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The graduation thesis contains 58 pages, 1 figure, 2 tables, 163 references.

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List of abbreviations and acronyms

AA	Amino acids
AAP	American Academy of Pediatrics
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARA	Arachidonic acid
BPD	Bronchopulmonary dysplasia
BUN	Blood urea nitrogen
BW	Birth weight
CL	Chloride
CLABSI	Central-line associated bloodstream infections
CRBSI	Catheter related blood stream infections
CRP	C-reactive protein
CVC	Central venous catheter
DHA	Docosahexaenoic acid
EN	Enteral Nutrition
EPO	Erythropoietin
ESPGHAN	European Society for Pediatric Gastroenterology Hepatology and Nutrition
FA	Fatty acids
GA	Gestational age
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
IM	Intramuscular(ly)
IU	International Units
IVH	Intraventricular hemorrhage
K	Potassium
Kcal	Kilocalorie(s)
Kg	Kilogram(s)
Na	Sodium
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PICC	Peripherally inserted central catheter
PN	Parenteral nutrition
RDS	Respiratory distress syndrome
REE	Resting energy expenditure
ROP	Retinopathy of prematurity
UVC	Umbilical venous catheter
WHO	World Health Organization

1. Introduction

Preterm birth is defined as delivery prior to completion of the 37th week of gestation and displays a significant global health issue (1). Preterm newborns can be categorized according to gestational age (GA) or birth weight (BW).
The BW-based classification includes low birth weight (<2500g), very low birth weight (<1500g) and extremely low birth weight (<1000g).
The GA-based classification is divided into late preterm infants (34 to 36 weeks of GA and six days), moderate preterm infants (32 to 33 weeks of GA and six days), very preterm infants (<32 weeks of GA) and extremely preterm infants (<28 weeks of GA) (1).

Approximately 15 million infants worldwide are born prematurely each year, which accounts for 10% of all live births (1). Around 85% of these preterm newborns are born between the GA of 32 and 36 weeks, while 10% are born between 28 and 32 weeks of gestation.
These newborns face an increased risk of mortality. In 2019, 900 000 children died worldwide due to complications related to premature birth (2). However, survival rates vary significantly between countries. In low-income countries, infants born before the 32nd week of gestation commonly die due to inadequate equipment and lack of early neonatal care, including breathing support, adequate feeding as well as maintenance of body temperature (3). In contrast, most infants younger than 32 weeks of gestation born in high-income countries survive (3).
Beyond the increased risk for mortality, preterm infants are more susceptible to adverse outcomes and developing disabilities associated with premature birth (1). With decreasing gestational age, the risk of such complications increases, with extremely preterm newborns facing the highest likelihood of complications and adverse outcomes (2).

Functional or anatomic immaturities usually cause short-term complications, that increase the risk for developing long-term complications.
Respiratory short-term complications include respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), apnea of prematurity, pneumothorax, and pulmonary hemorrhage. RDS is characterized by insufficient lung surfactant production resulting in symptoms like tachypnea, nasal flaring, intercostal retractions, and cyanosis (4).
Cardiovascular complications include patent ductus arteriosus that can lead to abnormal blood flow from the left side to the right side of the heart, resulting in an increased pulmonary blood

flow and decreased systemic circulation (5). Symptoms may include apnea, heart failure, or even respiratory distress.

Glucose abnormalities, both hyperglycemia and hypoglycemia, are common in premature infants due to reduced glucose reserves and limited gluconeogenesis capacity. These conditions can lead to severe outcomes like seizures and neurodevelopmental impairments (6–9).

Preterm infants are highly susceptible to infections, particularly bacterial sepsis. This can be life-threatening and may impact growth and long-term neurodevelopmental outcomes (5).

Additionally, due to premature infants' high energetic demands and their inability to coordinate sucking and swallowing, maintaining proper nutrition is a challenge and can stunt their growth (5). Conditions like necrotizing enterocolitis (NEC) can also exacerbate feeding problems and lead to long-term gastrointestinal (GI) complications.

The impact of immaturity often becomes evident in later stages of life when significant neurodevelopmental impairments are identified. These impairments can include cerebral palsy, mental retardation or problems with behavior and functioning; such as deficient attention skills, poor visual-motor functioning, reduced mathematical abilities, and hyperactivity (10).

Preterm babies are also at an increased risk for developing chronic lung diseases such as asthma (8). Furthermore, prematurity is associated with both short and long term impairments of growth, however preterm infants are more likely to experience a greater delay than term infants (11). Some sources even suggest that prematurity impacts mortality and morbidity in adulthood, highlighting the enduring consequences of premature birth (11).

2. Aims and objectives

This review aims to explore the challenges and complexities in identifying and maintaining optimal preterm nutrition, with the goal of facilitating their growth, which should mirror that of a fetus.

Given the unique conditions of premature newborns and their distinct metabolic needs, the appropriate management of nourishing premature infants should be individualized and involve proper planning and calculation. Among the existing literature, studies have observed and revised methods and strategies for optimally feeding premature newborns.

This paper will review the individual challenges faced and various factors contributing to the hurdle of nutrition in premature newborns. Different perspectives on certain aspects of nutrition will be discussed alongside the latest guidelines.

3. Growth management in prematurely born infants

3.1 Goals of growth

Growth of infants is determined by measuring weight gain, increasing length and head circumference and assessing body composition (12). The body composition describes the respective percentages of fat and fat-free mass of the infant's body, which are calculated by the body density. The body's density is the ratio between the body mass and the body volume and can be measured, for example, with densitometry (PEA POD) (13).

Many growth charts have been developed over the years, which are based on growth standards that describe the growth of a selected, healthy population, which grows under good nutritional conditions and minimal health limitations (12). These standards were assessed in a study by the World Health Organization (WHO), resulting in growth charts describing the development of children from term birth up to 5 years of age (12,14). However, growth velocity for preterm newborns is hard to determine. The growth of a fetus between 22 and 40 GW is considered the period of fastest human growth (15). Their weight increases over six-fold during this time.

The earlier an infant is born, the less prepared it is for the outside world (16). In the womb, the fetus grows in a protective environment provided by the mother. This dark environment shields loud sounds, and smoothly encloses the fetus, protecting it from hard touches while creating a calming surrounding and constantly supporting its metabolic needs (16). These conditions ensure an optimal development.
However, if babies are born prematurely, they are deprived of these optimal surroundings, leaving them in a challenging situation. The newborn must grow at the same velocities as an unborn infant but in a hugely different environment. To compensate for these surroundings and still ensure the same growth rates, the infants have increased nutritional needs but with simultaneously limited feeding volume tolerance. Their immature immune systems, as well as the missing protection of the womb from external pathogens, make them more susceptible to infections. All these difficulties may further lead to growth deficits affecting organ development.
Therefore, preterm newborns rely on healthcare professionals to accurately assess their development and tailor nutrition for optimal growth (15).

Most growth charts overlook preterm-specific conditions such as being outside the protective uterine cavity, thermoregulation, and increased fecal losses in their references. Additionally,

growth in preterm newborns can be inconsistent with periods of slow growth which can be indicative for inadequate nutrition or even reflect changes in nutrition. This is also called "growth faltering", describing slow growth which is not parallel to a centile of current age (17). These periods of slow growth are compensated by consequent accelerated growth periods referred to as "catch-up growth" (12). The purpose of catch-up growth is to restore the infant's state so it can follow its optimal growth trajectory. However, these phases of rapid growth may be associated with an increased risk of development of cardiovascular or metabolic diseases later in life (12).

The Fenton growth charts, were initially based on in-utero and postnatal development of fetuses as well as newborns from the 22 to 50 GW (12,18). However, these in-utero references are not particularly useful for monitoring a preterm infants' growth. Therefore, the Fenton charts were revised in 2013 to better reflect preterm growth. Data from various studies or reports have been collected to find references about population-based preterm size at birth, specifically concentrating on weight, length and head circumference (15).
The latest update about appropriate growth standards for preterm newborns is the 'Preterm Postnatal Follow-up study of the INTERGROWTH-21st project', which assesses fetal and postnatal growth of preterm infants born between 26 and 37 GW; in order to develop growth standards for preterm newborns (19). Additionally in 2017, the WHO released a prospective, observational longitudinal study to present fetal growth charts for estimated fetal weight as well as ultrasound biometric measurements (20).

According to the WHO in-utero measurements, the average fetal weight gain for fetuses between 23-25 GW will be 20-23 g/kg/day, between 26-29 GW 17-20 g/kg/day, between 30-34 GW 13-17 g/kg/day and between 35-37GW 10-13 g/kg/day (12).

3.2 Caloric goals

Energy requirements must be well estimated to provide adequate energy intake for the infant's growth. Insufficient energy intake can lead to growth impairment, tissue atrophy, impairment of behavioral and cognitive development, as well as the impaired immunity development resulting in serious morbidities (21). However, excessive energy intake can also lead to short or long-term complications including hyperglycemia, infections, decreased liver function or metabolic impairments (22).

Caloric goals can be calculated by taking in consideration the resting energy expenditure (REE), which describes the amount of energy consumed without any activity. Thereafter, physical activity, thermoregulation, fecal loss, and the infant's growth can be used to estimate daily energy requirements. Estimated REE for preterm infants are 60-70 kcal/kg/day (23) and the daily weight gain should be 17-20 g/kg/day. It is also assumed that every gram requires 3.6-4.7 kcal of energy in order to grow (17,23).

ESPGHAN committee has come to the conclusion and state in their guidelines, based on several cohort studies, that 115-140 kcal/kg/day are sufficient in order to keep adequate growth for enterally fed preterm infants (17).
Newborns which are parenterally fed have lower energy requirements as the nutrients are directly provided to the body and feeding does not use any energy for digestion or fecal losses. Therefore, energy requirements for parenterally fed preterm infants are 90-120 kcal/kg/day (24).

