Neonatology/Paediatrics – Guidelines on Parenteral Nutrition, Chapter 13

Neonatologie/Pädiatrie – Leitlinie Parenterale Ernährung, Kapitel 13

Abstract

There are special challenges in implementing parenteral nutrition (PN) in paediatric patients, which arises from the wide range of patients, ranging from extremely premature infants up to teenagers weighing up to and over 100 kg, and their varying substrate requirements. Age and maturity-related changes of the metabolism and fluid and nutrient requirements must be taken into consideration along with the clinical situation during which PN is applied. The indication, the procedure as well as the intake of fluid and substrates are very different to that known in PN-practice in adult patients, e.g. the fluid, nutrient and energy needs of premature infants and newborns per kg body weight are markedly higher than of older paediatric and adult patients. Premature infants <35 weeks of pregnancy and most sick term infants usually require full or partial PN. In neonates the actual amount of PN administered must be calculated (not estimated). Enteral nutrition should be gradually introduced and should replace PN as quickly as possible in order to minimise any side-effects from exposure to PN. Inadequate substrate intake in early infancy can cause long-term detrimental effects in terms of metabolic programming of the risk of illness in later life. If energy and nutrient demands in children and adolescents cannot be met through enteral nutrition, partial or total PN should be considered within 7 days or less depending on the nutritional state and clinical conditions.

Keywords: premature infant, low birth weight infant, newborn infant, monitoring, childhood

Zusammenfassung

Eine besondere Herausforderung bei der Durchführung parenteraler Ernährung (PE) bei pädiatrischen Patienten ergibt sich aus der großen Spannbreite zwischen den Patienten, die von extrem unreifen Frühgeborenen bis hin zu Jugendlichen mit einem Körpergewicht von mehr als 100 kg reicht, und ihrem unterschiedlichen Substratbedarf. Dabei sind alters- und reifeabhängige Veränderungen des Stoffwechsels sowie des Flüssigkeits- und Nährstoffbedarfs zu berücksichtigen sowie auch die klinische Situation, in der eine PE eingesetzt wird. Das Vorgehen unterscheidet sich deshalb ganz erheblich von der PE-Praxis bei erwachsenen Patienten, z.B. ist der Flüssigkeits-, Nährstoff- und Energiebedarf von Früh- und Neugeborenen pro kg Körpergewicht höher als bei älteren pädiatrischen und bei erwachsenen Patienten. In der Regel benötigen alle Frühgeborenen <35. SSW und alle kranken Reifgeborenen während der Phase des allmählichen Aufbaus der enteralen Nahrungszufuhr eine vollständige oder partielle PE. Die Zufuhrmengen der PE bei Neonaten müssen berechnet (nicht geschätzt) werden. Der Anteil der PE sollte zur Minimierung von Nebenwirkungen sobald wie möglich durch Einführung einer enteralen Ernährung vermindert (teilparenterale Ernährung) und schließlich komplett durch enterale Ernährung abgelöst werden. Eine unangemessene Substratzufuhr im frühen Säuglingsalter kann langfristig nachteilige Auswirkungen im Sinne einer metabolischen

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Programmierung des Krankheitsrisikos im späteren Lebensalter haben. Wenn bei älteren Kindern und Jugendlichen dagegen der Energie- und Nährstoffbedarf eines Patienten im Vorschul- oder Schulalter durch eine enterale Nährstoffzufuhr nicht gedeckt werden kann, ist abhängig von Ernährungszustand und klinischen Umständen spätestens innerhalb von 7 Tagen eine partielle oder totale PE zu erwägen.

Schlüsselwörter: Frühgeborenes, Low birth weight infant, Neugeborenes, Monitoring, Kindheit

Preliminary remarks

The majority of recommendations on substrate intake (with the exception of the chapters on "Amino acid requirements" and "Information on the selection and production of amino acid solutions" in the attachment, which have been specially drawn up for this set of guidelines) have been drawn up according to the "Guidelines on Paediatric Parenteral Nutrition", a combined study group from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, http://www. espghan.org) and the European Society for Clinical Nutrition and Metabolism (ESPEN, http://www.espen.org) [1]. Systematic literature research has already been carried out for the development of the European guidelines, therefore further research for the current guidelines was unnecessary.

