diet. 2021;122:89-102.

50. Grote V, Verduci E, Scaglioni S, et al. Breast milk composition and infant nutrient intakes during the first 12 months of life. Eur J Clin Nutr. 2016;70(2):250-256.

51. Jensen CL, Lapillonne A. Docosahexaenoic acid and lactation. Prostaglandins Leukot Essent Fatty Acids. 2009;81(2-3):175-178.

52. Lapillonne A, Groh-Wargo S, Gonzalez CH, et al. Lipid needs of preterm infants: updated recommendations. J Pediatr. 2013;162(3 Suppl):S37-S47.

53. Crawford M. Placental delivery of arachidonic and docosahexaenoic acids: implications for the lipid nutrition of preterm infants. Am J Clin Nutr. 2000;71(1 Suppl):275S-284S.

54. Bernard JY, De Agostini M, Forhan A, et al. The dietary n6:n3 fatty acid ratio during pregnancy is inversely associated with child neurodevelopment in the EDEN mother-child cohort. J Nutr. 2013;143(9):1481-1488.

55. Kitamura T, Kitamura Y, Hamano H, et al. The Ratio of Docosahexaenoic Acid and Arachidonic Acid in Infant Formula Influences the Fatty Acid Composition of the Erythrocyte Membrane in Low-Birth-Weight Infants. Ann Nutr Metab. 2016;68(2):103-112.

56. Rigourd V, Lopera I, Cata F, et al. Role of Daily Milk Volume and Period of Lactation in Nutrient Content of Human Milk: Results from a Prospective Study. Nutrients. 2020;12(2).

57. Rochow N, Moller S, Fusch G, et al. Levels of lipids in preterm infants fed breast milk. Clin Nutr. 2010;29(1):94-99.

58. Stoltz Sjostrom E, Ohlund I, Tornevi A, et al. Intake and macronutrient content of human milk given to extremely preterm infants. J Hum Lact. 2014;30(4):442-449.

59. Kien CL. Digestion, absorption, and fermentation of carbohydrates in the newborn. Clin Perinatol. 1996;23(2):211-228.

60. Shulman RJ, Schanler RJ, Lau C, et al. Early feeding, feeding tolerance, and lactase activity in preterm infants. J Pediatr. 1998;133(5):645-649.

61. Shulman RJ, Feste A, Ou C. Absorption of lactose, glucose polymers, or combination in premature infants. J Pediatr. 1995;127(4):626-631.

62. Griffin MP, Hansen JW. Can the elimination of lactose from formula improve feeding tolerance in premature infants? J Pediatr. 1999;135(5):587-592.

63. Kien CL, Liechty EA, Mullett MD. Effects of lactose intake on nutritional status in premature infants. J Pediatr. 1990;116(3):446-449.

64. Kien CL, McClead RE, Cordero L, Jr. Effects of lactose intake on lactose digestion and colonic fermentation in preterm infants. J Pediatr. 1998;133(3):401-405.

65. Mihatsch WA, von Schoenaich P, Fahnenstich H, et al. Randomized, multicenter trial of two different formulas for very early enteral feeding advancement in extremely-low-birth-weight infants. J Pediatr Gastroenterol Nutr. 2001;33(2):155-159.

66. Stathos TH, Shulman RJ, Schanler RJ, et al. Effect of carbohydrates on calcium absorption in premature infants. Pediatr Res. 1996;39(4 Pt 1):666-670.

67. Farrag HM, Cowett RM. Glucose homeostasis in the micropremie. Clin Perinatol. 2000;27(1):1-22, v.

68. Van Kempen AA, Romijn JA, Ruiter AF, et al. Adaptation of glucose production and gluconeogenesis to diminishing glucose infusion in preterm infants at varying gestational ages. Pediatr Res. 2003;53(4):628-634.

69. Zamir I, Tornevi A, Abrahamsson T, et al. Hyperglycemia in Extremely Preterm Infants-Insulin Treatment, Mortality and Nutrient Intakes. J Pediatr. 2018;200:104-110.e1.

70. Stensvold HJ, Strommen K, Lang AM, et al. Early Enhanced Parenteral Nutrition, Hyperglycemia, and Death Among Extremely Low-Birth-Weight Infants. JAMA Pediatr. 2015;169(11):1003-1010.

71. Collins CT, Gibson RA, Miller J, et al. Carbohydrate intake is the main determinant of growth in infants born <33 weeks' gestation when protein intake is adequate. Nutrition. 2008;24(5):451-457.

72. Zamir I, Stoltz Sjostrom E, Edstedt Bonamy AK, et al. Postnatal nutritional intakes and hyperglycemia as determinants of blood pressure at 6.5 years of age in children born extremely preterm. Pediatr Res. 2019;86(1):115-121.

73. Amissah EA, Brown J, Harding JE. Carbohydrate supplementation of human milk to promote growth in preterm infants. Cochrane Database Syst Rev. 2018;8:CD000280.

74. Klingenberg C, Muraas FK, Isaksen CE, et al. Growth and neurodevelopment in very preterm infants receiving a high enteral volume-feeding regimen - a population-based cohort study. J Matern Fetal Neonatal Med. 2019;32(10):1664-1672.

75. Thomas N, Cherian A, Santhanam S, et al. A randomized control trial comparing two enteral feeding volumes in very low birth weight babies. J Trop Pediatr. 2012;58(1):55-58.

76. Ziegler EE, O'Donnell AM, Nelson SE, et al. Body composition of the reference fetus. Growth. 1976;40(4):329-341.

77. Fusch C, Jochum F. Water, sodium, potassium and chloride. In Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. Koletzko B, Poindexter B, Uauy R, editors. Basel: Karger; 2014.

78. Gubhaju L, Sutherland MR, Horne RS, et al. Assessment of renal functional maturation and injury in preterm neonates during the first month of life. Am J Physiol Renal Physiol. 2014;307(2):F149-158.

79. Suarez-Rivera M, Bonilla-Felix M. Fluid and electrolyte disorders in the newborn: sodium and potassium. Curr Pediatr Rev. 2014;10(2):115-122.