Picture 1 illustrating the energy requirements per kilogram of a preterm newborn and a "Tour de France" racing cyclist

The image above illustrates the comparison between the energy needs of a preterm newborn and those of a competitive cyclist. While the premature infant requires approximately 130 kcal/kg per day, a racing cyclist needs around 115 kcal/kg/day. This shows the enormous energy requirements of such tiny individuals.

Despite the infant's minimal physical activity compared to the cyclist, their energy is primarily allocated to various physiological processes, resulting in even higher demands. Many challenges such as underdevelopment, the susceptibility to illnesses, undernutrition, and growth hurdles contribute to a state of energy deficiency. Their low capacity to store energy coupled with many medical conditions may further elevate their demands. Painful stimuli, stressful

situations and illness are states in which the metabolism increases and subsequently energy requirements.
Moreover, the exceptionally high metabolic energy of the brain, which accounts for 60% of the total metabolism, emphasizes the energy demands (25). In preterm newborns, critical brain development processes like forming of synapses, cellular component assembly as well as the expansion of certain brain areas, heightens the energy requirements (25).

Daily nutritional needs are composed of different components including proteins, lipids, carbohydrates, electrolytes, minerals, and vitamins. Each component needs to be provided in sufficient amounts to ensure appropriate development.

3.3 Nutritional needs of preterm newborns

Proteins

Proteins are built by the body from amino acids. Different amino acids have to be present to enable the synthesis of different proteins important for energy provision and well as anabolism of body mass. Proteins are also important for metabolic processes and cell signaling pathways in form of precursors and enzymes like transporters (26).
Individual amino acids should also be considered as they have selective functions. Glutamine for example is thought to contribute to the immune function, arginine to the gut health and taurine to a proper brain development (17). If amino acids are in excess, the body can degrade them to CO2 and ammonia and secrete them via urine and breathing.

Recommendations from ESPGHAN for protein intake in preterm newborns are 3.5-4.0 g/kg/day (17).

Inappropriate protein provision may either lead to decreased lean mass accretion, improper body composition or metabolic disturbances due to toxic levels of blood urea nitrogen (BUN) and subsequently poor growth (27).

Lipids

Lipids are not only an important energy source for newborns but are also components of many body structures. They are used for growth, development of the immune system and other metabolic pathways (28).

The recommendations for the daily lipid intake in preterm newborns should be at least 4.8 g/kg/day and maximally 8.1 g/kg/day considering fat deposition, malabsorption and loss due to unavoidable oxidation (17,29).

Especially in preterm newborns, the delivery of lipids must be appropriately compensated as the transferal of lipids from mother to child. Specifically essential fatty acids (FA) like arachidonic acid (ARA) and docosahexaenoic acid (DHA), mainly occurs in the third trimester of pregnancy (28). ARA and DHA are "conditionally essential" in preterm newborns, meaning their body cannot produce these acids in sufficient amounts to meet their physiological requirements and therefore need to be taken up by food (17). ARA and DHA are important components of the brain tissue as they constitute about 25-30% of all FA in the brain (30). They are crucial for forming synapses, the myelination of nerves and the brain immune function (30,31). Therefore, decreased values of ARA and DHA may be associated with problems in the neurodevelopment including visual development such as retinopathy of prematurity (ROP) (32,33). An additional intake of ARA and DHA are recommended, as several studies proved a decreased risk of ROP with supplementation (32,33). According to ESPGHAN guidelines, a DHA intake of 30-65 mg/kg/day and an ARA intake of 30-100 mg/kg/day within 3 days after birth until 40 weeks' postmenstrual age are recommended (17).

Carbohydrates

Carbohydrates are a major energy source for newborns (34). The body breaks down the carbohydrates to glucose in order to use it for metabolic processes. Most carbohydrates are provided as disaccharides like lactose or galactose but also as free glucose (35). Provision of adequate amounts are crucial to prevent hypoglycemia as well as hyperglycemia. Both states can lead to complications.

Beside the acutely dangerous state of hypoglycemia which may lead to seizures, coma or death, hypoglycemia is also associated with long-term consequences (36). The brain development suffers under a hypoglycemic state and can lead to developmental delay, cerebral palsy and neuropsychiatric problems (37).

Hyperglycemia is associated with an increased risk of infections, decreased functioning of the immune system and poor wound healing (38). Some studies even suggest higher mortality rates in preterm newborns with continuous hyperglycemia (39).

In the ESPGHAN guidelines the calculation for the optimal daily intakes of carbohydrates considers the daily energy intake of 115-140 kcal/kg/day, an enteral protein intake of 3.5-4.0 g/kg/day as well as 40-50% of non-protein energy intake composed of carbohydrates. With

these values, the committee comes to the conclusion that 11-15 g/kg/day of carbohydrates are appropriate for preterm newborns (34).

Electrolytes

Electrolytes such as sodium, potassium and chloride, are major constituents of the body. Proper regulation is essential to prevent deficiencies and conditions like patent ductus arteriosus or chronic lung diseases from excessive intake. Electrolyte deficiencies may disrupt the circulation or metabolic processes (40).

Sodium (Na) is vital for nerve conduction, fluid volume regulation either intravascular or interstitial, and bone mineralization (41). Preterm infants are already able to absorb sodium from the intestine but have increased excretion due to renal immaturity, leading to hyponatremia (42). Therefore, daily Na requirements vary in the first days of preterm life, in part due to slower renal maturation of preterm newborns when compared to term infants (43). According to ESPGHAN guidelines, the daily sodium intake for preterm newborns should be between 3 and 8 mmol/kg (17). The sodium losses in preterm are around 7 mmol/kg/day (44). Higher sodium supplementation are associated with an increased weight gain (17).

Chloride (Cl) maintains the osmotic pressure, regulates the electrolyte balance as well as the acid-base homeostasis (41). Chloride ensures ionic neutrality by balancing out the Na levels (41). It also plays a role in nerve conduction by regulating certain channels. Insufficient Cl supplementation can cause slow growth, constipation, lack of appetite, muscular weakness as well as delays in psychomotor development (45). The required daily intake for preterm newborns is 3-8 mmol/kg, similar to Na (17).

Potassium (K) is important for nerve conduction as it maintains the transmembrane electrochemical gradient. For ingested K uptake, it is important to note that 80% is transported into the cells due to insulin secretion during digestion (46). Recommended daily K intake for preterm babies is 2.3-4.6 mmol/kg (17).

Minerals

Minerals like calcium and phosphorus are important for the babies' bone health. Especially preterm infants are at high risk for developing bone diseases like rickets (47). The calcium taken up is stored to around 98% in bone tissue. Phosphorus is also needed for bone mineralization,

however only 80% of all consumed phosphorus is formed into bone tissue (17). The rest is used as building blocks for nucleic acid or energy metabolism. Consequently, phosphorus intake has to be higher than simply for bone mineral accretion (48).
In order to minimize bone mineral deficiencies and with it the risk for bone fractures, a minimum of 2.2-2.8 mmol/kg/day (90-110 mg/kg/day) of calcium and 2.2-2.6 mmol/kg/day (70-80mg/kg/day) of phosphorus are needed (17).
To estimate the daily adequate calcium intake, the intestinal calcium absorption rate has to be considered which is usually 60%. This leads to a required intake of about 3.0-5.0 mmol/kg/day of calcium (17).
Phosphorus intakes are absorbed by up to 90%, however phosphorus is not only needed for bone mineralization (48). For protein accretion and nucleic acid synthesis, phosphorus also has to be provided. For every gram of proteins, 0.35 mmol of phosphorus is needed (48). Consequently, 0.9 mmol/kg/day of phosphorus should be additionally provided. In total, phosphorus intake for preterm newborns for bone mineralization, protein accretion, nucleic acid synthesis as well as for energy metabolism should be about 2.2-3.7 mmol/kg/day (17).
It has been observed that bone pathologies in preterm infants have declined over the past 10-20 years which reflect the improvements concerning calcium and phosphorus deliver that have been made (48).

The mineral magnesium is partly needed for bone accretion as well as for muscle and soft tissue development (48). With an absorption rate of 40-50%, a daily magnesium intake for preterm infants fed with fortified human milk is about 0.4-0.5 mmol/kg (48).

Water soluble and fat soluble vitamins

Water soluble as well as fat soluble vitamins need to be provided to ensure body functioning and homeostasis. In preterm babies, vitamin levels and stores are often reduced and need adequate substitution to prevent any vitamin deficiencies and its consequences (49). Often multivitamin preparations are used to meet the required needs such as *Soluvid* for water-soluble vitamins and *Vitlipid* for fat-soluble vitamins.

Trace elements

Trace elements are also essential for growth and development and the function of the organ system. They are also provided as a prepared mixture containing all essential trace elements like zinc, copper, manganese, selenium and iodine like *Peditrace*.

Table 1: ESPGHAN CoN recommendations for enteral nutrient intakes in preterm newborns

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

ARA = arachidonic acid; CoN = Committee of Nutrition; DHA = docosahexaenoic acid; EPA = Eicosapentaenoic acid, ESPGHAN = European Society of Pediatric Gastroenterology, Hepatology and Nutrition; IU = International units. Figures in brackets represent ranges or upper intakes that might occasionally be needed in routine clinical practice under certain conditions. See text for details.

Source: Embleton ND, Jennifer Moltu S, Lapillonne A, van den Akker CHP, Carnielli V, Fusch C, et al. Enteral Nutrition in Preterm Infants (2022): A Position Paper From the ESPGHAN Committee on Nutrition and Invited Experts. J Pediatr Gastroenterol Nutr. 2023 Feb 1;76(2):248–68.

