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Principles of feeding the preterm infant

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Learning Objectives

- Understanding the differences in pre- and postnatal growth factors.
- The importance and impact of early aggressive nutritional support.
- Timing of nutritional support concerning start of parenteral and enteral nutrition.
- Supplementation of vitamins and micronutrients.
- Treatment of intestinal failure-associated liver disease.

Key Messages

- Human milk is preferred in preterm infants for its protective effects against necrotising enterocolitis, inflammation, and neurodevelopmental delay. As human milk does not meet the demands of very preterm infants for optimal growth and development, breast milk fortifier should be added.
- Start with small-volume enteral feeds (10–30 ml/kg/d) as soon as possible after birth and supplement with parenteral nutrition. In those below 2500 g, increase the enteral feeding intake with 20–30 ml/kg/d, if tolerated well.
- Very low birth weight infants are prone to postnatal growth retardation and altered body composition. Early parenteral amino acid and lipid administration can prevent protein loss and facilitate growth in the neonatal period.
- After a physiological weight loss of 7%–10 % 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 few weeks or months post-term. A pragmatic aim is not losing more than 1 Standard Deviation Score (SDS) in weight and HC from birth to discharge.
- Growth is essential for preterm infants. After discharge from the hospital, (fortified) breast milk or post-discharge formula should be given until a weight for age standard deviation score of −1 is reached or until 6 months corrected age (corrected for gestational age). Excessive catch up growth should be avoided.
- When supplementing amino acids, sufficient electrolyte supply (especially phosphate, potassium and magnesium) is needed to prevent neonatal refeeding-like syndrome.

1. Introduction and rationale of feeding the preterm infant

1.1. General

Preterm birth, defined as being born before 37 weeks of gestation, is the leading cause of perinatal mortality and morbidity in developed countries. Major innovations, such as artificial ventilation and antenatal steroids, have increased the survival rates significantly. However, short- and long-term morbidity rates, e.g. of growth failure and long-term neurodevelopmental impairment, are still high, and of great concern for neonatologists [1]. Low in-hospital growth velocity is associated with cerebral palsy, mental and psychomotor developmental index scores of <70, and neurodevelopmental impairment [2]. On the other hand, growing evidence suggests that excess catch-up growth is associated with

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cardiometabolic risks in later life. Preventing in-hospital growth retardation while not overfeeding is a challenge, that calls for adequate enteral and parenteral feeding strategies.

Over the last decades, dramatic improvements in neonatal medicine have resulted in increasing survival rates of preterm infants born as young as 22–24 weeks' gestational age and as small as 400–500 g. Nowadays, these very immature infants are regularly admitted to neonatal intensive care units. In these infants, it is a major challenge to achieve healthy growth in the weeks to months after birth. Although over the past decades much progress has been made in the field of nutrition, many uncertainties remain about the requirements of preterm infants. Although the short- and long-term effects of not meeting caloric and protein requirements have been shown to be associated with adverse outcomes, the exact needs for infants to promote optimal growth are still not defined [3].

1.2. Prenatal and postnatal growth factors

During infancy and childhood, growth is growth hormone (GH)-dependent, while prenatal growth is not. Although GH is high during pregnancy, GH has little effect on the fetal insulin-like growth factor (IGF) axis [4]. Both animal studies and human studies show that insulin-like growth factor type II (IGF-II) is the dominant factor for fetal growth. The role of IGF-II diminishes during pregnancy, with no influence on growth at the end of the third trimester. Of interest is that early fetal growth is independent of nutrient supply, since the influence of nutrition on IGF-II is limited. Insulin growth factor type I (IGF-I) takes over the role of growth regulator from IGF-II during the second half of pregnancy. IGF-I is mainly synthesized in the liver, under the control of insulin. Its production and secretion are also influenced by thyroid hormones, glucocorticoids, and nutrient supply. In healthy term-born infants IGF-I (which allows influence by the environment, e.g. by nutrition) remains dominant for the first 6 months after birth. Thereafter, there is a shift from insulin and IGF as the main controller to growth hormone, and thereby it is possible to gain maximal growth potential. Fetal IGF-I levels gradually increase during pregnancy; in preterm infants there is a quick surge in IGF-I levels after birth and thereafter IGF-I levels slowly seem to increase. Little is known to date on the long-term relevance of these findings and their impact on the possibility of preterm infants achieving their full growth potential.

1.3. Postnatal growth and growth failure

World Health Organization (WHO) in-utero data, indicating an average fetal 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 provide useful guidance. After birth, postnatal contraction of extracellular water spaces occurs, leading to significant weight loss. Interrupting the umbilical nutrient supply, which can not be fully compensated by enteral and parenteral nutrition in the first few days, leads to a temporary postnatal nutrition deficit, adding to this effect. This results in neonatal weight typically declining by 7–10 % (−0.8 Z-score), reaching a nadir at days 3–4 in both term and preterm infants. 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 few weeks or months post-term. A pragmatic aim is not losing more than 1 Standard Deviation Score (SDS) in weight and head circumference (HC) from birth to discharge [5].