80. Segar DE, Segar EK, Harshman LA, et al. Physiological Approach to Sodium Supplementation in Preterm Infants. Am J Perinatol. 2018;35(10):994-1000.

81. Ertl T, Sulyok E, Nemeth M, et al. Hormonal control of sodium content in human milk. Acta Paediatr Acad Sci Hung. 1982;23(3):309-318.

82. Becker GE, Smith HA, Cooney F. Methods of milk expression for lactating women. Cochrane Database Syst Rev. 2016;9:CD006170.

83. Codo CRB, Caldas JPS, Peixoto RRA, et al. Electrolyte and Mineral Composition of Term Donor Human Milk before and after Pasteurization and of Raw Milk of Preterm Mothers. Rev Paul Pediatr. 2018;36(2):141-147.

84. Chandran S, Chua MC, Lin W, et al. Medications That Increase Osmolality and Compromise the Safety of Enteral Feeding in Preterm Infants. Neonatology. 2017;111(4):309-316.

85. Bauer J, Gerss J. Longitudinal analysis of macronutrients and minerals in human milk produced by mothers of preterm infants. Clin Nutr. 2011;30(2):215-220.

86. Grossman H, Duggan E, McCamman S, et al. The dietary chloride deficiency syndrome. Pediatrics. 1980;66(3):366-374.

87. Roy S 3rd, Arant BS Jr. Hypokalemic metabolic alkalosis in normotensive infants with elevated plasma renin activity and hyperaldosteronism: role of dietary chloride deficiency. Pediatrics. 1981;67(3):423-429.

88. Klein CJ. Nutrient requirements for preterm infant formulas. J Nutr. 2002;132(6 Suppl 1):1395S-1577S.

89. Iacobelli S, Kermorvant-Duchemin E, Bonsante F, et al. Chloride Balance in Preterm Infants during the First Week of Life. Int J Pediatr. 2012;2012:931597.

90. Besouw M, Bockenhauer D. Potassium metabolism. In: Nephrology and fluid/electrolyte physiology. Neonatology questions and controversies. 3rd ed. Oh W, editor. Philadelphia: Elsevier; 2018.

91. Bonsante F, Iacobelli S, Chantegret C, et al. The effect of parenteral nitrogen and energy intake on electrolyte balance in the preterm infant. Eur J Clin Nutr. 2011;65(10):1088-1093.

92. Moltu SJ, Strommen K, Blakstad EW, et al. Enhanced feeding in very-low-birth-weight infants may cause electrolyte disturbances and septicemia--a randomized, controlled trial. Clin Nutr. 2013;32(2):207-212.

93. Bonsante F, Iacobelli S, Latorre G, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants--it is time to change the composition of the early parenteral nutrition. PLoS One. 2013;8(8):e72880.

94. Pieltain C, de Halleux V, Senterre T, et al. Prematurity and bone health. World Rev Nutr Diet. 2013;106:181-188.

95. Committee on Nutrition of the Preterm Infant ESoPGaN. Nutrition and feeding of preterm infants. Acta Paediatr Scand Suppl. 1987;336:1-14.

96. Rustico SE, Calabria AC, Garber SJ. Metabolic bone disease of prematurity. J Clin Transl Endocrinol. 2014;1(3):85-91.

97. Tsang RC, Uauy R, Koletzko B, et al. Nutritional needs of the preterm infant. Scientific basis and practical guidelines. Cincinnati, Ohio: Digital Educational Publishing; 2005.

98. Abrams SA, Committee on N. Calcium and vitamin d requirements of enterally fed preterm infants. Pediatrics. 2013;131(5):e1676-1683.

99. Mimouni FB, Mandel D, Lubetzky R, et al. Calcium, phosphorus, magnesium and vitamin D requirements of the preterm infant. World Rev Nutr Diet. 2014;110:140-151.

100. Widdowson E, Dickerson J. The composition of the body as a whole. In: Mineral Metabolism. Comar C, Bronner F, editors. New York: Academic Press; 1961.

101. Sparks JW. Human intrauterine growth and nutrient accretion. Semin Perinatol. 1984;8(2):74-93.

102. Rigo J, De Curtis M, Pieltain C, et al. Bone mineral metabolism in the micropremie. Clin Perinatol. 2000;27(1):147-170.

103. Rigo J, Pieltain C, Viellevoye R, et al. Calcium and Phosphorus homeostasis: pathophysiology; in: Neonatology. A Practical Approach to Neonatal Diseases. Buenocore G, al. e, editors. Rome: Springer; 2012.

104. Koo WW, Warren L. Calcium and bone health in infants. Neonatal Netw. 2003;22(5):23-37.

105. Cooke R, Hollis B, Conner C, et al. Vitamin D and mineral metabolism in the very low birth weight infant receiving 400 IU of vitamin D. J Pediatr. 1990;116(3):423-428.

106. Andrieux C, Sacquet E. Effects of Maillard's reaction products on apparent mineral absorption in different parts of the digestive tract. The role of microflora. Reprod Nutr Dev. 1984;24(4):379-386.

107. Seiquer I, Delgado-Andrade C, Haro A, et al. Assessing the effects of severe heat treatment of milk on calcium bioavailability: in vitro and in vivo studies. J Dairy Sci. 2010;93(12):5635-5643.

108. Rigo J, Salle BL, Picaud JC, et al. Senterre J. Nutritional evaluation of protein hydrolysate formulas. Eur J Clin Nutr. 1995;49 Suppl 1:S26-S38.

109. Picaud JC, Lapillonne A, Rigo J, et al. Nitrogen utilization and bone mineralization in very low birth weight infants fed partially hydrolyzed preterm formula. Semin Perinatol. 2002;26(6):439-446.

110. Carnielli VP, Luijendijk IH, van Goudoever JB, et al. Feeding premature newborn infants palmitic acid in amounts and stereoisomeric position similar to that of human milk: effects on fat and mineral balance. Am J Clin Nutr. 1995;61(5):1037-1042.