4. Nutritional challenges in preterm newborns

Many factors complicate the nutrition of preterm newborns whose conditions differ significantly from those of term babies. The most prominent influencing factors are described in the following abstract.

4.1 Neonatal factors

4.1.1 Gestational age

Premature infants are born before reaching full developmental maturity, resulting in insufficient preparation for extrauterine life. Many of their organs and physiological systems remain underdeveloped, making it challenging for a preterm child to grow adequately.

In order to maintain full nutrition and oral hydration of the newborn, the infants need to be able to suck rhythmically, swallow safely and coordinate these two processes with breathing (50). However, these processes are not yet fully developed in preterm newborns especially in infants younger than 32 GW (50). Only after the 34 GW, a newborn is able to maturely suck and swallow and will achieve and maintain a full nutrition necessary for appropriate growth (50). Nutritive sucking is described as the proper coordination of lip, cheek and tongue movement in order to cause expression of milk into the oral cavity (50). This process consists of suction and expression of milk. During suction, the infant creates a negative pressure in the oral cavity by the activation of perioral muscles. Expression causes the compression of the nipples by tongue and hard palate to cause milk ejection. In preterm newborns, these two processes are still arrhythmic and will not result in successful sucking (50).
Swallowing consists of different phases. An oral phase, in which a bolus is formed and sized, a pharyngeal phase, where the food bolus is forwarded through the pharynx to the esophagus and the esophageal phase, in which the bolus is transported through the esophagus to the stomach with the help of peristaltic movements of the esophageal (50).
Another process which is needed for successful swallowing is the aerodigestive protection. This coordinated mechanism, supported by several reflexes of the pharynx and esophagus, prevents food boluses from ascending, promotes their propulsion through proper esophageal clearance, and thereby protects the airways (50).
In preterm infants, these mechanisms are not yet developed. The infants will have difficulties to protect their airways as the aerodigestive protection is maintained by reflexes which are still absent at this age, and the immaturity of the esophageal motility also makes it difficult to complete the swallowing process. Sucking, swallowing and breathing need to be well coordinated in order to prevent aspiration, apnea or possible episodes of oxygen desaturation (50). However, in preterm newborns these processes are poorly coordinated (51).

The difficulty of feeding is also influenced by conditions like bronchopulmonary dysplasia (BPD). The lung development in infants especially the maturation of terminal respiratory sacs and alveoli occurs beyond the age of 34 to 36 GW (52). Babies which are born earlier will have immature lung structures and decreased surfactant production. These infants may need ventilation or oxygen therapy for support. However, ventilation therapy may also cause damage to the immature lung structures due to overstretching and lead to inflammation of the alveoli (53). BPD is considered to be a complication of prematurity and effected infants may have difficulties with feeding as they have a poor endurance (54). During the swallowing process the airflow is interrupted (50). An increase of the swallowing frequency may result in decreased respiration and thus a decreased gas exchange (50). Consequently, premature infants with lung problems like BPD will have difficulties to sufficiently breathe and swallow. They also have a lower sucking pressure and decreased sucking frequency (55). Appropriate feeding without additional help can therefore not be achieved in this condition. BPD is commonly connected with growth failure (54).

4.1.2 Gastrointestinal immaturity

The development of the gastrointestinal (GI) system is a prolonged process, with its maturation and development continuing well beyond birth. The development of the human GI tract encompasses anatomical differentiation and functional maturation which occur at different weeks of gestation (56). Anatomical differentiation is typically completed by the 20th GW, while functional development requires more time, with significant progress occurring after the 34th GW (56).

Proper functioning of the GI tract includes coordinated sucking and swallowing, continence of gastrointestinal sphincter tone, adequate gastric emptying and organized intestinal peristalsis (57). Full maturation of the GI tract is essential for adequate digestion and absorption of the ingested nutrients. Consequently, preterm newborns, whose GI tracts are not fully matured, are often unable to fully utilize the components of their enteral nutrition, potentially leading to nutritional crisis (57). Additionally, immature bowel function is associated with food intolerance (57). This includes malfunctioning of gastric emptying, stasis and delayed progress of food boluses which leads to symptoms like gastrointestinal reflux, abdominal distention, and constipation (58).

In addition to mechanical functions, the enzymatic and chemical functions of the intestines must also develop to ensure the digestion and absorption of all necessary nutrients. For instance, the secretion of hydrochloric acid by parietal cells, for the denaturation of proteins, is limited in preterm newborns (57). For the digestion of carbohydrates into monosaccharides enzymes like lactase, sucrase, maltase and others are responsible (57). However, lactase activity is reported to be low in preterm infants (59). The digestion of triglycerides is mediated by bile acid, which emulsifies fats into small fatty droplets (57). Bile levels as well as their reabsorption in the ileum are also decreased in preterm newborns (57).
With decreased enzyme activity, food digestion and its proper utilization cannot be guaranteed which makes sufficient nutrition challenging.

Another important component of the gut integrity is the gut microbiome. Many microbes colonize the human gut and will establish symbiosis with the host which is important for adequate digestion and immunity (60). This microbiome still needs to develop in newborn infants. Its composition is influenced by many factors including genetics, the maternal nutrition during pregnancy, the mode of delivery, gestational age of the newborn und their nutrition and many more (61). The symbiotic effect of this relationship remains as long as the composition of the microbiome is balanced. However, any disruption in this conformation will lead to a dysbiosis, which may have life-threatening consequences (57).
In preterm infants, the development of the microbiome is not only influenced by the above-mentioned factors. It is also affected by their admission to the neonatal intensive care unit where an abundance of diverse bacteria is present, capable of colonizing the infant. Artificial feeding, mechanical respiration or antibiotic therapies expose the newborn to potentially pathogenic bacteria (57). These cumulative influences may disrupt the development of an adequate microbiome in newborns or lead to a disruption in the normal bacterial flora potentially affecting the GI maturity and immune system maturation (62). This underlying condition can precipitate to a gastrointestinal emergency known as necrotizing enterocolitis (NEC) with microbial dysbiosis believed to play a crucial role in its development (63).

4.1.3 Neonatal Intensive Care Unit Environment

The neonatal intensive care unit (NICU) environment significantly influences the newborn's growth and development, with environmental factors exerting significant influence on clinical outcomes. While bright light and loud sounds can have adverse effects on infants, social

interactions with parents or NICU staff and gentle handling of the infant contribute positively to developmental outcomes.

The exposure to constant loud noises can lead to increased heart rates, decreased oxygen saturation, increased blood pressure, and changes in the respiratory rate (64). A study shows that reducing exposure to loud sounds, for instance by using earplugs, can improve the infants' stressed behavior, sleep patterns, and even weight gain (65). Recommendation for noise intensity on the NICU are <45 dB, however observation proof that the noise levels are often exceeding this target (64).

The light on the NICU does not correspond to the natural light cycles outside. Therefore, the infant is constantly exposed to light which may disturb their circadian rhythm and thus have effects on their cortisol excretion and stress levels (64). Bright light is associated with higher metabolic rates and poorer weight gain (66). Recommended lightening levels on the NICU range from 10 to 600 lux, yet observations indicate that actual lightening levels often exceed these recommendations, typically ranging between 400 and 1000 lux (67). Reducing light exposure and mimicking day-night cycles can stabilize heart rate, respiratory rate, and blood pressure and have been shown to contribute to weight gain of newborns due to improved feeding (64).

The NICU environment also influences the microbiome development of the newborns, which is crucial for immune function and disease prevention. Microbiome is forming an integral part of the human development and health (68). During pregnancy and birth, the infant is already exposed to an immense number of microbes. Successive exposure to microbes, occurring through skin-to-skin contact with the mother and breastfeeding, enriches the infant's microbial composition (68). Alterations and disturbances of this collection can lead to impaired functioning such as decreased intestinal barrier or decreased immune system. Every NICU harbors its individual composition of microbes, including both beneficial and potentially harmful organisms (68). Infants are introduced to their mother's microbiome, as well as to those of different nurses and doctors. This can promote the transmission of pathogenic microbes and hinder an adequate formation of a healthy microbiome. Furthermore, equipment like ECG leads or adhesive dressings can damage the integrity of the microbiome and promote bacterial or viral invasion. Every object is a possible reservoir for microbial contamination which induces a disbalance of the natural microbiome composition (68).

4.1.4 Antibiotic exposure

Over 90% of preterm newborns are already exposed to antibiotics in their first weeks of life. Especially on the NICU, they are used to fight life-threatening diseases like sepsis or other infections, which when left untreated, will lead to lifelong disabilities or even death. However, as a precautionary measure to avoid neonatal sepsis, many practitioners administer antibiotic treatment even without a proven positive blood culture (69).

Although antibiotics are indispensable, there are concerns about long-term side effects on the infants (70). Observations show that a prolonged antibiotic exposure has been associated with NEC and even late onset sepsis. Other long-term consequences connected to prolonged antibiotic usage are asthma, obesity, or autism spectrum disorder in childhood (70).

Antibiotics disturb the immune function of the infants as they are altering the composition of the intestinal microbiota and their diversity or even destroy beneficial bacteria in the gut (70). Early antibiotic exposure is when treatment is provided from day 0 or day 1 of life, and is associated with a higher risk of cerebral lesions and moderate to severe BPD (71). Therefore, antibiotics should be applied wisely and the side effects should be taken into consideration.

4.2 Maternal factors

4.2.1 Attachment and bonding

Inadequate nutrition may also be due to maternal factors. The maternal mental state, attachment and bonding between mother and infant play an important role for the development of the infant and may also influence the baby's feeding habits.