Introduction

Systematic review in a number of fields produced a series of published studies from which evidence-based recommendations can be drawn up for the neonatal period (1–28 days) and period of infancy (1–12 months). The situation in children and teenagers is, however, different with extremely limited data available from randomised controlled clinical studies on children after the neonatal period.

There is a special challenge in implementing parenteral nutrition (PN) in paediatric patients, which arises from the wide range of patients, ranging from extremely premature infants up to teenagers weighing up to and over 100 kg, and their varying substrate requirements. Age and maturity-related changes of the metabolism and fluid and nutrient requirements must be taken into consideration along with the clinical situation during which PN is applied. The indication, the procedure as well as the intake of fluid and substrates are very different to that known in PN-practice in adult patients Therefore, it makes sense to briefly present some of physiological features of paediatric patients that are significant for PN in order to understand the nutritional strategies used for children and teenagers.

- The fluid, nutrient and energy intake of premature infants and newborns is higher per kg body weight than that of older paediatric and adult patients (II).
- The substrate requirements of paediatric patients cannot be proportionally derived from adult requirements on the basis of body weight, but are determined according to age-specific, physiological conditions (II).
- The fluid, nutrient and energy intake during the postpartal adaptation and stabilisation phase is subject to specific conditions, which necessitates a specific approach (II).
- In comparison to older paediatric patients or adults, newborns and infants have an extremely low body store of nutrients and in many respects immature regulatory mechanisms, thus requiring an carefully adapted intake to suit their specific requirements in order to prevent imbalances (II).
- Inadequate substrate intake in early infancy can cause long-term detrimental effects in terms of metabolic programming of the risk of illness in later life (II).

Physiological principles

The *body water content* is age-related and diminishes from approx. 90% in a premature infant born after 24 weeks gestation to below 70% in a 12 month old infant [2], [3].

The *fluid volume* per kg body weight is higher in newborns than in older patients [4]. Contributing factors for this are *renal immaturity* (diminished ability to concentrate urine resulting in increased urine volume) [5], *higher energy expenditure*, greater body surface area compared to body volume and epidermis immaturity resulting in *high insensible perspiration* [6]. The regulatory mechanisms in the water and electrolyte balance are reduced in comparison to adults due to renal immaturity. Alongside the *diminished ability of the kidneys to concentrate urine* [7], the renal glomerular filtration rate, renal tubular reabsorption and elimination of H^+-ions are also lower when compared to those of older children [8], [9]. Based on body weight, the *energy and nutrient requirements* of newborns are *higher* than in older patients. This results from the increased (metabolic) activity and growth [10] resulting in increased nutrient substrate requirements [11], [12], [13], [14].

Apart from the known nutritional effects of nutrition, there is also increasing evidence of long-term changes in the metabolism triggered by nutrition in early childhood (early metabolic programming of early nutrition on health in later life) [15], [16].

Accordingly, newborns, infants and toddlers require an intake of nutrients that has been carefully adapted to suit their metabolic requirements to a far greater degree than older paediatric patients or adults. It is never appropriate to convert intake recommendations from other patient groups like adults on the basis of body weight and to apply them to infants or toddlers without taking into consideration the different physiological conditions. Apart from age-related changes in nutritional requirements, *adaptation processes after birth* (to a greater extent in premature infants) pose a special challenge with regard to the individual requirements for fluid and other nutrient substrates. There is a day-to-day increase in fluid and energy requirements due to the adaptation of metabolism and kidney functions as well as initial high perspiration. Daily adjustments to parenteral nutrition are, therefore, required over the first few days of a child's life [17]. This *adaptation and stabilisation phase* (5–7 days after the birth) is followed by the *phase of stable growth*. After the neonatal period, the hydration percentage in the fat-free body mass changes only slightly and the percentage of body water content is mainly determined by the percentage of fat in the body mass.