111. Lucas-Herald A, Butler S, Mactier H, et al. Prevalence and characteristics of rib fractures in ex-preterm infants. Pediatrics. 2012;130(6):1116-1119.

112. O'Reilly P, Saviani M, Tou A, et al. Do preterm bones still break? Incidence of rib fracture and osteopenia of prematurity in very low birth weight infants. J Paediatr Child Health. 2020;56(6):959-963.

113. Fewtrell MS. Does early nutrition program later bone health in preterm infants? Am J Clin Nutr. 2011;94(6 Suppl):1870S-1873S.

114. Mihatsch W, Fewtrell M, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Calcium, phosphorus and magnesium. Clin Nutr. 2018;37(6 Pt B):2360-2365.

115. Rigo J, Pieltain C, Christmann V, et al. Serum Magnesium Levels in Preterm Infants Are Higher Than Adult Levels: A Systematic Literature Review and Meta-Analysis. Nutrients. 2017;9(10).

116. Mills RJ, Davies MW. Enteral iron supplementation in preterm and low birth weight infants. Cochrane Database Syst Rev. 2012(3):CD005095.

117. Jin HX, Wang RS, Chen SJ, et al. Early and late Iron supplementation for low birth weight infants: a meta-analysis. Ital J Pediatr. 2015;41:16.

118. Jasani B, Torgalkar R, Ye XY, et al. Association of Umbilical Cord Management Strategies With Outcomes of Preterm Infants: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 2021;175(4):e210102.

119. Domellof M. Meeting the Iron Needs of Low and Very Low Birth Weight Infants. Ann Nutr Metab. 2017;71 Suppl 3:16-23.

120. Alm S, Stoltz Sjostrom E, Nilsson Sommar J, et al. Erythrocyte transfusions increased the risk of elevated serum ferritin in very low birthweight infants and were associated with altered longitudinal growth. Acta Paediatr. 2020;109(7):1354-1360.

121. Domellof M, Georgieff MK. Postdischarge Iron Requirements of the Preterm Infant. J Pediatr. 2015;167(4 Suppl):S31-S35.

122. Hambidge M. Human zinc deficiency. J Nutr. 2000;130(5S Suppl):1344S-1349S.

123. Bhatia J, Griffin I, Anderson D, et al. Selected macro/micronutrient needs of the routine preterm infant. J Pediatr. 2013;162(3 Suppl):S48-55.

124. (AAP) AAoP. Pediatric Nutrition Handbook, 6th edition. RE K, editor2009.

125. Diaz-Gomez NM, Domenech E, Barroso F, et al. The effect of zinc supplementation on linear growth, body composition, and growth factors in preterm infants. Pediatrics. 2003;111(5 Pt 1):1002-1009.

126. Friel JK, Andrews WL, Matthew JD, et al. Zinc supplementation in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr. 1993;17(1):97-104.

127. Staub E, Evers K, Askie LM. Enteral zinc supplementation for prevention of morbidity and mortality in preterm neonates. Cochrane Database Syst Rev. 2021;3:CD012797.

128. Alshaikh B, Abo Zeed M, et al. Effect of enteral zinc supplementation on growth and neurodevelopment of preterm infants: a systematic review and meta-analysis. J Perinatol. 2022;42(4):430-439.

129. Wulf K, Wilhelm A, Spielmann M, et al. Frequency of symptomatic zinc deficiency in very low birth weight infants. Klin Padiatr. 2013;225(1):13-17.

130. EFSA. Dietary Reference Values for nutrients; Summary report. EFSA supporting publication 2017:e15121. https://efsa.onlinelibrary.wiley.com/toc/23978325/2017/14/12; 2017.

131. Mactier H, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. Arch Dis Child Fetal Neonatal Ed. 2005;90(2):F103-F108.

132. Mactier H. Vitamin A for preterm infants; where are we now? Semin Fetal Neonatal Med. 2013;18(3):166-171.

133. Massaro D, Massaro GD. Lung development, lung function, and retinoids. N Engl J Med. 2010;362(19):1829-1831.

134. Tammela O, Aitola M, Ikonen S. Cord blood concentrations of vitamin A in preterm infants. Early Hum Dev. 1999;56(1):39-47.

135. Mactier H, McCulloch DL, Hamilton R, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. J Pediatr. 2012;160(6):954-959 e1.

136. Darlow BA, Graham PJ, Rojas-Reyes MX. Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2016(8):CD000501.

137. Wardle SP, Hughes A, Chen S, et al. Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2001;84(1):F9-F13.

138. Basu S, Khanna P, Srivastava R, et al. Oral vitamin A supplementation in very low birth weight neonates: a randomized controlled trial. Eur J Pediatr. 2019;178(8):1255-1265.

139. Rakshasbhuvankar AA, Simmer K, Patole SK, et al. Enteral Vitamin A for Reducing Severity of Bronchopulmonary Dysplasia: A Randomized Trial. Pediatrics. 2021;147(1).

140. Ye Y, Yang X, Zhao J, et al. Early Vitamin A Supplementation for Prevention of Short-Term Morbidity and Mortality in Very-Low-Birth-Weight Infants: A Systematic Review and Meta-Analysis. Front Pediatr. 2022;10:788409.

141. Biesalski HK. Vitamin D recommendations: beyond deficiency. Ann Nutr Metab. 2011;59(1):10-16.

142. Delvin EE, Salle BL, Glorieux FH, et al. Vitamin D metabolism in preterm infants: effect of a calcium load. Biol Neonate. 1988;53(6):321-326.

143. Delvin EE, Lopez V, Levy E, et al. Developmental expression of calcitriol receptors, 9-kilodalton calcium-binding protein, and calcidiol 24-hydroxylase in human intestine. Pediatr Res. 1996;40(5):664-670.

144. Salle BL, Delvin EE, Lapillonne A, et al. Perinatal metabolism of vitamin D. Am J Clin Nutr. 2000;71(5 Suppl):1317S-24S.

145. Backstrom MC, Maki R, Kuusela AL, et al. Randomised controlled trial of vitamin D supplementation on bone density and biochemical indices in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1999;80(3):F161-166.