Growth failure after preterm birth is still common and results from a complex interaction of many factors, including morbidities affecting nutrient requirements, endocrine abnormalities, central nervous system damage, difficulties in suck and swallow coordination, and administration of drugs that affect nutrient metabolism. In the past decades, the principal contributor to the high levels of postnatal growth restriction during hospital stay has been found to be malnutrition, often due to inadequate provision of nutrients [6]. Preterm birth, intra-uterine growth retardation (IUGR) and extra-uterine growth retardation (EUGR) are all associated with long-term adverse metabolic and cardiovascular consequences.

The incidence of EUGR varies between centres and increases with decreasing gestational age and birth weight. Factors that are independently associated with EUGR are male sex, need for assisted ventilation on day 1 of life, a history of necrotizing enterocolitis, oxygen dependency at 28 days of age, and the need for steroid use during the hospital stay [7].

The current feeding strategy for preterm infants includes early, aggressive parenteral nutrition containing carbohydrates, amino acids and lipids. Several studies have shown that preterm infants, despite these aggressive feeding strategies, are significantly lighter and shorter and have an altered body composition when reaching corrected term age than those born at term age.

2. Nutritional management of the preterm infant

Table 1 summarizes the recommendation for enteral (EN) and parenteral nutrition (PN) for preterm infants [8,9].

2.1. Fetal nutrition

During human pregnancy, the fetus receives nutrients via the umbilical cord. Besides glucose, used as a fuel, the fetus receives amino acids and lipids as well. In utero, the transfer of glucose across the placenta averages 8 mg/kg/min in the third trimester. Amino acids are also transferred across the placenta continuously. This transfer of amino acids greatly exceeds fetal protein accretion requirements. The amino acid excess is oxidized, thereby contributing significantly to fetal energy generation.

Lipids are transported to the fetus in the form of long-chain polyunsaturated fatty acids (PUFA). Although PUFAs are transported throughout gestation to the fetus, more than 90 % of fetal fat mass is deposited during the third trimester. Lipids are of particular relevance because of their numerous physiological functions (metabolic, energetic, and structural), and for the supply of essential n-3 and n-6 fatty acids, which are necessary for the development of the central nervous system of the fetus.

2.2. Neonatal nutrition: fluids, energy, macronutrients and micronutrients

After birth of a preterm infant it is necessary to start nutritional support immediately, firstly to prevent hypoglycaemia, and secondly to limit nutrition deficits and to enhance growth. In the first week after birth the amount and type of nutrition is dependent on enteral feeding tolerance and the fluid needs in the first days after birth. Feeding enterally is preferred over parentally as far it is tolerated. Limiting the period of parenteral feeding reduces the risk of metabolic and electrolyte imbalance, catheter related sepsis, discomfort related to puncturing (central) venous access, catheter related thrombosis and intestinal failure-associated liver disease (IFALD). However, because most preterm infants cannot be fully fed enterally after birth, parenteral nutrition is started directly after birth and weaned thereafter as enteral feeding is increased.

Table 1
Recommendations for enteral and parenteral nutrition.

	Enteral Nutrition (EN)	Parenteral Nutrition (PN)
Fluids, ml/kg/day	150-180 (135–200)	140-160 (–180)
Energy, kcal/kg/day	115-140 (–160)	90–120
Protein/amino acids, g/kg/day	3.5–4.0 (–4.4)	2.5–3.5
Protein/energy ratio (g/100 kcal)	2.8–3.6	2.9–3.9
Fat, g/kg/day	4.8–8.1	1.5–3.0
Carbohydrate, g/kg/day	11-15 (–17)	11.5–14.4
Calcium mmol/kg/day		
first day		0.8–2.0
growing premature	3.0–5.0	1.6–3.5
Phosphorus mmol/kg/day		
first day		1.0–2.0
growing premature	2.2–3.7	1.6–3.5
Calcium/phosphorus ratio	≤1,4	0.8–1.0
Iron (mg/kg/day)	2.0–3.0	0.20–0.25

Figures in brackets represent ranges or upper intakes that might occasionally be needed in clinical practice under certain conditions.

Parenteral nutrition requires venous access that can be either peripheral or central. In the case of prolonged dependency on parenteral nutrition or hyperosmolar solutions, central venous access is recommended.

2.2.1. Fluids

Preterm infants have high fluid requirements due to immature renal function, high water losses, higher surface area to body volume ratio, and high growth rates. Fluid tolerance is limited in the first days of life due to renal adjustment, with large variability between infants depending on the individual clinical situation and dietary needs, parenteral and/or enteral needs. The optimal water intake may also differ depending on macronutrient intake, as higher intakes of protein likely require higher fluid intakes. Commonly, fluid supply is increased daily in the first week of life. In the first days postnatally, when intake mainly depends on parenteral supply, fluid intake is increased daily, from around 60–80 ml/kg/d, depending on birth weight, to 150–180 ml/kg/d on day 6 [8]. In the stable phase, when enteral feeding is the primary fluid resource, 135–150 ml/kg/day may be considered safe to maintain body homeostasis and avoid renal compromise, and in individual preterm infants enteral fluid intakes up to 200 ml/kg/day may be appropriate and safe depending on the current clinical status [9].