Indications for parenteral nutrition

Neonatal patients

- All premature infants <35 weeks of pregnancy and most ill term infants require full or partial PN whilst enteral nutrition is gradually introduced (IV).
- The percentage of PN should be reduced as quickly as possible by the introduction of enteral nutrition (partial PN) and finally be replaced completely by enteral nutrition in order to minimise any side-effects from exposure to PN (II).

Commentary

There are a variety of reasons why premature infants (<35 weeks gestation) and seriously ill full-term infants may be unable to receive adequate enteral nutrition after birth, such as gastrointestinal tract immaturity with threat of developing necrotising enterocolitis, muscular and neurological immaturity, illnesses etc., and, hence, will require immediate PN in most cases.

The choice of nutrition administered (oral, enteral, partial PN or total PN) should be made on an individual basis according to medical indication and based on the principle of such nutrition being "as non-invasive as possible". This process promotes low complication rates [18], [19], [20], [21] and is the reason why the highest possible percentage of nutrition should be administered orally, or enterally wherever possible. If this is not possible, (partial) parenteral nutrition should be used to supplement the enteral intake to provide adequate nutrition [22].

Premature infants are born with low food reserves (low subcutaneous fatty tissue, low glycogen reserves in the liver) in comparison to full-term newborns. There is specific risk of hypoglycaemia in connection with their high nutrient requirements. Premature infants <35 full weeks of pregnancy should therefore be prophylactically (re)introduced to solid food whilst administering (partial) PN. The "optimum supply" with various different nutritional components in premature and ill newborns is still being discussed. Principally it makes sense to differentiate between the recommendations for the adaptation and stabilisation phase and the recommendations for the phase of stable growth, due to differing nutritional requirements.

Published recommendations (e.g. [11], [15], [23], [24], [25], [26]) do not always take into consideration the specific conditions of the adaptation and stabilisation phase after birth (5–7 days after birth), which precede the phase of stable growth.

This means that the stunted growth occurring during that phase (compared to intrauterine percentiles) is often not regained by the pregnancy due date [27]. There are discussions about this target stating that the majority of eutrophic premature infants should have once again attained their birth percentile by the pregnancy due date. This target seems necessary, because growth retardation could be a risk factor for long-term neurological development [27], [28], [29]. The potential long-term risks of growth retardation and the side-effects of increased substrate intake in the newborn period have to be weighed up as there is no evidence-based data on long-term development when considering the different growth rates of premature infants. The ideal target for premature infants is usually seen as growth corresponding with intrauterine growth percentiles. It is, therefore, necessary to adapt the nutrient supply to the respective needs of the individual premature infant. This is also the case in the phase of continual growth (see below), where the target is not only to attain a positive nitrogen balance, as in the adaptation and stabilisation phase, but also to promote catch-up growth wherever possible right up to the birth percentile.

Older children and teenagers

- If the energy and nutrient demands of a patient cannot be met through enteral nutrition during pre-school or school age, then partial or total PN is to be considered within 7 days at the latest in dependance on the nutritional state and clinical conditions (C).

Commentary

The beginning of (partial) parenteral nutrition in patients above the period of infancy should be specific to the individual circumstances, age and illness of the child or teenager. In contrast to infants, a period of inadequate nutrition and depletion of the body's store can be tolerated in pre-school and school children with positive nutritional status for up to seven days subject to their clinical conditions.

Energy and nutrient requirements

Energy requirements

Energy requirements are age-related (see Table 1) and influenced by illness and therapy. Tables can provide sufficient help in typical clinical situations providing a rough approach to calculating the estimated requirements of individual patients, with the appropriate additions and deductions (e.g. in cases of pyrexia/respiratory therapy). The estimate should account for the fact that all details are based on data taken from healthy patients. Individual circumstances (e.g. reduced physical activity in case of bed rest, infections, inflammatory processes, energy losses from the stomata etc.) result in differences between the actual energy requirements and the calculated (estimated) energy requirements.