146. Braegger C, Campoy C, Colomb V, et al. Vitamin D in the healthy European paediatric population. J Pediatr Gastroenterol Nutr. 2013;56(6):692-701.

147. Vierge M, Laborie S, Bertholet-Thomas A, et al. [Neonatal intoxication to vitamin D in premature babies: A series of 16 cases]. Arch Pediatr. 2017;24(9):817-824.

148. Natarajan CK, Sankar MJ, Agarwal R, et al. Trial of daily vitamin D supplementation in preterm infants. Pediatrics. 2014;133(3):e628-634.

149. Anderson-Berry A, Thoene M, Wagner J, et al. Randomized trial of two doses of vitamin D3 in preterm infants <32 weeks: Dose impact on achieving desired serum 25(OH)D3 in a NICU population. PLoS One. 2017;12(10):e0185950.

150. Bozkurt O, Uras N, Sari FN, et al. Multi-dose vitamin d supplementation in stable very preterm infants: Prospective randomized trial response to three different vitamin D supplementation doses. Early Hum Dev. 2017;112:54-59.

151. Munshi UK, Graziano PD, Meunier K, et al. Serum 25 Hydroxy Vitamin D Levels in Very Low Birth Weight Infants Receiving Oral Vitamin D Supplementation. J Pediatr Gastroenterol Nutr. 2018;66(4):676-679.

152. Fort P, Salas AA, Nicola T, et al. A Comparison of 3 Vitamin D Dosing Regimens in Extremely Preterm Infants: A Randomized Controlled Trial. J Pediatr. 2016;174:132-138 e1.

153. Thibeault DW. The precarious antioxidant defenses of the preterm infant. Am J Perinatol. 2000;17(4):167-181.

154. Perrone S, Salvi G, Bellieni CV, et al. Oxidative stress and nutrition in the preterm newborn. J Pediatr Gastroenterol Nutr. 2007;45 Suppl 3:S178-182.

155. Kositamongkol S, Suthutvoravut U, Chongviriyaphan N, et al. Vitamin A and E status in very low birth weight infants. J Perinatol. 2011;31(7):471-476.

156. Greer FR. Fat-soluble vitamin supplements for enterally fed preterm infants. Neonatal Netw. 2001;20(5):7-11.

157. Bell EF, Hansen NI, Brion LP, et al. Serum tocopherol levels in very preterm infants after a single dose of vitamin E at birth. Pediatrics. 2013;132(6):e1626-e1633.

158. Kitajima H, Kanazawa T, Mori R, et al. Long-term alpha-tocopherol supplements may improve mental development in extremely low birthweight infants. Acta Paediatr. 2015;104(2):e82-89.

159. Bell EF. Upper limit of vitamin E in infant formulas. J Nutr. 1989;119(12 Suppl):1829-1831.

160. Nutrition Committee CPS. Nutrient needs and feeding of premature infants. CMAJ. 1995;152(11):1765-1785.

161. Pichler E, Pichler L. The neonatal coagulation system and the vitamin K deficiency bleeding - a mini review. Wien Med Wochenschr. 2008;158(13-14):385-395.

162. Clarke P, Mitchell SJ, Wynn R, et al. Vitamin K prophylaxis for preterm infants: a randomized, controlled trial of 3 regimens. Pediatrics. 2006;118(6):e1657-1666.

163. Clarke P. Vitamin K prophylaxis for preterm infants. Early Hum Dev. 2010;86 Suppl 1:17-20.

164. Shearer MJ. Vitamin K deficiency bleeding (VKDB) in early infancy. Blood Rev. 2009;23(2):49-59.

165. Fiesack S, Smits A, Rayyan M, et al. Belgian Consensus Recommendations to Prevent Vitamin K Deficiency Bleeding in the Term and Preterm Infant. Nutrients. 2021;13(11).

166. Greer FR. Vitamin K the basics--what's new? Early Hum Dev. 2010;86 Suppl 1:43-7.

167. Greene HL, Hambidge KM, Schanler R, et al. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. Am J Clin Nutr. 1988;48(5):1324-1342.

168. Salas AA, Kabani N, Travers CP, et al. Short versus Extended Duration of Trophic Feeding to Reduce Time to Achieve Full Enteral Feeding in Extremely Preterm Infants: An Observational Study. Neonatology. 2017;112(3):211-216.

169. McClure RJ. Trophic feeding of the preterm infant. Acta Paediatr Suppl. 2001;90(436):19-21.

170. Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. Cochrane Database Syst Rev. 2013(3):CD000504.

171. Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2014(12):CD001970.

172. Bozkurt O, Alyamac Dizdar E, et al. Prolonged minimal enteral nutrition versus early feeding advancements in preterm infants with birth weight </=1250 g: a prospective randomized trial. J Matern Fetal Neonatal Med. 2020:1-7.

173. Salas AA, Li P, Parks K, et al. Early progressive feeding in extremely preterm infants: a randomized trial. The American journal of clinical nutrition. 2018;107(3):365-370.

174. Salas AA, et al. Can early progressive feeding increase the number of days alive on full enteral feeding in extremely preterm infants? J Invest Med 2018;66(2):559.

175. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2017;8:CD001241.

176. Dorling J, Abbott J, Berrington J, et al. Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants. N Engl J Med. 2019;381(15):1434-1443.

177. Cavell B. Gastric emptying in infants fed human milk or infant formula. Acta Paediatr Scand. 1981;70(5):639-641.

178. Ewer AK, Durbin GM, Morgan ME, et al. Gastric emptying in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1994;71(1):F24-F27.

179. Perrella SL, Hepworth AR, Gridneva Z, et al. Gastric Emptying and Curding of Pasteurized Donor Human Milk and Mother's Own Milk in Preterm Infants. J Pediatr Gastroenterol Nutr. 2015;61(1):125-129.

180. Yigit S, Akgoz A, Memisoglu A, et al. Breast milk fortification: effect on gastric emptying. J Matern Fetal Neonatal Med. 2008;21(11):843-846.