2.2.2. Energy

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). In general, parenteral energy requirements are lower than enteral requirements, particularly if there is significant intestinal immaturity as is usually the case in preterm infants. The estimated average extra energy requirements for growth are ~3.6–4.7 kcal/g. To achieve 17–20 g/kg/d 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 60–70 kcal/kg/d would be 106–138 kcal/kg/d. Allowing for energy lost in stool (5%–10 %), this equates to a total energy intake for enteral nutrition of approximately 115–160 kcal/kg/d. 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 in the appropriate proportions might have implications for long-term health. Studies suggest that the optimal enteral PER for preterm born infants is 2.8–3.6g/100 kcal, with PERs at the higher end of this range associated with improved weight gain and FFM accretion.

Concerning the administration of early PN in very low birth weight infants (VLBW), to approximate intra-uterine lean body mass accretion and growth, energy intakes of 90–120 kcal/kg/day should be provided [10].

Concerning EN a reasonable range of total energy intake for most healthy growing preterm born infants is 115–140 kcal/kg/d. Energy intakes >140 kcal/kg/d 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 160 kcal/kg/d. Provided that energy and protein intakes are within the recommended ranges, a PER of 2.8–3.6g/100 kcal is recommended.

2.2.3. Carbohydrates

Preterm-born infants are at increased risk of hypoglycaemia as well as hyperglycaemia. Carbohydrates are a major source of energy and an appropriate dose is crucial in preventing hypo- and hyperglycaemia. Glucose is the principal circulating carbohydrate, the primary source of energy for the brain and the only carbohydrate in PN. The balance between supply and consumption of glucose determines the plasma glucose levels. The supply is partly exogenous by enteral or parenteral nutrition and partly derived from endogenous production, e.g. gluconeogenesis and glycogenolysis. Glucose can be used in cells for energy generation or it can be stored, in the form of fat or glycogen. In utero, the transfer of glucose across the placenta averages 8 mg/kg/min, which is not reached by endogenous glucose production in preterm infants after birth. Therefore, preterm infants depend on parenteral glucose administration. Furthermore, the insulin response to hyperglycaemia is limited in VLBW and, especially, in small-for-gestational-age babies, insulin resistance is more pronounced. Next to glucose, lipid emulsions may help to stabilize glycaemia as their glycerol content is a substrate for gluconeogenesis.

2.2.3.1. PN. It is recommended to start with a glucose infusion at 4–8 mg/kg/min directly after birth, with a daily increase rate of 1–2 mg/kg/min, or more if hypoglycaemia (<45 mg/dl or <2.5 mmol/L) occurs. Generally the target is 8–10 mg/kg/min with a maximum glucose administration of 12 mg/kg/min. If blood glucose levels exceed 8 mmol/L, glucose administration can be decreased by 2 mg/kg/min at a time, but glucose administration should not be below 4 mg/kg/min. Repetitive blood glucose levels >10 mmol/L (>180 mg/dL) should be treated with insulin therapy, when reasonable adaptation of glucose infusion rate has been insufficient. Insulin therapy at a low starting dose is preferred. Consider insulin infusion at a rate of 0.01–0.04 IU/kg/h, depending on the blood glucose level and, if necessary, increase the insulin up

to 0.2 IU/kg/hr to keep the blood glucose between 3 and 8 mmol/L (54–145 mg/dl) [11,12].

2.2.3.2. EN. The carbohydrate concentration of human milk is quite stable and increases from ~6.2g/100 ml to 7.1g/100 ml during the first month of life. The predominant digestible carbohydrate is the disaccharide lactose but free glucose, galactose, and human milk oligosaccharides (HMOs) comprise about 15%–30 %. Carbohydrates constitute 45%–50 % of nonprotein calories in human milk and standard preterm formulas. The relative contribution of carbohydrate to total nonprotein energy might be of importance. At equal protein and energy intakes, carbohydrate improves nitrogen retention compared with fat. A carbohydrate intake of 11–15 g/kg/d is recommended [9].

2.2.4. Amino acids

Amino acids are pivotal in early life as precursors for protein (and thus growth), for neurotransmitters, as transport molecules, and in cell signalling. Each amino acid has a unique function. Amino acids are classified as essential or non-essential, depending on whether they can be derived only from the diet (essential), or whether they can also be produced endogenously from other substrates in sufficient amounts (non-essential). Of the 20 amino acids present in proteins, 9 are essential in human adults. However, due to immaturity of different enzyme systems, premature infants are not able to synthesize an additional 4 amino acids, namely arginine, glycine, proline and tyrosine (so-called conditionally essential amino acids).