Table 1: Benchmark for overall parenteral energy intake (incl. amino acids) in stable patients [1]

age (years)	*kcal/kg body weight/day*
premature infants	110–120
0–<1	90–100
1–<7	75–90
7–<12	60–75
12–18	30–60

The actual requirements of the treated patient can be narrowed down further (e.g. weight chart) by means of monitoring measures (cf. chapter "Complications and monitoring" (http://www.egms.de/en/gms/2009-7/000076.shtml)).
If the desired therapy effect (e.g. percentile parallel growth) is not attained with the estimated energy requirements and monitoring offers no solid references regarding an adequate energy intake, then various formulas can be helpful when calculating the evaluation. The equations (WHO 1985, Schofield 1985, and Harris-Benedict 1919 [30], [31], [32]) have, however, also been established for healthy children and have to be corrected for individual patients as specified in the figures published in tables. Measuring the energy expenditure is rarely carried out routinely during daily clinical routines and is indicated, if, despite estimation aids and monitoring, there are still doubts regarding an adequate energy intake.
We refer to the "Guidelines on Paediatric Parenteral Nutrition" of ESPGHAN and ESPEN for a more detailed overview of aspects regarding the energy requirements of children of various age groups and in case of varying clinical pictures [1].

Carbohydrate requirements

- The endogenous glucose production varies from approx. 2 mg/kg/min (3 g/kg/day) in adults to approx. 8 mg/kg/min (11.5 g/kg/day) glucose in premature infants (II).
- The maximum glucose oxidation is approx. 7 mg/kg/min (10 g/kg/day) in premature infants, and approx. 12 mg/kg/min (18 g/kg/day) in full-term infants and infants (II–III).
- In full-term infants and children up to two, the glucose intake should usually not exceed approx. 12 mg/kg and min (18 g/kg and day) (C).
- The glucose intake should also be adapted to the age and/or clinical situation (e.g. malnutrition, acute illness, drug administration) (C).
- An excessively high carbohydrate intake can result in net lipogenesis with hepatic fat deposition and steatosis of the liver (II–III).

Commentary

Glucose is the sugar used for PN and usually contributes substantially to osmolarity in the PN solution. The osmolarity of a glucose solution rises significantly with increasing concentration from 255 mosm/l in a 5% glucose solution to 1020 mosm/l in a 20% glucose solution. Based on experience, glucose concentrations of up to 12.5% are well tolerated through a peripheral vein cannula as long as no other osmolarity-increasing agents are added.
Glucose can be directly metabolised by the central nervous system. The endogenous glucose production varies from approx. 2 mg/kg/min (3 g/kg/day) in adults to approx. 8 mg/kg/min (11.5 g/kg/day) glucose in premature infants [33], [34], [35], [36]. The maximum glucose intake should not exceed the glucose oxidation rate in PN. Maximum glucose oxidation is approx. 7 mg/kg/min (10 g/kg/day) [37], [38] in premature infants and approx. 12 mg/kg/min (18 g/kg/day) in full-term newborns and infants under long-term PN [39], [40], [41]. In critically ill children with burns, maximum glucose oxidation of 5 mg/kg/min has been described [41].
Excessive glucose intake results in net lipogenesis and subsequent fat deposition [42], [43]. Excessive intake can lead to hepatic steatosis with an impairment of the liver function [44], [45].

Special characteristics in neonatal patients (hyper/hypoglycaemia)

- Higher incidence of hyperglycaemia with increasing immaturity (lower gestational age) (II).
- An early start of parenteral glucose together with amino acids (2–3 g/kg and day) from the very first day onwards contributes to preventing hyperglycaemia in premature infants. An early insulin therapy is also promising but associated with risks. Further controlled

studies should be awaited prior to a general recommendation (B).