181. Riskin A, Cohen K, Kugelman A, et al. The Impact of Routine Evaluation of Gastric Residual Volumes on the Time to Achieve Full Enteral Feeding in Preterm Infants. J Pediatr. 2017;189:128-134.

182. Abiramalatha T, Thanigainathan S, Ninan B. Routine monitoring of gastric residual for prevention of necrotising enterocolitis in preterm infants. Cochrane Database Syst Rev. 2019;7:CD012937.

183. Klingenberg C, Embleton ND, Jacobs SE, et al. Enteral feeding practices in very preterm infants: an international survey. Arch Dis Child Fetal Neonatal Ed. 2012;97(1):F56-F61.

184. Miller M, Vaidya R, Rastogi D, et al. From parenteral to enteral nutrition: a nutrition-based approach for evaluating postnatal growth failure in preterm infants. JPEN J Parenter Enteral Nutr. 2014;38(4):489-497.

185. de Waard M, Li Y, Zhu Y, et al. Time to Full Enteral Feeding for Very Low-Birth-Weight Infants Varies Markedly Among Hospitals Worldwide But May Not Be Associated With Incidence of Necrotizing Enterocolitis: The NEOMUNE-NeoNutriNet Cohort Study. JPEN J Parenter Enteral Nutr. 2019;43(5):658-667.

186. Spath C, Zamir I, Sjostrom ES, et al. Use of Concentrated Parenteral Nutrition Solutions Is Associated With Improved Nutrient Intakes and Postnatal Growth in Very Low-Birth-Weight Infants. JPEN J Parenter Enteral Nutr. 2020;44(2):327-336.

187. Adamkin DH. Early aggressive nutrition: parenteral amino acids and minimal enteral nutrition for extremely low birth weight (<1 000 g) infants. Minerva Pediatr. 2007;59(4):369-377.

188. Miller M, Donda K, Bhutada A, et al. Transitioning Preterm Infants From Parenteral Nutrition: A Comparison of 2 Protocols. JPEN J Parenter Enteral Nutr. 2017;41(8):1371-1379.

189. Brennan AM, Kiely ME, Fenton S, et al. Standardized Parenteral Nutrition for the Transition Phase in Preterm Infants: A Bag That Fits. Nutrients. 2018;10(2).

190. Moltu SJ, Blakstad EW, Strommen K, et al. Enhanced feeding and diminished postnatal growth failure in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr. 2014;58(3):344-351.

191. Roggero P, Gianni ML, Orsi A, et al. Implementation of nutritional strategies decreases postnatal growth restriction in preterm infants. PLoS One. 2012;7(12):e51166.

192. Butler TJ, Szekely LJ, Grow JL. A standardized nutrition approach for very low birth weight neonates improves outcomes, reduces cost and is not associated with increased rates of necrotizing enterocolitis, sepsis or mortality. J Perinatol. 2013;33(11):851-857.

193. Loomis T, Byham-Gray L, Ziegler J, et al. Impact of standardized feeding guidelines on enteral nutrition administration, growth outcomes, metabolic bone disease, and cholestasis in the NICU. J Pediatr Gastroenterol Nutr. 2014;59(1):93-98.

194. Jadcherla SR, Dail J, Malkar MB, et al. Impact of Process Optimization and Quality Improvement Measures on Neonatal Feeding Outcomes at an All-Referral Neonatal Intensive Care Unit. JPEN J Parenter Enteral Nutr. 2016;40(5):646-655.

195. Belling-Dierks F, Glaser K, Wirbelauer J, et al. Does rapid enteral feeding increase intestinal morbidity in very low birth weight infants? A retrospective analysis. J Matern Fetal Neonatal Med. 2017;30(22):2690-2696.

196. Johnson MJ, Leaf AA, Pearson F, et al. Successfully implementing and embedding guidelines to improve the nutrition and growth of preterm infants in neonatal intensive care: a prospective interventional study. BMJ Open. 2017;7(12):e017727.

197. Dutta S, Singh B, Chessell L, et al. Guidelines for feeding very low birth weight infants. Nutrients. 2015;7(1):423-442.

198. Barrett CE, Thornton K, Boateng B. A retrospective review of the incidence of necrotizing enterocolitis in very low birth weight neonates before and after the establishment of feeding guidelines. J Invest Med 2011;59(2):450-451.

199. Stocks J. Effect of nasogastric tubes on nasal resistance during infancy. Arch Dis Child. 1980;55(1):17-21.

200. Purcell M. Response in the newborn to raised upper airway resistance. Arch Dis Child. 1976;51(8):602-607.

201. Tonkin SL, Partridge J, Beach D, et al. The pharyngeal effect of partial nasal obstruction. Pediatrics. 1979;63(2):261-271.

202. Watson J, McGuire W. Nasal versus oral route for placing feeding tubes in preterm or low birth weight infants. Cochrane Database Syst Rev. 2013(2):CD003952.

203. Lagercrantz H, Edwards D, Henderson-Smart D, et al. Autonomic reflexes in preterm infants. Acta Paediatr Scand. 1990;79(8-9):721-728.

204. Ducrocq J, Cardot V, Tourneux P, et al. Use of the oculocardiac reflex to assess vagal reactivity during quiet sleep in neonates. J Sleep Res. 2006;15(2):167-173.

205. de Boer JC, Smit BJ, Mainous RO. Nasogastric tube position and intragastric air collection in a neonatal intensive care population. Adv Neonatal Care. 2009;9(6):293-298.

206. Quandt D, Schraner T, Ulrich Bucher H, et al. Malposition of feeding tubes in neonates: is it an issue? J Pediatr Gastroenterol Nutr. 2009;48(5):608-611.

207. Arens R, Reichman B. Grooved palate associated with prolonged use of orogastric feeding tubes in premature infants. J Oral Maxillofac Surg. 1992;50(1):64-65.

208. Aynsley-Green A, Adrian TE, Bloom SR. Feeding and the development of enteroinsular hormone secretion in the preterm infant: effects of continuous gastric infusions of human milk compared with intermittent boluses. Acta Paediatr Scand. 1982;71(3):379-383.