Amino acids are continuously synthesized and broken down for protein synthesis and gluconeogenesis. There is an inverse relation between postconceptional age and the speed of this process. Due to the fixed sequence of amino acids in all proteins, the rate of protein synthesis will be determined by the first limiting amino acid pool. When an essential amino acid is deficient protein synthesis stops and proteolytic rates increase.

A significant proportion of the amino acids that are released by protein breakdown is re-used for protein synthesis. However, part of it will be lost by renal excretion. This loss is approximately 0.6–1.1 g/kg/day in preterm infants. Since protein synthesis is an energy-demanding process, sufficient non-protein caloric intake should be administered as well.

During the past decades the beneficial effects of starting amino acid administration directly after birth have been shown. This can reverse a negative nitrogen balance, which indicates facilitation of protein synthesis and thereby growth. Furthermore, early amino acid administration increases plasma amino acid concentrations towards the ranges found in fetuses and healthy term newborns.

Early amino acid administration will generally result in improved growth at 36 weeks postmenstrual age or at hospital discharge, although this is not consistently reported in all studies. Furthermore, retrospective analyses showed that an increase of 1 g/kg/day of protein intake during the first week of life is associated with an 8-point increase in mental developmental index (Bayley Scales of Infant Development) at 18–22 months corrected age.

Very recently it was shown in extremely low birth weight infants, that administration of parenteral amino acids also has a safety upper limit. In a randomized trial, an extra dose of 1 g of amino acids per day in addition to usual nutrition (2.5–3.5 g/k/day) for the first 5 days after birth resulted in no significant difference in the incidence of death or survival without neurodisability at a corrected age of 2 years [13]. In an analysis of secondary outcomes, the results were consistent with a possible increase in moderate to-severe neurodisability among infants who received the extra dose. Higher intake levels are not needed to support growth and may have adverse effects on neurodevelopment. A sub-study to that trial suggested that the (extremely) high amino acid intake, requires extra administration of electrolytes (phosphate, potassium and magnesium) to prevent neonatal refeeding-like syndrome, which can lead to sepsis, intraventricular haemorrhage, chronic lung disease, impaired neurodevelopment and increased mortality [14].

Not only the timing and quantity, but also the quality (composition) of the amino acid solution is of great importance in achieving optimal growth and development.

There is however too limited evidence regarding the use of additional supplementation of the amino acids glutamine, arginine, or taurine to decrease neonatal morbidities. In practice, there is a very limited number of products available to provide to preterm infants.

There is much debate on how to examine tolerance of amino acid infusion in preterm infants. Amino acids that are in excess of protein synthesis capacity are irreversibly oxidized to CO_2 and ammonia, which is detoxified into urea.

It is important to mention that increased urea concentrations are not only a sign of intolerance, but often reflect dehydration or amino acid oxidation, when insufficient essential amino acids or calories are available.

2.2.4.1. PN. It is recommended to supply amino acids on the first postnatal day with at least 1.5 g/kg/d to achieve an anabolic state. From postnatal day 2 onwards the intake should be between 2.5 g/kg/d and 3.5 g/kg/d and this should be accompanied by non-protein intakes >65 kcal/kg/d and adequate micronutrient intakes [15].

2.2.4.2. EN [9]. Very preterm infants are given at least 3.5–4.0 g protein/kg/d together with sufficient other macro- and micronutrients to support appropriate somatic growth (including head growth). 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.

Low urea concentrations after the first few weeks of life may indicate that 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.

2.2.5. Lipids

Lipids are an attractive source of nutrition, because of their high energy density (9 kcal/g) – compared to protein and glucose (each 4 kcal/g). These extra calories can be used for the high-energy cost of protein synthesis. The high energy density is furthermore useful since fluid restriction is commonly necessary in preterm infants.

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 is a suspension of fat globules with a variable fat concentration of about 3.2–4 g/100 ml. The core of the milk fat globule consists of 98%–99 % triglycerides surrounded by a membrane of phospholipids, cholesterol, and other highly active bioactive components. About 15%–20 % of fatty acids in human milk are PUFAs.

Saturated, monounsaturated, and polyunsaturated fatty acids differ in their metabolic and physiological properties. While saturated fatty acids serve primarily as an energy source, polyunsaturated fatty acids play an important role as components of structural lipids, for example in biological membranes. The availability and metabolism of long-chain PUFAs have direct implications for cell membrane functions and the formation of bioactive

eicosanoids. Brain grey matter and the retina are particularly rich in long-chain PUFAs, and complex neural functions are related to energy supply and the composition of dietary fatty acids. PUFAs of the n-6 series (linoleic acid (LA) and metabolites), and PUFAs of the n-3 series (α-linolenic acid (ALA) and metabolites) cannot be synthesized de novo by higher organisms and are, thus, essential nutrients. Furthermore, in premature infants there is a limited capacity to synthesize arachidonic acid (AA) and docosahexaenoic acid (DHA) from linoleic acid (LA) and α-linolenic acid (ALA). Therefore these fatty acids are also considered essential. Clinical trials in preterm infants fed formulae containing both AA and DHA have shown beneficial effects on the developing visual system and measures of cognitive development during the first year of life. Reduced concentrations of both AA and DHA are associated with increased risk of retinopathy of prematurity (ROP), septicaemia, and severe bronchopulmonary dysplasia [16].