Bonding relates to the feelings, thoughts and behaviors parents have towards their child. Good bonding is a very important factor for the cognitive, social, and emotional development of an infant. Observations show that good bonding has positive effects on the infant's social skills, school readiness, as well as academic success (72). However, bonding is crucial when facing nutritional challenges of preterm newborns. Ravn et al. (2012) observed that a good mother-infant interaction enhances successful breastfeeding (73). The maternal mental state influences and interaction between mother and child. Mothers with an unstable psychological state struggle to establish a strong bond with their child (74). Solid bonding improves the interaction and communication between mother and infant. A mother, who has established a strong bond with her infant, is more attuned to their needs and is better at understanding the cues her infant

provides. In particular, preterm infants often lack common early hunger cues, making attentive maternal behavior crucial for improving feeding patterns and increasing the nutritional intake (74).

Oxytocin is involved in the formation of social bonds and is associated with increased mother-infant bonding (75). Additionally, oxytocin is hypothesized to be released in stressful situation in order to decrease psychological stress levels. It has been observed that high oxytocin levels lower the secretion of norepinephrine levels in stress situations and thus keep the blood pressure and heart rate at normal levels (75). Consequently, stress levels of mothers and infants can be reduced by strong bonding and enhance milk production as well as the digestion of nutrition by the infant (74).

A strong emotional bond also boosts the mother's confidence and persistence in feeding their child. Rosenblad et al. (2022) found that mothers who were more confident in breastfeeding perceived better state-regulation in their infants (76). The state-regulation describes the infants ability to maintain their behavioral and psychological states referring to crying, sleeping and feeding (76).

Better state-regulation and more persistence feeding is essential in establishing effective feeding routines as well as improving adequate nutrition.

4.2.2 Breast milk extraction

Another challenge in providing proper nutrition for preterm infants is problems with breast milk extraction. Preterm babies may not be able to suck, swallow or even latch on the breast to extract milk (77). However, the breast tissue requires regular feeding stimulation to produce breast milk. If the baby is unable to suck and extract the milk, stimulation will be insufficient and as a consequence less milk is produced by the breast tissue.

Another reason for insufficient milk production may be the underdevelopment of the glandular breast tissue during pregnancy (77). Particularly in mothers of preterm babies, the breast may not be fully developed to provide sufficient nutrition for the infant. The development of this tissue and the milk production itself can also be influenced by previous breast reduction surgeries, radiation therapies, hormonal imbalances as well as the intake of certain medications.

5. Enteral nutrition

Enteral nutrition of newborns is necessary in preterm babies as they have not established the ability to suck and swallow and therefore can not be orally fed.

Enteral nutrition in preterm newborns is done by different routes, either the application of a nasogastric or orogastric tube (7). Different feeding strategies have been developed, detailing how to feed preterm newborns enterally, ensuring appropriate weight gain and growth is maintained and risk of complications are reduced (7). Infants who weigh less than 1800g or who are younger than 32nd GW require tube feeding, as only after the 34th GW babies are able to coordinate sucking, swallowing and breathing and therefore can only be orally fed (50).

5.1 Trophic feeds

Trophic feeds, also referred to as minimal enteral feedings, are small volume enteral feeds. They are hypocaloric feedings which have the purpose of stimulating the gut and acclimate it to enteral feeds. The amount of feeds are insignificant and only reach 20 ml/kg/day. They are distributed over the day so that the gut is stimulated in regular intervals, every three hours (7).
In enteral fasting, the gut lacks stimulation which is associated with complications like decrease in size or even gut atrophy (7). Intestinal enzymes do not develop without any trigger and with a lack of enteral nutrients, the gut becomes more permeable and thus susceptible for the invasion by pathogens (78). Other complications associated with enteral fasting are hyperbilirubinemia, infections, cholestasis, or metabolic complications (79).
Therefore, early initiation of trophic feeding is recommended and should start within the first six hours of life (7). According to Chitale et al. (2022), an early initiation of enteral feeding is suggested, as it is thought to be associated with lower risk of mortality (80). Concerns about an increased risk for NEC with early trophic feeds initiation could not be confirmed by a meta-analysis (81). Further benefits of an early initiation include a better feeding tolerance and faster maturation of the gut motility (7). Trophic feeds are best started with unfortified breast milk. Alternatively, pasteurized donor milk can be used (7).

5.2 Advancement of feeds

It is important to increase enteral nutrition in appropriate amounts to avoid complications such as NEC (7). A meta-analysis detected that an early advancement of enteral feeding, meaning before the fourth day of life, compared to a late advancement, after the fourth to seventh day of life, did not show an increased risk for the development of NEC (81). Other observations even suggest a reduced risk of mortality, NEC, sepsis and feeding tolerance when advancing the feeds faster (82). Furthermore, the newborns that had their enteral feeding increased at an earlier stage, subsequently reached the full feeds earlier on (81). In a systematic review of Yang et al.

(2022), it is stated that rapid advancement of 30 ml/kg/day or more, would reduce the time to regain birth weight by nearly 4 days and shortened hospital stays by up to 3 days (82).
According to ESPGHAN guidelines, an appropriate daily advancement is about 18-30 ml/kg starting after the 4th day of life (17).

5.3 Feeding techniques in enteral nutrition

The different feeding techniques are evaluated in studies and have advantages and disadvantages in different conditions. Infants can be fed intermittently or via a continuous infusion.

Intermittent feeding

Intermittent feeding is defined as delivering enteral nutrition several times a day for about 15 to 30 minutes every two to three hours (83). This method is used in order to mimic the natural, physiologic feeding routine. It stimulates the secretion of digestive hormones like gastrin, gastric inhibitory peptide and insulin and therefore leads to the stimulation and development of the gastrointestinal tract (84). Additionally, intermittent feeding induces greater protein synthesis, as the cyclic ingestion of amino acids and the secretion of insulin leads to an induction of anabolic pathways in skeletal muscles (85).
However, intermittent feeding may be associated with a higher risk of feeding intolerance (86). With bolus infusions, the capacity of the small GI tract may be easier exceeded than with continuous feeds.

Continuous feeding

Continuous feeding is the administration of enteral nutrition at a constant speed for 24 hours (87). This method is more suitable for infants with a birth weight lower than 1000g or infants with gastrointestinal diseases (88). As the nutrition is continuously administered, digestive hormones, like gastrin and insulin, are constantly present at higher levels. This enables a better absorption of nutrients and lower energy expenditure for the hormonal surges (89). Respectively, intermittent feeding is associated with higher energy consumption (90).
However, a study by Jawaheer et al. (2001) showed, that continuous feeding may cause biliary stasis and gallbladder enlargement, because gallbladder emptying only occurs after bolus feeds (91). A study by Rogers et al. (2010) showed that nutrient losses of key minerals and fats were observed in the method of continuous feeding (92). These losses were minimized in bolus feeds. It was therefore hypothesized that the nutrients may be lost within the delivery system which is more likely in continuous feeding.

Comparing these two methods, a meta-analysis has shown that the time to achieve full feeds in preterm infants is longer in the continuous feeding method than with intermittent feeds (86). However, according to the above-mentioned meta-analysis, other variables like feeding intolerance, growth parameters, risk for NEC and many more, did not show a significant difference between the two feeding methods.

5.4 Types of food in enteral nutrition

5.4.1 Maternal milk

Maternal milk is the best choice of nutrition for a newborn as it provides many benefits for their growth and development. Especially colostrum, the initial milk secretion from the mother's mammary glands, is rich in many immunoactive substances which can help protect infants against infectious diseases.

Observations indicate that infants fed with human milk have fewer respiratory and gastrointestinal infections in their early weeks of life, compared to newborns who are not fed with human milk (93).

Additionally, human milk feeding is associated with lower rates of late-onset sepsis in preterm newborns. This beneficial effects is due to the presence of maternal antibodies and other factors supporting the host defense like lactoferrin, cytokines and lysozymes in maternal milk (94). Furthermore, the immunoactive substances like IgA antibodies and lactoferrin also contribute to the development of the mucosal immune system, preventing inflammation (95). The positive effect on the gut's integrity and the provision of immunological factors, aid the infant in defending against pathogens.

Oligosaccharides in the breast milk act as a probiotic agent. They prevent the adhesion of pathogenic bacteria to the intestinal wall and promote the development of a healthy microbiome (95). This supports the colonization of beneficial commensal bacteria in the infant's intestine. Preterm infants, who are at increased risk for developing NEC, particularly benefit from the intake of human milk. A comparative study by Montjaux-Régis et al. (2011) observed that preterm infants fed with their mother's own raw milk had decreased incidences of NEC, as well as improved weight gain (96).

Further research by Maayan-Metzger et al. (2012) observed lower rates of ROP in preterm infants fed with human milk compared to preterm infants fed with formulas (97).

Several studies have also shown that preterm infants fed with human milk have lower levels of low-density lipoproteins, blood pressure, as well as decreased rates of metabolic syndrome when they reach adolescence compared to those fed with formulas (98,99). Moreover, the overall risk of mortality is up to 12% lower in infants fed with human breast milk than in non-breastfed infants (100).
According to the WHO, breastfed children are less likely to become overweight or obese and tend to perform better in intelligence tests (101).

5.4.1.1 Colostrum

The colostrum is crucial for newborn infants due to its high content of immunomodulating factors like lactoferrin, oligosaccharides and immunoglobulins, making it "the infant's first immunological protective agent" (102). Especially lactoferrin, a glycoprotein, is important for its antioxidant, anti-microbial, anti-inflammatory as well as immunomodulating functions (102).