209. Razak A. Two-Hourly versus Three-Hourly Feeding in Very Low-Birth-Weight Infants: A Systematic Review and Meta-Analysis. Am J Perinatol. 2020;37(9):898-906.

210. Bozzetti V, Paterlini G, De Lorenzo P, et al. Impact of Continuous vs Bolus Feeding on Splanchnic Perfusion in Very Low Birth Weight Infants: A Randomized Trial. J Pediatr. 2016;176:86-92 e2.

211. Grant J, Denne SC. Effect of intermittent versus continuous enteral feeding on energy expenditure in premature infants. J Pediatr. 1991;118(6):928-932.

212. Wang Y, Zhu W, Luo BR. Continuous feeding versus intermittent bolus feeding for premature infants with low birth weight: a meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2020;74(5):775-783.

213. Castro M, Asbury M, Shama S, et al. Energy and Fat Intake for Preterm Infants Fed Donor Milk Is Significantly Impacted by Enteral Feeding Method. JPEN J Parenter Enteral Nutr. 2019;43(1):162-165.

214. Martini S, Aceti A, Furini M, et al. Effect of Different Tube Feeding Methods on the Delivery of Docosahexaenoic and Arachidonic Acid: An In Vitro Pilot Study. JPEN J Parenter Enteral Nutr. 2019;43(4):550-556.

215. Dollberg S, Kuint J, Mazkereth R, et al. Feeding tolerance in preterm infants: randomized trial of bolus and continuous feeding. J Am Coll Nutr. 2000;19(6):797-800.

216. Corvaglia L, Martini S, Aceti A, et al. Cardiorespiratory events with bolus versus continuous enteral feeding in healthy preterm infants. J Pediatr. 2014;165(6):1255-1257.

217. Akintorin SM, Kamat M, Pildes RS, et al. A prospective randomized trial of feeding methods in very low birth weight infants. Pediatrics. 1997;100(4):E4.

218. Schanler RJ, Shulman RJ, Lau C, et al. Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. Pediatrics. 1999;103(2):434-439.

219. Toce SS, Keenan WJ, Homan SM. Enteral feeding in very-low-birth-weight infants. A comparison of two nasogastric methods. Am J Dis Child. 1987;141(4):439-444.

220. Lau C. Development of Suck and Swallow Mechanisms in Infants. Ann Nutr Metab. 2015;66 Suppl 5:7-14.

221. Gewolb IH, Vice FL. Abnormalities in the coordination of respiration and swallow in preterm infants with bronchopulmonary dysplasia. Dev Med Child Neurol. 2006;48(7):595-599.

222. Hanin M, Nuthakki S, Malkar MB,et al. Safety and Efficacy of Oral Feeding in Infants with BPD on Nasal CPAP. Dysphagia. 2015;30(2):121-127.

223. Dalgleish SR, Kostecky LL, Blachly N. Eating in "SINC": Safe Individualized Nipple-Feeding Competence, a Quality Improvement Project to Explore Infant-Driven Oral Feeding for Very Premature Infants Requiring Noninvasive Respiratory Support. Neonatal Netw. 2016;35(4):217-227.

224. Leibel SL, Castro M, McBride T, et al. Comparison of Continuous positive airway pressure versus High flow nasal cannula for Oral feeding Preterm infants (CHOmP): randomized pilot study. J Matern Fetal Neonatal Med. 2020:1-7.

225. Ferrara L, Bidiwala A, Sher I, et al. Effect of nasal continuous positive airway pressure on the pharyngeal swallow in neonates. J Perinatol. 2017;37(4):398-403.

226. Watson J, McGuire W. Responsive versus scheduled feeding for preterm infants. Cochrane Database Syst Rev. 2015(10):CD005255.

227. Foster JP, Psaila K, Patterson T. Non-nutritive sucking for increasing physiologic stability and nutrition in preterm infants. Cochrane Database Syst Rev. 2016;10:CD001071.

228. Fucile S, McFarland DH, Gisel EG, et al. Oral and nonoral sensorimotor interventions facilitate suck-swallow-respiration functions and their coordination in preterm infants. Early Hum Dev. 2012;88(6):345-350.

229. Rustam LB, Masri S, Atallah N, et al. Sensorimotor therapy and time to full oral feeding in <33weeks infants. Early Hum Dev. 2016;99:1-5.

230. McKechnie AC, Eglash A. Nipple shields: a review of the literature. Breastfeed Med. 2010;5(6):309-314.

231. Chow S, Chow R, Popovic M, et al. The Use of Nipple Shields: A Review. Front Public Health. 2015;3:236.

232. Maastrup R, Walloee S, Kronborg H. Nipple shield use in preterm infants: Prevalence, motives for use and association with exclusive breastfeeding-Results from a national cohort study. PLoS One. 2019;14(9):e0222811.

233. Poindexter B. Approaches to Growth Faltering. In: Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Koletzko B, Poindexter B, Uauy R, editors. Basel: Karger; 2014.

234. Lane RH. Fetal programming, epigenetics, and adult onset disease. Clin Perinatol. 2014;41(4):815-831.

235. Rochow N, Raja P, Liu K, et al. Physiological adjustment to postnatal growth trajectories in healthy preterm infants. Pediatric research. 2016;79(6):870-879.

236. Landau-Crangle E, Rochow N, Fenton TR, et al. Individualized Postnatal Growth Trajectories for Preterm Infants. JPEN J Parenter Enteral Nutr. 2018;42(6):1084-1092.

237. Asbury MR, Unger S, Kiss A, et al. Optimizing the growth of very-low-birth-weight infants requires targeting both nutritional and nonnutritional modifiable factors specific to stage of hospitalization. Am J Clin Nutr. 2019;110(6):1384-1394.

238. Molony C, Hiscock R, Kaufman J, et al, Growth trajectory of preterm small-for-gestational-age neonates. J Matern Fetal Neonatal Med 2021;1-7.

239. Moro GE, Arslanoglu S, Bertino E, , et al. XII. Human Milk in Feeding Premature Infants: Consensus Statement. J Pediatr Gastroenterol Nutr. 2015;61 Suppl 1:S16-9.