2.2.5.1. PN [17]. Parenteral lipid emulsions can contain both long- and medium-chain triglycerides. The physical, chemical, and metabolic properties of triglycerides are determined by their fatty acid contents. It is recommended to start lipid emulsions immediately after birth and no later than on day two of life, and for those in whom enteral feeding has been withdrawn they can be started at the time of PN initiation. Lipid intake should not exceed 4 g/kg/day. In order to prevent essential fatty acid deficiency, a lipid emulsion providing a minimum of 250 mg g/kg/day linoleic acid (LA) can be given. This lipid emulsion dosage also ensures an adequate intake of alpha-linolenic acid (ALA) with all lipid emulsions currently registered for paediatric use.

In preterm infants on short-term PN, pure soya-based intravenous lipid emulsions (ILEs) may provide less balanced nutrition than composite ILEs. For PN lasting longer than a few days, pure soya-based ILEs should no longer be used, and composite ILEs with or without fish oil should be the first choice.

A major concern during administration of parenteral lipids is the development of parenteral nutrition-associated liver disease (PNALD) which is part of intestinal failure-associated liver disease (IFALD). IFALD represents a spectrum of symptoms varying from mild cholestasis to end stage liver disease requiring liver transplantation. The prevalence of IFALD in infants differs widely, ranging from 15 to 85 %. The most significant risk factor is prematurity. This may be due to the reduced bile acid pool size and immature enterohepatic circulation in preterm infants. Furthermore, preterm infants are more likely to be in need of long-term PN, especially in case of necrotizing enterocolitis.

Concerning the use of parenteral lipids there has been a development over the past decades in the type of lipid emulsions. The pure soybean oil-based lipid emulsions are considered to be the first-generation lipids. Soybean oil is very rich in n-6 polyunsaturated fatty acids (PUFA), at around 60 % of the total fatty acid content. Nowadays, soybean oil is looked at with concern, mainly because of the excess of n-6 PUFAs that can lead to increased oxidative stress. The mechanism by which soybean oil emulsions contribute to the development of IFALD probably depends on the high level of phytosterols and n-6 PUFAs.

Second-generation lipid emulsions are a mixture of soybean oil (SO) and coconut or olive oil, the former delivering medium-chain triglycerides. Hereby, the amount of n-6 PUFA is decreased, potentially reducing the inflammatory consequences such as IFALD. Third-generation lipid mixtures typically contain soybean oil for the supply of essential fatty acids, coconut for the delivery of medium-chain triglycerides for rapid provision of energy, olive oil to reduce the n6:n3 ratio and to supply vitamin E, and fish oil for its anti-inflammatory effects.

Beneficial effects of these 4-component mixtures on liver function have been described both in adults and in children, but not yet in preterm infants. However beneficial effects on growth and infection rates are seen in preterm infants. In a recent meta-analysis, mixed lipid emulsions were associated with a 25 % reduction in episodes of sepsis compared with pure soybean oil emulsions. At present, fish oil is increasingly gaining favour for the treatment of IFALD, despite the limited nature of the outcome studies [18–21].

2.2.5.2. EN [9]. 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 [17]. 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 nonprotein calories. Human milk is a suspension of fat globules with a variable fat concentration of about 3.2–4 g/100 ml. Mature human milk fed at 160–180 ml/kg/d will provide a mean fat intake of up to 7 g/kg/d with an upper interquartile range of ~8.1 g/kg/d. These intakes appear safe even in extremely low-birth weight infants. A LA intake of 385–1540 mg/kg/d, a minimum ALA intake of 55 mg/kg/d and a LA to ALA ratio of 5–15:1 are considered acceptable. Adding AA and DHA to enteral feeds is thought to be a reliable way of ensuring adequate supplies of these PUFAs. Considering a range of DHA intake of 30–65 mg/kg/d, and an AA:DHA ratio ranging from 0.5 to 2, an AA intake up to 100 mg/kg/d appears safe.

The tolerance of lipids can be checked by determining plasma triglyceride (and cholesterol) levels.

2.2.6. Calcium, phosphorus and vitamin D

The total amounts of calcium and phosphorus accreted in fetal life are correlated with body weight. In preterm infants the retention of Ca and P is proportional to growth. To ensure appropriate mineralisation of bone in very low birth weight infants and to diminish the risk of fractures and clinical symptoms of osteopenia, supplementation with sufficient amounts of calcium, phosphorus and vitamin D is necessary.

Calcium absorption depends on calcium and vitamin D intakes, and calcium retention is additionally related to absorbed phosphorus. The calcium to phosphorus ratio may be an important determinant of calcium absorption and retention. Targeting a Ca retention of 2.2–2.8 mmol (90–110 mg)/kg/d is appropriate to minimize mineral bone deficiency and the risk of fractures in preterm infants. As inorganic phosphate (Sodium–Potassium-Phosphate) easily precipitates in solutions, the use of organic phosphate solutions (2-sodium-glycerophosphate) is recommended.