At birth, the immune system of a newborn is still immature, relying primarily on IgG immunoglobulins, which are present at levels comparable to those in adults and are provided by the mother via the placenta during pregnancy (103). IgA immunoglobulin are acquired by the newborn infant through breastfeeding, playing a critical role in the first-line defense against pathogens (102). A comparative study by Köhler et al. (2002) found that IgA levels in breast-fed infants are higher than in formula-fed infants (104). Other observations show that the IgA content is higher in colostrum and breast milk of mothers of preterm babies than in mothers of term babies, indicating that the mother's body adapts to provide additional immunological support for preterm infants (105).
Preterm infants are in need for immunological support as they are at increased risk for developing diseases like NEC or late-onset sepsis (102). Therefore, the early administration of colostrum is critical. Ideally, colostrum is already provided within the first six hours of life (7). It is administered with a syringe into the preterm newborn's mouth to ensure the absorption of immunoglobulin A and lactoferrin by the buccal mucosa (106).

5.4.1.2 Maternal milk composition

Maternal milk is composed of water, proteins, lipids, carbohydrates, minerals, and vitamins. Depending on the mother's condition, the lactational stage and the time of expression, the composition of maternal milk can vary among lactating women (107).

The protein content of maternal milk in the first two postnatal weeks is between 1.5 to 2.2 g/dl and decreases to 1.0 to 1.4 g/dl after the third postnatal week. The main types of protein in human milk are whey and casein. Whey is a soluble protein that makes up about 20% of all milk proteins (107). It includes proteins like alpha-lactalbumin, lactoferrin, lysozyme and others, which have immunomodulatory and gastrointestinal functions (107). Casein, on the other hand, is a denser protein, making up about 80% of milk proteins. They can be subdivided into alpha -, beta - and kappa-caseins and they possess immunomodulatory and antibacterial properties, as well as an antithrombotic and antihypertensive activity (107). In human milk, whey and casein are found in a ratio of 80:20 respectively.

The lipid content in human breastmilk is around 2.6 to 3.7 g/dl (107). Fats make up around 3.9% of human milk and account for 40-50% of the total energy intake. Most lipids in human milk are triglycerides which contain many different types of fatty acids. They can be either short-, medium-, long- or very-long chain FA, as well as saturated or unsaturated (mono- or polyunsaturated). Every type of FA has important health benefits for the newborn (107).

The carbohydrate content in human milk ranges from approximately 7 to 7.3 g/dl (107). Various types of carbohydrates are present with lactose being the predominant carbohydrate, accounting for 70-85% of all carbohydrates in human milk. However, preterm infants often struggle to digest lactose due to their lower lactase levels compared to term babies (107). Nonetheless, undigested lactose still provides important biological benefits in the intestine. It promotes the growth of beneficial microbiota and facilitates the absorption of calcium, magnesium and zinc (107). Additionally, undigested lactose that reaches the colon undergoes bacterial fermentation and can eventually be absorbed there.

Other carbohydrates include oligosaccharides, which are short-chain or complex carbohydrate formations, that vary in their form. Oligosaccharide have immunomodulatory and antimicrobial functions as well a prebiotic effect (108). Prebiotics are food components that are not digested in the GI tract and reach the colon intact. In the colon, they promote the growth of the beneficial microbiota, contributing to gut health.

The sodium content in preterm milk is higher than term milk in the first two weeks of life, but eventually fall to the same levels as term milk which are 12 to 25 mg/dl (107).

Calcium and phosphorus are not sufficiently available in human milk to meet the newborn's needs and ensure a healthy bone development (107).

Vitamin D and iron are also very low in human milk and need supplementation to provide adequate nutrition (107).

Other electrolytes, minerals and trace elements like potassium, magnesium and zinc are also not present in human milk in sufficient amounts and need to be supplemented (107).

To ensure the composition of human milk is able to fully meet the daily nutrition needs of a preterm infant, quite high volumes would need to be administered. For example, the daily protein requirement for preterm infants is 3.5-4.0 g/kg/day. Human breast milk contains 1.5 to 2.2 g/dl. For a 1000g heavy infants the required intake would be 350 to 450 ml per day. However, daily fluid intakes for preterm infants should not exceed 140-160 ml/kg/day which would correspond to 140-160ml for a 1000g heavy infant. In order to provide sufficient proteins, nearly double the volume tolerated by the preterm baby would need to be administered. This also applies for lipid as well as carbohydrate administration. Therefore, fortifiers are needed to increase the concentration of contents without increasing the volume. Fortifiers for human breast milk are discussed in the chapter below.

5.4.1.3 Difference between breast milk from mothers of preterm and term infants

Mother's breast milk composition varies according to the age of the infants. Expressed breast milk from mothers who gave birth to preterm infants has a different composition than the breast milk of mothers with term babies.

A systematic review and meta-analysis from Fenton et al. (2014) studied the differences in composition between preterm and term mother's milk (109). Their observations show that the energy content per 100 ml of breast milk is higher in preterm breast milk than in term breast milk. In the babies' second week of life, the energy content of preterm breast milk is 71 kcal per 100 ml, whereas the term breast milk only contained 67 kcal per 100 ml. In week three and four, the energy content of preterm breast milk increases, whereas the energy content for term breast milk slightly decreases. The protein content of preterm breast milk is also higher than term breast milk. In the first week of life, mother's milk for preterm babies contains 2.2 g proteins per 100 ml, whereas term breast milk only contains 1.8 g proteins per 100 ml. The protein content in breast milk generally decreases over the following weeks in preterm as well as in term breast milk, however the protein content in preterm breast milk is always greater than in term breast milk (109).
The fat composition is also observed to be higher in preterm breast milk. Around 2.6 g of fat per 100 ml are estimated for preterm breast milk whereas term breast milk only contains 2.2 g

of fat per 100 ml (109). The fat content gradually increases over the first weeks of life, however the fat content in preterm breast milk stays always higher than in term breast milk.
Only calcium and phosphorus contents in preterm breast milk are observed to be lower than in term breast milk. In the second week of life, the calcium content in preterm breast milk is 25 mg of calcium per 100 ml compared to 28 mg of calcium per 100 ml in term breast milk. The phosphorus content in the second week of life is 15 mg per 100 ml in preterm and 17 mg per 100 ml in term breast milk.

5.4.2 Fortifiers

Human milk components are not dense enough in order to provide adequate nutrition for the preterm infant. Much more volume of breast milk is needed to meet the daily requirements for proteins than the maximal amount of volumes tolerated by infants. Additionally, the high volumes would, on one hand, not be tolerated by the baby and on the other hand provide much more calories to the infants than required.
For an adequate protein provision, which is around 3.5 to 4.0 g/kg, the infant would need to receive around 350 to 400 ml per day, which equals around 180 to 240 kcal/kg (27). The average needs of a preterm infant however are much lower, around 115-140 kcal/kg/day. Overnutrition might even be harmful for the infants and would cause metabolic stress or lead to inappropriate body compositions (27). Therefore, fortifiers can be used to enrich the breast milk with additional nutritional components.

The composition of different fortifier products varies among manufacturers. The table below from the ESPGHAN guidelines compares different fortification products according to their nutritional composition, in relation to the breast milk composition and the required daily intakes of a preterm infant.
Below, table 2 details how some fortifiers are rich in carbohydrates (2.7 g/dl) and low in fats (0 g/dl). They take their main energy source from carbohydrates (Milupa – Aptamil HMF and Nutricia – Nutriprem HMF).
Other products provide their energy mainly through fat. Their fat composition is as high as 0.7 g/dl and their carbohydrates reach between 1.3 to 2.5 g/dl (Nestle – PreNan HMF and Abbott – Similac Human Milk Fortifier hydrolized Protein Concentrated Liquid).
However, all products provide nearly the same amount of total energy (14.4 – 17.4 kcal/dl).
It is still unclear which of the products are more beneficial for the best growth of infants, however some clinical trials suggest that products with increased fat contents may lead to amino

acid oxidation and therefore an impaired protein synthesis (110). Excessive amino acid secretions lead to increased BUN levels and are toxic for the infants (27). A more balanced fat to carbohydrate ratio is favored.

ESPGHAN recommendations determine an appropriate fortification composition, based on a fluid intake of 160 ml/kg/day and comprise 1.7g of proteins, 0.5 g of fats, 1.2 g of carbohydrates per 100 ml (27).

Table 2: Macronutrient composition of fortifier products available in Europe and North America, human milk composition and targeted levels according to ESPGHAN

Routine Fortifier	Fat [g/dl]	Protein [g/dl]	CHO [g/dl]	Energy [kcal/dl]	Ref
Milupa – Aptamil HMF	0	1.1	2.7	15.2	[30]
Mead Johnson - EnfaCare	1	1.1	0.4	15.0	[32]
Nutricia - Nutriprem HMF	0	1.1	2.7	15	[33]
Abbott – Similac Advance Liquid HMF	0.36	1.0	1.8	14.4	[34]
Nestle - PreNan HMF	0.72	1.4	1.3	17.4	[31]
Abbott – Similac Human Milk Fortifier Hydrolized Protein Concentrated Liquid	0.7	1.7	2.5	15	[35]
Native human milk	3.4 - 4.0	1.0 - 1.3	7.0 - 8.0	65	[7,8,11]
Recommended nutrient composition (assuming a TFI	4.4	2.7 (-3.0)	8.8	86	ESPGHAN
of 150 ml/kg/d)					

Source: Fusch C. ESPGHAN Committee of Nutrition (CoN) Position Paper on Enteral Nutrition for Preterm Infants: Breast milk fortification, Supplementary Digital Content no. 19. 2022.

The recommended starting period for fortification use varies within the literature. One suggestion is to introduce the fortification as soon as full enteral nutrition is reached, which implies an administration of 150 ml/kg/day (27). The fortification provided initially is at half strength and after the first two days, full strength fortification can be used. However, other studies reported that full strength fortification is well tolerated by infants from the first day onwards (111). Consequently, ESPGHAN guidelines conclude that there is no definitive recommendation for the timing of fortification initiation. Early introduction may be as safe as late introduction. ESPGHAN recommends the introduction of fortifiers when enteral nutrition reaches 40 to 100 ml/kg/day (27).