Commentary

There are often fluctuations in blood sugar levels in premature infants during the adaptation and stabilisation phase which can be influenced by low substrate reserves (hypoglycaemia) or insulin resistance (hyperglycaemia) [46], [47], [48]. Common definitions of hypo- or hyperglycaemia, respectively, are a blood glucose level of 50 mg/dl (2.75 mmol/l) or 150 mg/dl (8.3 mmol/l), respectively, although these levels are not based on short and long term outcome studies. The incidence of hyperglycaemia increases with diminishing gestational age [49], [50]. An early supply of intravenous insulin in hyperglycaemia has been proposed in order to more rapidly attain the targeted energy intake and a positive nitrogen balance [51], but this advantage should be weighed against potential complications. There are no controlled studies regarding the advantages and disadvantages of an early insulin therapy in premature infants. It has also been suggested that an added amino acid supply of 2–3 g/kg body weight and day should be started from the very first day to reduce hyperglycaemia during the adaptation and stabilisation phase, since it may stimulate endogenous insulin secretion and hence reduce the frequency and extent of neonatal hyperglycaemia [52]. This approach should be evaluated further in controlled studies.

Amino acid requirements

- The requirements for essential amino acids are higher per kg body weight in infants, and particularly in premature infants, than in older children or adults (II).

Commentary

Crystalline amino acid solutions in concentrations of 3.5–15% (osmolarity 450–1450 mosmol/l) are used in PN. Some specifics are to be taken into consideration when using amino acid solutions in children compared to adults due to the special amino acid metabolism and growth-specific requirements.
The composition of amino acid solutions which are suitable for infants and toddlers, have to be adapted to the demands of metabolic immaturity and requirements of physical growth. Apart from the eight classic essential amino acids (Phe, Thr, Val, Leu, Ile, Tyr, Ser, Met), cysteine, tyrosine, histidine, taurine, glutamine and arginine are regarded as essential or conditionally essential especially in premature infants (see “Information on the selection and production of amino acid solutions” in the attachment).

Amino acid requirements for newborns

- Some amino acids regarded as non-essential in older children and adults are regarded as conditionally essential amino acids in newborns (II).
- Amino acid imbalances can result in toxic organ damage and may be involved in the development of PN-associated cholestasis (II).
- Ursodesoxycholic acid and the reduction of protein intake have a positive effect on the development of PN induced cholestasis in newborns (II).

Commentary

The need for essential amino acids is higher in premature infants than in older children or adults [11].
Various metabolic pathways for metabolising amino acids are immature in newborns (phenylalanine hydroxylase, tyrosine-aminotransferase, cystathionase [53], [54]). As a consequence amino acids regarded as non essential in adults i.e. cysteine, tyrosine, histidine, taurine, glutamine and arginine, become “conditionally” essential amino acids in newborns [55], [56]. Other amino acids like methionine quickly reach high levels because key enzymes are immature. Amino acid imbalances develop quicker in newborns than in adults or older children due to the immaturity of the neonatal metabolism. Such imbalances could have potential negative effects on organ development [57].
The plasma amino acid levels in infants receiving parenteral nutrition differ to those in breast-fed infants despite extensive endeavours to create optimised amino acid solutions for infants [58], [59], [60]. This is partly due to the poor solubility or stability of various amino acids (e.g. glutamine, tyrosine, cysteine) such that not all admixtures can be used. The nitrogen balance is not significantly influenced by the diverse composition of amino acid solutions [61], [62].
The maximum intake is basically influenced by two given facts:

1. Physiological rate of protein synthesis subject to age: According to data by Pohlandt et al. [63]and Micheli [64] premature infants, who are physiologically in approx. week 30 of pregnancy, have a maximum rate of protein synthesis with protein requirements of approx. 2.7 g/kg body weight/day, which returns to <2.0 g/kg body weight/day until week 40 of pregnancy. A positive nitrogen balance can usually be attained in premature infants with an amino acid intake of 2.5 g/kg body weight/day and 60–90 kcal/kg body weight/day [65]. In individual cases an amino acid intake of up to 3.5–4 g/kg body weight/day may be necessary in order to achieve protein synthesis according to the intrauterine ratio [64].
2. Urea and ammoniac concentrations in plasma:
The urea production rate is a sensitive measurement for amino acid utilisation. Monitoring plasma concentrations of functional proteins like, for example,

prealbumin, fibrinogen or retinol binding protein can provide information about the sufficient amino acid supply of the liver. It should be considered that strong insulin secretion due to high glucose intake guides the n-flow to the muscles.