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. Adequate phosphorus intakes are essential to accrete lean tissue (each gram of protein requires approximately 0.35 mmol of phosphorus). Phosphate is not only the most abundant intracellular anion, but also plays an important role in many metabolic processes. For example, phosphate is incorporated in the phospholipids that form cell membranes, in the nucleic acids RNA and DNA, and in adenosine-3-phosphate (ATP) which is crucial for intracellular energy metabolism. Phosphate is also needed for various hormones and enzymes, including glyceraldehyde-3-phosphate, needed for glycolysis, and 2,3 diphosphoglycerate needed for the oxygen dissociation of haemoglobin. The provision of low phosphate PN with unfortified human milk increases the risk of both early and late hypophosphataemia. Hypophosphataemia is associated with hypercalcaemia, cardiorespiratory failure, bronchopulmonary dysplasia, hyperglycaemia, sepsis and mortality. Infants born small

for gestational age and those with maternal pre-eclampsia, are at the highest risk for refeeding-like syndrome and hypophosphataemia when high doses of amino acids are provided without sufficient phosphate suppletion.

Vitamin D is important for supporting a large number of physiological processes such as neuromuscular function and bone mineralization. The pathways of vitamin D absorption and metabolism are fully operative in premature infants from about 28 weeks of gestation. Considering the high prevalence of vitamin D deficiency in pregnant women a higher enteral vitamin D supply in preterm infants is recommended: premature infants <1250 g: 1000 IU/day, and those >1250 g: 800 IU/day [9].

2.2.6.1. PN [22]. Current guidelines recommend a parenteral intake of calcium during the first day of life of 0.8–2.0 mmol/kg/day (32–80 mg/kg/day) and for the growing premature infant 1.6–3.5 mmol/kg/day (100–140 mg/kg/day). For phosphorus during the first day of life 1–2 mmol/kg/day phosphorus (31–62 mg/kg/day) and for the growing premature infant 1.6–3.5 mmol/kg/day (77–118 mg/kg/day).

2.2.6.2. EN [9]. Early fortification of human milk with phosphate is recommended, followed by early introduction of multicomponent breastmilk fortifiers to optimize bone mineral outcomes. Because only 50–65 % of enterally delivered calcium is absorbed, a higher enteral intake of calcium is recommended. A Ca intake of 3.0–5.0 mmol (120–200 mg/kg/d) and in addition a P intake of 2.2–3.7 mmol (70–115 mg P/kg/d) of P are recommended. The recommended molar calcium to phosphate ratio to ensure adequate Ca retention is $\leq$ 1.4 ($\leq$1.8 in mass). Preterm infants fed artificial milk formula may require higher mineral intakes than those fed human milk.

2.2.7. Iron

Iron is an essential micronutrient that plays a critical role in many cellular functions and processes, including growth and brain development. Premature infants are especially susceptible to iron deficiency anaemia because of their smaller iron store and greater iron requirements compared to term infants. Human milk and standard formula feeds contain insufficient iron for the needs of premature infants. There is strong evidence that iron deficiency leads to long-term injury to cognitive and motor development. On the other hand, iron overload is harmful for the liver, the immune system and the brain. Furthermore, iron is a pro-oxidant, and non-protein bound iron has been suggested to promote the production of oxygen free radicals and thereby an increase in retinopathy of prematurity. Excess iron supplementation has been shown to increase the risk of infections, delay psychomotor development and decrease growth in length. Thus, one must prevent not only iron deficiency but also iron overload [23].

Systematic reviews clearly show that iron supplements effectively prevent iron deficiency anaemia in preterm infants but there is no benefit in exceeding standard doses of iron (ie, 2–3 mg/kg/d) in VLBW infants [24]. 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 versus later (~4–8 weeks of age) is associated with a lower need for blood transfusions in VLBW infants [25].

2.2.7.1. PN [26]. In patients receiving PN, iron supplementation should preferentially be given enterally rather than parenterally, if tolerated. Routine provision of iron in parenteral nutrition should not be given for short-term PN (<3 weeks). Patients receiving long-term PN, who cannot maintain adequate iron status using enteral iron supplements, should receive parenteral iron supplementation. Parenteral iron can be given daily added to the PN mixture or as intermittent, separate infusions. If given daily, and assuming no enteral iron supplementation, routine parenteral iron supplements should be given at a dose of 200–250 mcg/kg/day in preterm infants.

2.2.7.2. EN [9]. A daily iron intake of 2–3 mg/kg/d starting at 2 weeks of age is recommended for VLBW infants. Infants who receive erythropoietin treatment need a higher dose (up to 6 mg/kg/d). Supplementation should be continued until the age of 6–12 months, depending on diet.