Not only does the breast milk composition differ between mothers, the mother's own breast milk may also change from day to day. Therefore, **individualized fortifiers** may contribute to an optimal nutrient provision.

Adjustable fortifiers are adjusted according to the infants' BUN levels (27). They reflect the protein utilization and therefore their requirements. High BUN levels indicate excessive protein intake and low levels may reflect that there is a higher metabolic capacity for protein intakes. To assess an infants' BUN levels, frequent blood sampling is needed. However, the changes to BUN levels in response to any intervention may be delayed, due to slow acting metabolic adaptations.
For targeted fortifiers, the mother's breast milk is collected and analyzed concerning its composition and the infants' requirements (27). According to guideline recommendations, macronutrients are added to a satisfactory level which meets their needs. This method requires more effort from the staff but may be optimal in mothers whose milk has unequal compositions.

Both, adjusted and targeted fortification can contribute to improved growth rates in preterm infants (112,113). Targeted fortifiers, in particular, can effectively compensate nutritional deficiencies and support better growth (27).
Markedly, donor milk is susceptible to decreased protein content. Mostly, donors of breast milk are mothers with prolonged or excessive milk production, meaning most mothers donate their milk after they have fully provided for their own child. Evidence shows that protein content decreases during lactation (107). Additionally, the process of pasteurization also decreases the protein content. This makes individualized fortifiers especially useful for donor milk.

5.4.3 Donor breast milk

Donor breast milk is donated by lactating mothers to a milk bank, where it undergoes processing before being provided to other infants. This practice supports infants, whose mothers may struggle in expressing breast milk and providing sufficient amounts for their baby. Donor milk serves as an alternative for those babies, offering similar nutritional benefits.

The first milk bank opened in 1909 in Vienna, Austria (114). In America, the first milk bank was established in 1919. However in the 1980s, milk banks started closing due to the fear of transmitting HIV (115). Nowadays, the donated milk is pasteurized, screened and serologically tested to ensure the safety of donor milk distribution (115).
In Europe, there are currently 282 active milk banks in 31 countries with 18 more planned (116).

Prior to donation, the donor must undergo several screening tests, an interview and get a medical approval. Mothers are not allowed to take medications, drink alcohol and smoke during their phase of donation.

Human milk is treated like a human body substance, so extracting, processing and storing it must be done in an appropriate manner (115). The mothers extract their feeds, freeze it and transport it to the milk bank. The milk bank combines the milk from up to four different mothers and takes a bacterial culture to exclude any contamination. Later, the milk undergoes Holter pasteurization (62.5°C for 32 minutes) (115). After pasteurization, another culture is taken. Before pasteurization, any pathogen isolated greater than 10^4 colony forming units per ml cannot be used. Additionally, any positive culture found before or after pasteurization, cannot be used. The milk is then frozen and awaits the recipient. The process of pasteurization has several effects on human milk. The primary aim of this procedure is to deactivate bacterial and viral components like cytomegalovirus. The main nutritional components like fats, carbohydrates or salts stay unchanged (115). However, as proteins are sensitive to warm temperatures, about 13% of all protein content is denatured during this process (115).

The pasteurization process negatively affects some bioactive and immunological factors in maternal breast milk. It has been observed that the concentrations of IgA antibodies in the pasteurized milk are 51% lower than before the process (117). IgG antibodies are reduced to 66% and IgM antibodies are completely destroyed (115). Lactoferrin levels are lowered by 91% of its original level (117). The lysozyme activity in the human milk, responsible for attacking bacterial walls and serving as an immunological component, is reduced by 75% (115).

Donor milk is especially useful for babies in very vulnerable states which includes prematurity. Observations show that donor milk has advantages over preterm formulas as they contain bioactive substance which reduce the risk of NEC and sepsis, whereas preterm formulas contain substances which increase the risk (118).

5.4.4 Special formulas

Formulas created for preterm infants are recommended when sufficient maternal milk or donor milk is not available.

The formulas try to mimic the properties of human milk as closely as possible. These special formulas contain extra calories and minerals to ensure they meet the preterm infant's needs. A study by Yu et al. (2019) shows that preterm formulas have an advantage over donor milk as they contribute to a greater weight gain (119). Formulas have a higher caloric density and

protein content. Children fed with preterm formula regained their birth weight faster than those fed with donor milk (120).
The feeding tolerance of formulas are observed to be similar to feeding tolerance of human milk (120). However, the time taken to reach full enteral nutrition was longer than with human milk or donor milk. As mentioned above, feeding infants with formulas may increase the risk of NEC and sepsis (120).

The composition of preterm formula is the following:
The protein content ranges from 2.2 to 3.3 g/dl (107). The amounts can vary among manufacturers. The whey:casein ratio in preterm formulas is usually adapted to the human milk ratio, 80:20. Higher whey content makes digestion for the infant easier due to its higher solubility.
Fat concentrations in range between 3.4 and 6.7 g/dl also vary according to the manufacturer (107).
Carbohydrates are found in amounts between 7.0 to 10.9 g/dl (107). Every component of the preterm formula is present in higher amounts than simple human milk from mothers with preterm infants. In particular, lipids and carbohydrates are added in higher amounts and may be the reason for greater weight gain.

6. Parenteral nutrition

Parenteral nutrition (PN) is a crucial method to sufficiently nourish preterm newborns if enteral nutrition is not tolerated or the intestine fails to digest and absorb nutrients. PN helps limit catabolic processes and covers their nutritional needs to enable growth (121).
Ideally, parenteral nutrition is a temporary feeding method used until the newborn can fully transition to enteral feeding.
Indications for initiating parenteral nutrition include preterm newborns born before 31st +0 GW and those older than 31st +0 GW if sufficient progress is not made with enteral nutrition in the first 72h after birth (122). Preterm and term infants with underlying GI disorders or other critical illnesses also benefit from parenteral nutrition (122).
While infants are fed parenterally, enteral feeds are also introduced simultaneously whenever feasible to maintain gut integrity (123). The transition from parenteral to enteral nutrition is made gradually. Enteral nutrition is increased while parenteral nutrition is weaned as long as it is tolerated. This transition phase is particularly vulnerable to inadequate nutrition, which may result in negative growth outcomes (124). To maintain good nutritional intake, the PN should

be reduced slightly faster than enteral nutrition is increased (125). Excessive fluid intake may impede the baby's tolerance to enteral nutrition (125).
Parenteral nutrition can be discontinued once enteral nutrition constitutes two-thirds of the total fluid intake, between 140-150 ml/kg/day (126). During the transition from parenteral to enteral nutrition, careful consideration should be given not only to the volume but also the tolerance, type, and composition of enteral feeds to avoid nutritional deficits (127).

6.1 Vascular access for parenteral nutrition in preterm newborns

In order to administer parenteral nutrition, a reliable venous access has to be established. There are peripheral intravenous lines as well as central venous catheters (CVC).

Peripheral intravenous lines

Peripheral venous catheters are inserted into small veins of hand, feet, or even the scalp of the preterm newborn. They are easily and quickly placed, making them the preferred choice for short-term parenteral nutrition and fluids.
Peripheral parenteral nutrition should be considered when short-term parenteral nutrition is anticipated (less than 5 days). It can also be used when a central line is impractical, or to avoid delays in starting or interrupting the delivery of parenteral nutrition (128).
When using peripheral lines, the maximum osmolarity for solutions should be limited to ensure safety. Solutions with an osmolarity up to 900 mOsm/l can be safely administered via peripheral venous access (129). For example, lipid emulsions or isotonic solutions are suitable for peripheral administration as well as glucose solutions of maximally 12,5% (128,130). Higher osmolarity fluids pose a greater risk for tissue damage in case of extravasation (131). Due to the tendency of displacement of peripheral accesses, special care should be taken when administering higher osmolar solutions. Therefore, peripheral venous access is a preferred method of administration for some parts of the nutritional supply (125).

Central venous catheters

There are different types of central venous catheters. They can either be peripherally inserted central catheters (PICCs) or centrally inserted CVCs.
PICCs are inserted into a peripheral vein in the arm and advanced to the central vein. In contrast, centrally inserted CVCs are placed into large veins such as the subclavian, jugular, or femoral vein and extended to the superior vena cava or right atrium. They can also be inserted into the umbilical vein known as umbilical venous catheter (UVC) (128).

According to ESPGHAN guidelines, non-tunneled PICC are recommended fort short- and medium-term use, while cuffed, tunneled CVC are used for long-term applications (132).

The use of umbilical vessel catheterization is often used for short-term access as recent studies suggest higher incidences of catheter related blood stream infections (CRBSI) in long-term umbilical venous catheterization (up to 28 days) compared to short-term catheterization (133).

Central lines are used for the delivery of high concentration nutrients or fluids. Due to their large bore, highly concentrated substances as well as high-volume mixtures can be safely administered which are particularly necessary for preterm infants requiring high concentrated nutritional solutions (134).

Conclusion

A randomized comparative trial found that neonates receiving parenteral nutrition via peripheral catheters are more likely to be in nutritional deficiency than those receiving PN via a central venous catheter (135). This is due to the limited capacity of peripheral lines being unable to accommodate highly concentrated or high-volume nutrient mixtures.

However, in the early development of preterm newborns, adequate and sufficient nutrition is essential for brain growth. The use of central venous catheter enables the administration of highly concentrated nutrient solutions making them the recommended choice for prolonged parenteral nutrition in preterm newborns (136).

Although the placement of CVCs is more invasive, they offer more stability, reducing the need for frequent changing and thereby lowering the risk of sepsis (136).