Nitrogen balance studies in premature infants receiving parenteral nutrition show that approx. 380 mg (70%) are retained from an intake of 530 mg nitrogen, similar to the ratios found in enteral nutrition [66], [67]. Amino acid imbalances in PN are also discussed as a factor for developing cholestasis in young infants (a frequent side effect of long-term PN; up to 50% of long-term ELBW-premature infants receiving parenteral nutrition develop cholestasis [68]) [18], [69], [70].

Amino acid requirements in older children and teenagers

References are made to the recommendations for enteral intake of amino acids due to insufficient data regarding the parenteral intake of amino acids in older children [71] (see Table 2).

Table 2: Reference values for enteral protein intake according to new reference values for nutrient intake in Germany, Austria and Switzerland (DACH reference values) [71]

Age	g/kg body weight/day		g/day	
	m	f	m	f
0–<1 month	2.7		12	
1–<2 months	2.0		10	
2–<4 months	1.5		10	
4–<6 months	1.3		10	
6–<12 months	1.1		10	
1–<4 years	1.0		14	13
4–<7 years	0.9		18	17
7–<10 years	0.9		24	24
10–<13 years	0.9		34	35
13–<15 years	0.9		46	45
15–<19 years	0.9	0.8	60	46

Lipid emulsions

- Lipid emulsions are an integral component of longer-term PN in children (C).
- Lipid emulsion should usually amount to approx. 25–40% of the non-protein energy in patients receiving total parenteral nutrition (C).
- A glucose intake over 18 g/kg body weight and day induces net lipogenesis in infants and should generally be avoided (B).
- To prevent a deficiency of essential fatty acids, a minimum intake of 0.25 g/kg body weight and day of linoleic acid is recommended in premature infants and a minimum intake of 0.1 g/kg body weight and day linoleic acid is recommended in full-term newborns and children (C).
- In infants the parenteral lipid intake should usually not exceed 3–4 g/kg body weight and day (0.13–0.17 g/kg body weight and h) (B) generally and in older children it should not exceed 2–3 g/kg body weight and day (0.08–0.13 g/kg body weight and h) (C).
- Premature infants, full-term newborns and infants should usually receive lipid emulsions over 24 h (B) or in case of cyclic infusion after the first few months of life along with the residual PN (C).
- Triglyceride concentrations in serum or plasma should be specified in patients receiving lipid emulsions especially if there is increased risk of hyperlipidemia (e.g. high lipid intake, catabolism, sepsis, ELBW) (C).
- A reduction in lipid intake should be considered if triglyceride concentrations in serum or plasma in continuous infusions exceed 250 mg/dl (2.8 mmol/l) in infants or 400 mg/dl (4.5 mmol/l) in older children (C).

Commentary

Lipid emulsions are used in PN in paediatric patients as they provide an energy source with low osmolarity and high energy content per volume unit. In addition, they also safeguard the essential fatty acid supply. The CO_2 production is lowered compared to PN with a high proportion of carbohydrates [72], [73], [74]. The nitrogen metabolism can be improved by adding lipid emulsions to PN [75], [76], [77].

Lipid oxidation depends on the overall energy intake and consumption, intake of carbohydrates and triglycerides and the carbohydrate/lipid ratio [72], [73]. Lipid oxidation decreases as the carbohydrate intake increases and is replaced by lipid storage. Lipogenesis takes place in infants with a carbohydrate intake of 18 g/kg/day and above [39], [72]. In older children the level of carbohydrate intake, above which net lipid deposition takes place, is lower. Lipid oxidation reaches its maximum at a parenteral lipid intake of 40% of non-protein energy intake in neonates [74] or 50% in infants [72]. Generally a lipid intake of 25–40 % of non-protein calories is recommended.

A deficiency of essential fatty acids can be biochemically shown in parenterally fed premature infants only after a few days with continuous glucose but not lipid infusion [78], [79], [80]. At least 0.25 g/kg body weight/day of linoleic acid should be administered to premature infants in order to prevent a deficiency of essential fatty acids [80], [81]. An intake of 0.1g/kg body weight/day is probably sufficient in full-term infants and older children. The different linoleic acid content in varying lipid emulsions has to be taken into consideration in the calculation for lipid intake. It is difficult to define the minimum requirements of alpha linolenic acid. The majority of data on this subject has been gained from animal experiments [82].