3. Early parenteral nutrition

Most preterm infants are unable to tolerate full enteral feeding due to immaturity of the gastrointestinal tract. Therefore parenteral nutrition (PN) is needed to provide sufficient energy and protein substrate for these infants. However, while PN is life-saving, it is also associated with increased risk of sepsis from catheter-associated infections and progressive liver dysfunction from prolonged parental lipid use. This has improved with the newer generation PN-solutions.

Both growth and disease demand a high energy and amino acid intake. The body weight of a preterm infant of 1 kg consists of only 1 % fat and 8 % protein and has a non-protein caloric reserve of 110 kcal/kg body weight. When preterm infants do not receive exogenous substrates after birth, either enteral or parenteral, the infant reaches a catabolic state immediately. When receiving only glucose after birth, the estimated protein loss is approximately 1 % of the endogenous body protein per day. The resulting protein deficit may be difficult if not impossible to recoup, and thereby hampers the infant's growth and neurodevelopment. It is therefore of importance that PN is started immediately after birth. Furthermore it has been shown that early nutrition practice (first week after birth), as characterized by total daily energy intake (both PN and EN) was found to be a significant mediator of the association between critical illness during the first weeks of life and later outcomes. For example, an increase in total daily energy intake of only 1 kcal/kg/d was associated with a 2 % decrease in the odds of bronchopulmonary dysplasia or death [27].

4. Early enteral nutrition

Enteral feeding has three main functions in preterm infants;

- provision of nutrients
- mechanical and biochemical activation of the gut
- immunomodulation.

4.1. Amount of feeding

At birth, the gastro-intestinal tract of the premature infant is immature, both morphologically and functionally. Motility is sparse, barrier function is incomplete, and immunological defence is immature. Due to the hospital environment and antibiotic use, the prevailing microbiota are abnormal. All of these factors predispose to necrotizing enterocolitis (NEC). Because gut hormone secretion and motility are stimulated by ingesting milk, delayed enteral feeding could diminish functional adaption of the gastrointestinal tract, and result in later intolerance of enteral and oral feeding.

Minimal enteral feeding (MEF) is synonymous with gut priming, minimal EN, trophic feeding, or hypocaloric feeding, and is defined as small volumes of milk (typically 12–24 ml/kg/d) without advancement in feed volumes during the first 3–7 days. Numerous

studies and systematic reviews suggest that MEF is superior to no enteral feeds, but not better than earlier advancement of enteral intake. Overall there are no consistent effects on NEC or all-cause mortality [28,29].

Current guidelines recommend starting with small volume enteral feeds (eg 10–30 ml/kg/d) as soon as possible after birth in most preterm infants and to advance feeds as clinically tolerated. In stable preterm infants where the clinician considers that the feed volume can be increased, a routine daily increment of 18–30 ml/kg/d is recommended, especially in breastmilk-fed infants [9].

4.2. Route and feeding frequency

Depending on the gestational age at birth, the corrected age and the respiratory condition of the neonate, enteral nutrition is offered orally or by gastric tube. The coordination of reflexes needed for safe drinking (sucking, swallowing, breathing) are generally not mature enough until 32–34 weeks post-conceptional age. Also in near term and term infants, early feeding skills may be immature. It is recommended to assess the readiness to drink individually, using a scoring system for cue-based feeding or early feeding skills. Training nursing staff and parents to carefully read the infant's signals can prevent negative experiences in the oral area and prevent stress, apnoea and later feeding problems [30].

The optimal frequency of enteral feeding during the day is not well established, as long-term outcome data are lacking. As compared to continuous feeding, intermittent supply of enteral nutrition likely causes cyclic release of gastrointestinal hormones, which stimulate maturation and motility of the gastrointestinal tract and lead to faster achievement of full enteral nutrition. There are indications that preterm infants with a gestational age of <30 weeks achieve full enteral nutrition faster with less food intolerance when feeding is given in 12 instead of 8 portions per day [31].

4.3. Choice of milk

Human milk has a number of benefits for preterm infants. It provides antibodies, enzymes, probiotics, hormones and growth factors. Moreover, human milk seems to reduce the incidence of several adverse outcomes, such as necrotizing enterocolitis (NEC), late-onset sepsis, retinopathy of prematurity and abnormal brain development. Besides, infants fed their own mothers' milk are known to tolerate full enteral feeding earlier than their formula-fed peers.

However, human milk lacks sufficient protein and energy for optimal growth and development of the preterm infant. Energy and macronutrient content differs widely between mothers and can be influenced by several factors, such as stage of lactation, frequency of breastfeeding, time of the day, parity, maternal diet, and age. As the protein content of breast milk and the neonate's need for protein varies, 'targeted' fortification has been proposed.

Mothers of preterm infants often have insufficient milk supply in the first days postpartum. Maternal illness, the technique of pumping milk, maternal medication, and postpartum stress can all hamper lactation. Professional lactational support is often required. Nowadays, in most neonatal intensive care units banked donor milk is supplied. The safety of donor milk can be guaranteed if selection of donors and pasteurization and discarding of milk is performed according to a protocol. Although, pasteurization, freezing and thawing of milk reduce the bioactivity of several human milk components, donor milk is nonetheless considered the optimal alternative to milk from the child's own mother.