Additionally, CVC have a lower risk of causing irritations and damage to small peripheral veins. Peripheral accesses tend to displace easily and cause direct damage, such as thrombophlebitis, leading to extravasation of the administered fluids into the surrounding tissue (134). These issues can jeopardize the appropriate nutritional supply (132).

Overall, CVCs are the preferred method of administration for parenteral nutrition. Their reliability and stability ensure that the preterm infant receives the nutrients necessary for their growth and development.

6.2 Components of parenteral nutrition in preterm infants

Parenteral nutrition in preterm newborns should be started as soon as possible, ideally within the first eight hours of life (122). Early administration of parenteral nutrition limits catabolic processes and prevents hypocalcemia, reducing energy requirements from the beginning (121). In the first four days of life, 40 to 60 kcal/kg/day should be administered to prevent the above-mentioned complications (126). However, these energy levels are not sufficient to achieve normal rates of growth (121). Therefore, the daily caloric values of the parenteral nutrition are gradually increased over time to reach full parenteral nutrition. For examples, over a course of four days, energy values can be escalated from 75 to 120 kcal/kg/day (126).

Parenteral nutrition consists of proteins, lipids, vitamins, electrolytes, trace elements and glucose. Depending on the day of life, the composition is adjusted each day until full parenteral nutrition is achieved.

According to ESPHGAN guidelines, a preterm newborn, on its first day of life, should receive around 80 ml/kg of fluids. This mixture should include 1.5 g/kg amino acids and 1 to 2 g/kg lipids (126,137,138). Electrolytes like sodium, potassium and chloride are added only on the second day of life (138).

Minerals like calcium, phosphate and magnesium are also included. On the first day of life, 0.8 to 2 mmol/kg calcium, 1-2 mmol/kg phosphate and 0.1-0.2 mmol/kg magnesium should be administered (139). Additionally, 1g of vitamin per kilogram and 5.8-11.5 g/kg of glucose are provided on the first day (140).

Over the next few days, the amounts of each component are gradually increased until full parenteral nutrition is reached.

At full enteral nutrition, the fluid intake for a premature newborn older than 5 days comprises of 140-160 ml/kg/day (138). Amino acids (AA) are added in amounts of 3-4 g/kg/day (137). Furthermore, 3-4 g/kg/day of lipids are added (141). Electrolytes are added in amounts of 2-5 mmol/kg/day of sodium, 1-3 mmol/kg/day potassium and 2-5 mmol/kg/day chloride are added to the parenteral nutrition (138). Minerals are administered at 1.5-2.5 mmol/kg/day of calcium, 1.6-2.6 mmol/kg/day of phosphate and 0.2-0.3 mmol/kg/day of magnesium (139). Vitamins are provided at 1g/kg/day and glucose at 11.5-14.4 g/kg/day (140).

6.3 Types of parenteral nutrition in preterm infants

Parenteral nutrition is available in individually tailored as well as standardized solutions.

The advantage of an individualized solution is that they can be specifically customized for a certain patient to meet his unique needs and ensure the optimal nutritional support (142). These solutions can be adjusted daily based on laboratory values and other reflective indicators. This approach is particularly beneficial in infants who are very fragile or vulnerable, such as those with very low birth weight, who require intense nutritional monitoring.
Standardized solutions often fail to meet the complex nutritional needs of preterm newborns and hence are prone to developing nutrient deficits (142). Consequently, tailored nutrition with close observation and frequent adjustments is beneficial for their adequate growth (143).

The actual beneficial aspect of individualized nutrition lies not only in the customized solution itself, but also in the frequency of monitoring and observation of the infant. This makes individualized parenteral solution particularly suitable for more vulnerable groups of premature infants (143).
On the other hand, according to the ESPGHAN guidelines on pediatric parenteral nutrition, standardized parenteral solutions "should generally be used over individualized parenteral nutrition in the majority of pediatric and newborn patients" (142). These solutions are suitable for most the patients and offer adequate nutrition. A study by Krohn et al. (2005) has shown that standardized solutions offer better electrolyte balance for calcium and phosphate intakes (144). A study by Simmer et al. (2013) revealed that standardized solutions provide higher nutrient intakes and eventually lead to a greater weight gain and less nutritional deficits (145).

6.4 Side effects of parenteral nutrition in preterm newborns

Benefits and disadvantages of PN should be carefully evaluated to determine the optimal duration of parenteral nutrition and appropriate time for transitioning to enteral nutrition.

On one hand, parenteral nutrition is a method which provides the ideal energy composition. The energy sources can be immediately used, as they do not need to be digested or processed (127). However, PN may also be concomitant with side effects and complications. One significant source of complications is the CVC, which can cause blood stream infections in parenterally

nourished infants. Furthermore, PN can negatively affect various organ systems.

The most common complication of CVC usage are central-line associated bloodstream infections (CLABSI), which are highly dangerous for preterm newborns and associated with high morbidity and mortality (130). CLABSI often lead to intestinal failure and can negatively impact the neurodevelopment of babies (130,146). The incidence of catheter-related invasive infections ranges between 5- 40% (136).
A CVC can also become mechanically occluded. Nutritional components like lipids or calcium phosphate complexes may precipitate in the catheter, causing occlusion (130). Thrombus formation in the catheter is another serious complication as it can lead to embolization in major vessels such as the superior or inferior vena cava or the pulmonary artery (130). Thrombotic events are associated with increased morbidity and mortality of preterm newborns (130).
Extravasation of infused fluids into extravascular space is rather rare when using CVC, however, it can be life-threatening if it leads to cardiac tamponade, pleural effusion, or cardiac effusion.

Long-term PN can also lead to metabolic bone diseases, caused by imbalances in calcium, phosphorus or vitamin D levels, aluminum contamination, or disturbed energy levels (130). Symptoms include frequent fractures, osteoporosis, and pain.
Moreover, PN can cause liver diseases. Excessive administration of certain components like amino acids or glucose can harm the liver. Hyperinsulinemia resulting from PN is associated with steatosis, and increased energy supply leading to liver lesions (130).
The lack of enteral nutrition decreases bile flow, potentially leading to bile acid sludge formation and cholestasis (130).

6.5 Monitoring of parenterally fed preterm newborns

Newborns receiving PN should be regularly monitored to detect any changes or abnormalities. Monitoring helps to reflect the efficacy and adequacy of PN composition for each infant. Nutritional deficits can be detected before clinical symptoms arise, which allows for early intervention, preventing negative outcomes (147). However, monitoring should occur at intervals that provide sufficient information without harming or distressing the infant.

Key monitoring parameters include the following.

Blood glucose is measured at least twice a day (121). Hypoglycemia and hyperglycemia can occur quickly and pose a life-threatening risk to the newborn. Frequent blood sampling is necessary to maintain blood glucose values within the target range.

Electrolytes, BUN and creatinine should be measured every one to two days initially, then reduced to two to three times weekly (121). Sodium levels reflect the renal tubular reabsorption. BUN indicates protein intake, low values suggest insufficient protein intake, while high values indicate excessive intake (147). BUN levels below 1.6 mmol/l are considered inadequate (147). Creatinine reflects the kidney function.

Serum calcium, serum phosphate and alkaline phosphatase should be monitored after the first week of PN and then every two weeks (121). These values assess bone mineralization and help identify potential metabolic bone diseases (147). Additionally, calcium and phosphate are also measured in urine samples. Absence of both minerals in urine suggests inadequate intake. If only calcium is present in the urine, phosphate intake is too low, and vice versa.

Triglycerides should be monitored once infants receive at least 2 g/kg/day of lipids, to ensure adequate lipid intake, as well as liver function (121).

Liver function can also be assessed by monitoring alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholestasis parameters bilirubin and gamma-glutamyl transferase (GGT). These are assessed after the first week of PN and then every one to two weeks (121).

The iron status should be monitored to ensure adequate levels, as iron is essential for blood production, erythropoiesis, and impacts motor skills and language development (147). Iron is supplemented parenterally in infants who cannot maintain an adequate iron status using enteral iron supplements. Monitoring is important to prevent iron deficiency or iron overload.

7. Supplementations for preterm newborns

7.1 Vitamins

7.1.1 Vitamin D

Vitamin D insufficiency is prevalent in premature newborns. A study by Park et al. (2015) investigated the vitamin D status of 278 preterm newborn infants. The results revealed that approximately 98,9% had vitamin D deficiency which highlights the critical need for vitamin D supplementation (148).

Vitamin D plays a vital role in bone metabolism and the development of the innate immune system. The active form of vitamin D, 1,25dihydroxyvitamin D is responsible for regulating the intestinal absorption of calcium. Mineral bone deficiency typically results from a lack of calcium and phosphate, but vitamin D deficiency also contribute to a poor bone health (149).

Vitamin D deficiency has no official definition according to serum levels, however the ESPGHAN committee agreed to define severe vitamin D deficiency as serum 25-hydroxy vitamin D levels below 25 nmol/l (149). Sufficient values for premature infants are > 50 nmol/l, however values over 120 nmol/l should be avoided to prevent hypervitaminosis. Several studies have investigated the optimal daily intake of vitamin D for preterm infants, comparing the intake of 400 IU and 800IU. They concluded that the intake of 800 IU per day is more effective in raising serum levels of 25-OH Vitamin D and improving the bone density (150,151). Additionally, higher vitamin D intakes are associated with better immune system development. One study found that infants receiving 800 IU/day vitamin D3 had an increased expression of T regulatory cells compared to those receiving only 400 IU/day (152).
Based on the available data, ESPGHAN guidelines recommend 400 to 700 IU/kg/day of vitamin D supplementation during first month of preterm infants with a body weight <1800g (149). The maximum recommended intake is 1000 IU per day.

7.1.2 Vitamin K

Vitamin K is responsible for the synthesis of coagulation factors II (prothrombin), VII, IX and X as well as anticoagulation proteins C and S (149).