240. Rochow N, Landau-Crangle E, So HY, et al. Z-score differences based on cross-sectional growth charts do not reflect the growth rate of very low birth weight infants. PLoS One. 2019;14(5):e0216048.

241. Toftlund LH, Halken S, Agertoft L,et al. Catch-Up Growth, Rapid Weight Growth, and Continuous Growth from Birth to 6 Years of Age in Very-Preterm-Born Children. Neonatology. 2018;114(4):285-293.

242. Nasuf AWA, Ojha S, Dorling J. Oropharyngeal colostrum in preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2018;9:CD011921.

243. Tao J, Mao J, Yang J, et al. Effects of oropharyngeal administration of colostrum on the incidence of necrotizing enterocolitis, late-onset sepsis, and death in preterm infants: a meta-analysis of RCTs. Eur J Clin Nutr. 2020;74(8):1122-1131.

244. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev. 2019;7:CD002971.

245. Silano M, Milani GP, Fattore G, et al. Donor human milk and risk of surgical necrotizing enterocolitis: A meta-analysis. Clinical nutrition (Edinburgh, Scotland). 2019;38(3):1061-1066.

246. Josephson CD, Caliendo AM, Easley KA, et al. Blood transfusion and breast milk transmission of cytomegalovirus in very low-birth-weight infants: a prospective cohort study. JAMA Pediatr. 2014;168(11):1054-1062.

247. Omarsdottir S, Casper C, Naver L, et al. Cytomegalovirus infection and neonatal outcome in extremely preterm infants after freezing of maternal milk. Pediatr Infect Dis J. 2015;34(5):482-489.

248. Kurath S, Halwachs-Baumann G, Muller W, et al. Transmission of cytomegalovirus via breast milk to the prematurely born infant: a systematic review. Clin Microbiol Infect. 2010;16(8):1172-1178.

249. Lanzieri TM, Dollard SC, Josephson CD, et al. Breast milk-acquired cytomegalovirus infection and disease in VLBW and premature infants. Pediatrics. 2013;131(6):e1937-1945.

250. Stark A, Cantrell S, Greenberg RG, et al. Long-term Outcomes after Postnatal Cytomegalovirus Infection in Low Birthweight Preterm Infants: A Systematic Review. Pediatr Infect Dis J. 2021;40(6):571-581.

251. Gunkel J, de Vries LS, Jongmans M, et al. Outcome of Preterm Infants With Postnatal Cytomegalovirus Infection. Pediatrics. 2018;141(2).

252. Turner KM, Lee HC, Boppana SB, et al. Incidence and impact of CMV infection in very low birth weight infants. Pediatrics. 2014;133(3):e609-15.

253. Cossey V, Vanhole C, Eerdekens A, et al. Pasteurization of mother's own milk for preterm infants does not reduce the incidence of late-onset sepsis. Neonatology. 2013;103(3):170-176.

254. De Curtis M, Candusso M, Pieltain C, et al. Effect of fortification on the osmolality of human milk. Arch Dis Child Fetal Neonatal Ed. 1999;81(2):F141-143.

255. listed Na. Commentary on breast-feeding and infant formulas, including proposed standards for formulas. Pediatrics. 1976;57(2):278-285.

256. Ellis ZM, Tan HSG, Embleton ND, et al. Milk feed osmolality and adverse events in newborn infants and animals: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2019;104(3):F333-F340.

257. Pearson F, Johnson MJ, Leaf AA. Milk osmolality: does it matter? Arch Dis Child Fetal Neonatal Ed. 2013;98(2):F166-169.

258. Agarwal R, Singal A, Aggarwal R, et al. Effect of fortification with human milk fortifier (HMF) and other fortifying agents on the osmolality of preterm breast milk. Indian Pediatr. 2004;41(1):63-67.

259. Kreins N, Buffin R, Michel-Molnar D, et al. Individualized Fortification Influences the Osmolality of Human Milk. Front Pediatr. 2018;6:322.

260. Kreissl A, Zwiauer V, Repa A, et al. Effect of fortifiers and additional protein on the osmolarity of human milk: is it still safe for the premature infant? J Pediatr Gastroenterol Nutr. 2013;57(4):432-437.

261. Sauret A, Andro-Garcon MC, Chauvel J, et al. Osmolality of a fortified human preterm milk: The effect of fortifier dosage, gestational age, lactation stage, and hospital practices. Arch Pediatr. 2018;25(7):411-415.

262. Choi A, Fusch G, Rochow N, et al Target Fortification of Breast Milk: Predicting the Final Osmolality of the Feeds. PLoS One. 2016;11(2):e0148941.

263. Srinivasan L, Bokiniec R, King C, et al. Increased osmolality of breast milk with therapeutic additives. Arch Dis Child Fetal Neonatal Ed. 2004;89(6):F514-F517.

264. Sievers E, Santer R, Oldigs H-D, et al. Gastrointestinal passage time in preterm infants. Monatsschr Kinderheilkd 1995;143 SuppL 2, S76-S80.

265. Picaud JC, Rigo J, Normand S, et al. Nutritional efficacy of preterm formula with a partially hydrolyzed protein source: a randomized pilot study. J Pediatr Gastroenterol Nutr. 2001;32(5):555-561.

266. Mihatsch WA, Hogel J, Pohlandt F. Hydrolysed protein accelerates the gastrointestinal transport of formula in preterm infants. Acta Paediatr. 2001;90(2):196-198.

267. Mihatsch WA, Franz AR, Hogel J, et al. Hydrolyzed protein accelerates feeding advancement in very low birth weight infants. Pediatrics. 2002;110(6):1199-1203.

268. Cooke R, Embleton N, Rigo J, et al. High protein pre-term infant formula: effect on nutrient balance, metabolic status and growth. Pediatr Res. 2006;59(2):265-270.

269. Florendo KN, Bellflower B, van Zwol A, et al. Growthe in preterm infants fed either a partially hydrolyzed whey or an intact casein/whey preterm infant formula. J Perinatol. 2009;29(2):106-111.