Fresh mother's own milk (MOM) contains higher amounts of macronutrients, and immunoactive and trophic factors than pasteurized MOM or donor human milk (DHM). Nevertheless, fortified pasteurized DHM instead of preterm formula may reduce NEC rates in preterm infants, whereas other neonatal morbidity and mortality rates are unaltered. It is recommended to use MOM as the first choice of feeding in both preterm as well as term infants. In the case of insufficient MOM availability, fortified DHM is conditionally recommended over preterm formula in preterm infants born at <32 weeks' gestation or with a birth weight <1500 g. There is insufficient evidence to formulate general recommendations on pasteurization of MOM from CMV-positive women, to prevent potential harm of vertically transmitted postnatal cytomegalovirus infections [9].

Breast milk is also used for non-nutritional purposes. Although clear clinical benefits have not been proven consistently, administration of buccal colostrum for its immunological effects appears safe, and is generally appreciated by infants and parents. Oral feeding of small amounts of breast milk is increasingly used as an effective non-pharmacological intervention for painful procedures. In the case of sufficient availability of MOM, breast milk may also be used for enemas in cases of constipation.

Current guidelines recommend adding breast milk fortifier to meet the very preterm infant's nutritional requirements; this contains extra protein, energy, vitamins and minerals. Fortifiers contain approximately 1.3–1.6 g of protein per 100 ml of milk. Fortification can be started when 40–100 ml/kg/d of enteral feeding is tolerated [9].

4.4. Pre- and probiotics

4.4.1. Prebiotics

Human milk contains more than 130 different oligosaccharides that are fermented in the term infant's colon. Preterm infants show some absorption of intact human milk oligosaccharides, but most resist digestion in the small intestine and undergo fermentation in the colon. The composition of oligosaccharides in human milk is genetically determined, explaining the large variability in oligosaccharide composition which exists. Therefore, it is difficult to define the exact or ideal oligosaccharide composition when trying to replicate human milk. One type of oligosaccharide mixture (GosFos) (which contains galactose and fructose oligosaccharides) has been systematically studied in formula feeds for term and preterm infants. It has been hypothesized that GosFos may accelerate feeding advancement, reduce the incidence of gastrointestinal complications such as necrotizing enterocolitis, improve immunological functions, reduce the incidence of hospital-acquired infections, and improve long-term outcome, but there are no data available from studies in preterm babies to support these assertions [32].

4.4.2. Probiotics

Probiotics are live microbial supplements that colonize the gut while providing benefits to the host. The benefits include an improved gut barrier, enhanced mucosal IgA responses, and increased production of anti-inflammatory cytokines thereby reducing the incidence of necrotizing enterocolitis (NEC). There is still debate on the efficacy of probiotics in preventing NEC. The most recent meta-analysis did not find strong evidence for the prevention of surgical NEC by probiotic supplementation. It did however show a reduction in NEC-related mortality [33]. There was no significant reduction of nosocomial sepsis.

It is advised that the use of probiotics is limited to the specific strains of probiotics that have been shown to be safe and efficacious and that have been studied in a large number of VLBW infants. If all safety conditions are met, the use of *L. rhamnosus* GG or the

combination of *B. infantis* Bb-02, B. lactis Bb-12, and Str. thermophilus TH-4 a, is recommended to reduce NEC stage 2 or 3 [33].

5. Post-discharge feeding

Preterm-born infants often remain smaller and have suboptimal bone mineral mass throughout infancy, and even during adulthood compared to term-born infants. Therefore, after discharge, a sufficient amount of nutrients is needed to achieve or continue optimal growth and development. Excessive catch-up growth and obesity early in life are associated with metabolic syndrome in later life. Continued growth monitoring is recommended to adapt feeding to individual requirements and to prevent under- or overfeeding and its negative consequences later in life. Human milk, with supplementation, is preferred for preterm infant feeding. If human milk is lacking, a formula feed designed for preterm infants is the second-best option. Standard formula feeds are designed for term infants, and are based on the composition of mature breast milk. They are relatively low in calories, and contain too little protein for optimal brain development and growth of preterm infants.

Special post-discharge feeding for preterm infants until a weight for age standard deviation score of −1 is reached and for no longer than 6 months after term can be considered.

6. Summary

Nutritional support for the VLBW infant should be started as early as possible, not only for growth but also for optimal neurocognitive development. Large weight losses should be avoided but growth up to − 1 SD of the initial birthweight can be accepted. Nutrition may need to include parenteral nutrition in the first few days after birth as intestinal function is immature. Parenteral nutrition should be started on the day of birth, with glucose, amino acids, and lipids, and gradually increased in the first days of life. It is recommended to start with small volume enteral feeds as soon as possible after birth. There is a strong preference for milk from the child's own mother in all neonates. In very low birth weight infants, (pasteurized) donor milk is considered the best alternative, if MOM falls short.

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