During pregnancy, the transfer of vitamin K from the mother to the fetus is insufficient and breast milk also does not contain adequate amounts to meet the needs of an infant. In most cases, term infants only reach 50% of adult levels of vitamin K while preterm infants levels are even lower than their term counterparts (153). Additionally, conditions like liver diseases in preterm infants can further aggravate the production of clotting factors (149).
Therefore, supplementation with vitamin K is crucial for all newborns to prevent complications like vitamin K deficiency bleeding. This complication can occur early (within the first 24h), in the first week of life, or even after the first week of life, and is associated with high mortality rates (149).

Prophylactic vitamin K administration is standard practice for every newborn. However, due to the scarcity of studies concerning dosing of vitamin K supplementation in preterm newborns, the dosing regiments vary among medical centers.

The American Academy of Pediatrics (AAP) recommends a single dose of 0.3 mg/kg administered intramuscularly for preterm infants weighting <1000g (154).
ESPGHAN guidelines on parenteral nutrition recommend an intravenous or intramuscular injection of 0.1-0.2 mg/kg vitamin K at birth for preterm newborns, followed by a continuous daily parenteral intake of 10-20 µg/kg (155).

7.2 Probiotics

Probiotics are defined as "live organisms that, when administered in adequate amounts, confer a health benefit to the host" (156). Within medical curing strategies, probiotics are becoming increasingly popular.
Probiotics improve the intestinal barrier by reinforcing the tight junctions between enterocytes and enhance the mucus layer on the intestinal gut (157). Additionally, they help colonize the gut with beneficial bacteria in order to create a balanced microflora that can prevent the overgrowth of pathogenic bacteria and protect against diseases (158). Several studies showed that probiotics are useful for reducing the risk NEC, sepsis and even mortality rates among preterm infants (159).
Despite the benefits of probiotics use, it is still unclear which type of strains, dosages, and duration of probiotic administration are most beneficial (159). The market currently offers a wide range of probiotic products, some of which lack quality and are often administered without robust evidence of their benefits.
The administration of probiotics may not always be appropriate and safe for every infant. Observations have shown that probiotic use can have side effects including systemic infections, excessive immune stimulation, gastrointestinal issues, and the potential for gene transfer of antibiotic resistances (160). Further observations have indicated, that some probiotic strains can exploit the weakened and immature host defense of preterm infants, allowing dangerous, opportunistic pathogens to worsen the infant's condition (161). Notably, *B infantis* and *L rhamnosus GG* have been associated with bacteremia (159). There have been instances where infants on the NICU developed probiotics-induced bacteremia due to cross colonization, even if they did not directly receive probiotic supplementation (159).

Therefore, it is crucial to carefully evaluate the benefits and risks of different probiotic strains in reducing the risks of NEC.

According to available data, the ESPGHAN committee recommends the use of *L rhamnosus GG ACT 53103* at dosages from 1-6 x 10^9 CFU or the combination of *B infantis Bb-02*, *B lactis Bb-12*, and *Str thermophilus TH-4* at dosages of 3.0-3.5 x 10^8 CFU of each strain. These strains and their combinations have been shown to reduce rates of NEC (159).
The duration of probiotic supplementation should be tailored individually for each infant, considering their specific conditions and risk factors (159). Further research and observations are necessary to establish standardized guidelines for effective and safe use of probiotics in preterm infants.

7.3 Iron supplements

Sufficient iron levels are crucial in preterm newborns due to iron's role in heme synthesis, oxygen transport, and cellular energy metabolism. These infants are born with lower iron stores and have higher iron requirements than term infants, driven by their rapid growth. Additionally, preterm infants often stay in the NICU for extended periods, where frequent blood sampling is necessary and can further deplete their iron levels (162). Iron deficiency can lead to anemia, which is associated with adverse outcomes in brain development, resulting in long term consequences including poor cognitive and behavioral performances into adolescence (163).
Adequate supplementation can reduce iron deficiency anemia, decrease the need for blood transfusions, and improve developmental outcomes (17). The initiation of iron supplementation seems to play a critical role in preterm health outcomes. Infants who received supplementation between their second to third week of life required fewer blood transfusion than those who received iron supplementation only between week four and eight (17).
However, excessive iron is toxic to living cells and can cause oxidative stress (163). Furthermore, high iron levels can support bacterial growth, increasing the risk for infection. Iron overload has been associated with poor neurodevelopment and stunted growth of infants (162). Ferritin is a good marker for assessing the iron status. Levels < 35-40 µg/l indicate an iron deficiency whereas levels >300-350 µg/l indicate an iron overload.
Based on available data, the ESPGHAN committee recommends starting iron supplementation with 2-3 mg/kg/day from the second week of life (163). Infants receiving erythropoietin have

higher iron requirements, necessitating iron supplementation up to 6 mg/kg/day. Supplementation should continue beyond the hospital stay until the infant is six to twelve months old.

8. Discussion

The nutritional management of preterm newborns presents a complex, multifactorial challenge. One of the main difficulties is not only meeting their daily caloric requirements but also accommodating their accelerated growth rates and increased energetic needs. The aim is to replicate the conditions the infant would have experienced in utero. Preterm infants grow at significantly higher rate necessitating greater caloric provision.

Additionally, preterm infants often develop medical conditions such as chronic illnesses, sepsis, or other inflammatory conditions, which further elevate their metabolic demands.

To make up for these increased needs, the health care providers must enhance nutritional availability. However, further challenges complicate this seemingly simple task. Due to their immaturity, their digestive system is still underdeveloped and their capacity to absorb the nutrients efficiently is also reduced. Consequently, not all nutrients and calories provided can eventually be utilized effectively.

Moreover, the preterm infant's inability to suck and swallow appropriately makes the provision of oral feedings difficult. Very premature babies may require a total parenteral nutrition in their first days of life. However, this feeding method also entails risks and may hinder the development of the gastrointestinal system which further impedes appropriate nutrition. Furthermore, the administration of antibiotic treatment and a subsequent disruption of the microbiome complicate a proper development of the GI system.

Another challenge is providing a large amount of calories, in a relatively small volume of fluid, as preterm newborns can only tolerate limited amounts. Additionally, normal breast milk often falls short in covering the nutritional needs essential for a preterm baby. In order to obtain the optimal composition of the newborn's diet in small volumes, fortifiers need to be added.

Despite this, human milk remains the best option for preterm newborns as it provides immunoactive substances, essential for the development of the newborn's immune system. Ensuring a consistent supply of human breast milk poses another challenge particularly in mothers of preterm infants as they may encounter difficulties in expressing sufficient amounts of milk to meet their infant's daily needs.

The diverse challenges require meticulous attention to detail. In order to effectively manage the nutrition and ensure an optimal development of preterm newborns, the adherence to certain guidelines and principles can help to achieve this goal.

Every preterm infant needs an individual calculation of their daily caloric goals based on their weight. These needs must be continually reassessed especially in their early days of life. Health care providers should stick to the latest consensus and guidelines.

Moreover, prioritizing high quality nutrition is essential. While human breast milk is the first choice, donor breast milk can be used as an alternative. Monitoring is vital to track the newborn's nutritional status, progress, and development and helps with adjusting feedings accordingly.

Health care professionals strive to optimize every aspect of nutrition for premature newborns, recognizing their increased vulnerability. It is clear that adequate nutrition plays a pivotal role in influencing the developmental and health outcomes of preterm infants. Many adverse outcomes can be mitigated if great attention is paid to their nutrition.

9. Conclusion

The nutrition of preterm newborns poses significant challenges and is highly individual, as every premature baby develops at its own pace. The infant's progress depends on underlying conditions like morbidities or critical illnesses.

While concepts have been developed for the nutrition of preterm newborns, these must be constantly adapted and revised due to the potential for unexpected complications that can hinder the development of the infant. Although many studies have investigated optimal methods on how to nourish preterm infants, studies provide contradictory results and a consensus remains elusive.

Health care providers are exhorted to carefully weigh different study findings and monitor the infants accordingly.

Meanwhile, clear guidelines are available for the provision of adequate preterm nutrition, to support adequate growth, despite the difficult circumstances for preterm infants.

Even though, there are more recent studies available which give greater clarity regarding proper nutrition, challenges still remain. The conditions which influence the newborn's status are multifaceted and a great amount of attention to detail is required to follow and mitigate every influencing factor with care.

Nevertheless, with growing insight and knowledge, the expertise in optimal nutrition for premature infants is advancing and hence leading to improvement in outcomes and development.

10.Summary

In summary, preterm newborns exhibit heightened energetic demands due to their immaturity and potential complications, necessitating careful consideration of the composition of their nutrition. Nutrition plays a pivotal role in addressing and attenuating the effects of prematurity as well as underdevelopment.

However, prematurity comprises challenges like the inability to suck and swallow as well as the immaturity of the lung and the GI system all of which impede a proper nutrition and consequently complicate adequate growth. Additionally, premature infants are exposed to environments such as NICU and receive medications which may influence their status.

Various feeding methods are evaluated and precisely tailored according to their advantages and disadvantages, specific for the preterm infant's condition. Parenteral nutrition may be necessary for extremely premature newborns to prevent catabolic processes and ensure consistent supply. The transition to enteral nutrition should be performed smoothly to prevent a nutrient deficient state. Enteral nutrition is best provided with human breast milk as it meets the caloric goals, as well as provides beneficial immunoactive substances.

Fortifiers and supplementations are required in preterm newborns as their heightened energy demands cannot be solely met with mothers' milk and preterm infants often lack certain vitamins or trace elements.

Keywords: premature infant, nutritional challenge, immaturity of the GI system, parenteral nutrition, enteral nutrition, human breast milk, fortifiers, supplementations

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12.CV

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