270. He W, Pan JH. [Clinical effect of extensively hydrolyzed formula in preterm infants: an analysis of 327 cases]. Zhongguo Dang Dai Er Ke Za Zhi. 2017;19(8):856-860.

271. Yu MX, Zhuang SQ, Wang DH, et al. [Effects of extensively hydrolyzed protein formula on feeding and growth in preterm infants: a multicenter controlled clinical study]. Zhongguo Dang Dai Er Ke Za Zhi. 2014;16(7):684-690.

272. Li XM, Jiang J, Wu Y, et al. [Effect of different feeding initiation formulas on very low birth weight infants]. Zhongguo Dang Dai Er Ke Za Zhi. 2019;21(8):777-782.

273. Ng DHC, Klassen JR, Embleton ND, et al. Protein hydrolysate versus standard formula for preterm infants. Cochrane Database Syst Rev. 2019;7:CD012412.

274. Uribarri J, del Castillo MD, de la Maza MP, et al. Dietary advanced glycation end products and their role in health and disease. Adv Nutr. 2015;6(4):461-473.

275. Caudill MA, Strupp BJ, Muscalu L, et al. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. FASEB J. 2018;32(4):2172-2180.

276. Bernhard W, Lange R, Graepler-Mainka U, et al. Choline Supplementation in Cystic Fibrosis-The Metabolic and Clinical Impact. Nutrients. 2019;11(3).

277. Andrew MJ, Parr JR, Montague-Johnson C, et al. Nutritional intervention and neurodevelopmental outcome in infants with suspected cerebral palsy: the Dolphin infant double-blind randomized controlled trial. Dev Med Child Neurol. 2018;60(9):906-913.

278. Brown JV, Embleton ND, Harding JE, et al. Multi-nutrient fortification of human milk for preterm infants. Cochrane Database Syst Rev. 2016(5):CD000343.

279. Alyahya W, Simpson J, Garcia AL, Mactier H, Edwards CAet al. Early versus Delayed Fortification of Human Milk in Preterm Infants: A Systematic Review. Neonatology. 2020;117(1):24-32.

280. Rochow N, Fusch G, Zapanta B, et al. Target fortification of breast milk: how often should milk analysis be done? Nutrients. 2015;7(4):2297-310.

281. Morlacchi L, Mallardi D, Gianni ML, et al. Is targeted fortification of human breast milk an optimal nutrition strategy for preterm infants? An interventional study. J Transl Med. 2016;14(1):195.

282. Arslanoglu S, Boquien CY, King C, et al. Fortification of Human Milk for Preterm Infants: Update and Recommendations of the European Milk Bank Association (EMBA) Working Group on Human Milk Fortification. Front Pediatr. 2019;7:76.

283. Fabrizio V, Trzaski JM, Brownell EA, et al. Individualized versus standard diet fortification for growth and development in preterm infants receiving human milk. Cochrane Database Syst Rev. 2020;11:CD013465.

Table 1. ESPGHAN CoN recommendations for enteral nutrient intakes

	ESPGHAN 2010 Recommendation	**ESPGHAN 2022 Recommendation**
Fluid (ml/kg/day)	135-200	**150-180 (135-200)**
Energy (kcal/kg/day)	110-135	**115-140 (-160)**
Protein (g/kg/day)	3.5-4.5	**3.5-4.0 (-4.5)**
Fat (g/kg/day)	4.8-6.6	**4.8-8.1**
Linolenic acid (mg/kg/day)	385-1540	**385-1540**
a-Linoleic (mg/kg/day)	>55	**≥55**
DHA (mg/kg/day)	12-30	**30-65**
ARA (mg/kg/day)	18-42	**30-100**
EPA (mg/kg/day)	-	**< 20**
Carbohydrate (g/kg/day)	11.6-13.2	**11-15 (-17)**
Sodium (mmol/kg/day)	3.0-5.0	**3.0-5.0 (-8.0)**
Chloride (mmol/kg/day)	3.0-5.0	**3.0-5.0 (-8.0)**
Potassium (mmol/kg/day)	1.7-3.4	**2.3-4.6**
Calcium (mmol/kg/day)	3.0-3.5	**3.0-5.0**
Phosphorus (mmol/kg/day)	1.9-2.9	**2.2-3.7**
Magnesium (mmol/kg/day)	0.3-0.6	**0.4-0.5**
Iron (mg/kg/day)	2-3	**2.0-3.0 (-6.0)**
Zinc (mg/kg/day)	1.1-2.0	**2.0-3.0**
Copper (µg/kg/day)	100-132	**120-230**
Selenium (µg/kg/day)	5-10	**7-10**
Manganese (µg/kg/day)	<27.5	**1-15**
Iodine (µg/kg/day)	11-55	**11-55**
Chromium (µg/kg/day)	0.03-1.23	**0.03-2.25**
Molybdenum (µg/kg/day)	0.3-5	**0.3-5.0**
Thiamine (B1) (µg/kg/day)	140-300	**140-290**
Pantothenic acid (mg/kg/day)	0.33-2.1	**0.6-2.2**
Biotin (µg/kg/day)	1.7-16.5	**3.5-15**
Niacin (µg/kg/day)	380-5500	**1100-5700**
Ascorbic acid (vitamin C) (mg/kg/day)	11-46	**17-43**
Riboflavin (B2) (µg/kg/day)	200-400	**200-430**
Pyridoxine (µg/kg/day)	45-300	**70-290**
Folic acid (µg/kg/day)	35-100	**23-100**
Cobalamin (B12) (µg/kg/day)	0.1-0.77	**0.1-0.6**
Vitamin A (iU/kg/day)	1333-3300 (400-1000µg retinol ester/kg/d)	**1333-3300 (400-1000µg retinol ester/kg/d)**
Vitamin D (iU/kg/day)	800-1000 iU/day	**400-700 iU/kg/day (<1000)**
Vitamin E (mg/kg/day)	2.2-11	**2.2-11**
Vitamin K (µg/kg/day)	4.4-28	**4.4-28**

Footnote: figures in brackets represent ranges or upper intakes that might occasionally be needed in routine clinical practice under certain conditions. See text for details.