In children there is only one case study on alpha linolenic acid deficiency [83]. All lipid emulsions used in Germany contain alpha linolenic acid.
It is also difficult to define the upper limit for lipid intake. In premature infants an intake of 3 g/kg body weight/day is well tolerated as a continuous infusion according to the concentration of plasma triglycerides and cholesterol and also the ratio of non-esterified fatty acids/albumin [84], [85], [86]. In premature infants it may be desirable to achieve a lipid intake surpassing the oxidation capacity in order to attain weight gain and lipid deposition. Caution is, however, recommended in premature infants weighing less than 1000 g as tolerance to intravenous lipid emulsions may be more limited [87].
Maximum lipid oxidation of 4 g/kg body weight/day is attained in full-term infants with a glucose intake below 18 g/kg per day [73], [75].
It is important to monitor plasma triglycerides because lipid utilisation varies depending on age, the severity of the illness and various other factors.
An increase in the concentration of plasma triglycerides is to be expected if the infusion speed of the lipid emulsions exceeds the speed of hydrolosis of the triglycerides. In premature infants the gradual increase in lipid intake compared to immediate administration of the target amount did not result in raised lipid tolerance [88]. If a gradual increase of 0.5 to 1 g/kg per day is carried out, this can serve the purpose of monitoring with measurements of plasma triglycerides concentrations.
In premature infants tolerance of a lipid infusion is raised by continuous versus intermittent administration [84], [86], [88]. In stable patients intermittent administration can also be carried out within the framework of cyclic home PN.
The speed of triglyceride hydrolysis depends on lipoprotein lipase activity. The activity of the post heparin lipoprotein lipase can be raised by administering heparin but this does not increase lipid utilisation [89], [90]. Raised lipoprotein lipase activity results in increased non-esterified fatty acids, which are not necessarily metabolised at the same speed [90], [91].
Lipid supply may result in enhanced lipid peroxidation and the formation of free radicals [92], [93], [94]. An increased lipid utilisation by reducing the carbohydrate/lipid ratio, at a constant lipid intake and therefore reduced energy intake, results in a reduction of lipid peroxidation and free radical formation [92]. PN should be supplemented with multi-vitamin preparations including both vitamin C and vitamin E (alpha-tocopherol) which have anti-oxidative effects [95], [96], [97].
PN with 20% lipid emulsions results in more physiological phospholipid and cholesterol levels, due to its low phospholipid content compared with PN containing classic 10% lipid emulsions [98]. At the same time there is, however, a lower proportion of long-chain polyunsaturated fatty acids (LC-PUFA) contributed by the phospholipid emulsifier. LC-PUFAs are “conditionally” essential for premature infants. Deficiency could result in malformations of the retina and central nervous system [99], [100].

Vitamin requirements

No age differentiation is indicated in literature due to the limited data situation.

Neonatal patients, older children and teenagers

- Vitamin supplementation should be given during parenteral nutrition (C).
- The vitamin requirements of premature infants and newborns (excluding Vitamin D and K) as well as in infants and children have not been extensively examined (IV).
- No parenteral vitamin supplement available on the German market meets the current recommendations for premature infants (IV).
- Vitamin preparations should, if possible, be administered together with the lipid emulsion (C).
- Premature and ill full-term infants should be given their first two doses of Vitamin K subcutaneously/intramuscularly or intravenously (II).
- An oral intake of 1000 IU Vitamin D/day is adequate in extremely premature infants (II).

Commentary

The optimum time to begin vitamin supplementation in newborns and premature infants is not clear. It should be taken into consideration, that water soluble vitamins, with the exception of Vitamin B12, are inadequately stored. Insufficient thiamine intake can result in severe lactic acidosis within only a few days in children on PN [101]. It is, therefore, recommended that vitamin substitution is started early with PN.
Vitamin intake should be administered daily. All clinical studies have been carried out with commercially available vitamin preparations, therefore existing intake recommendations [11], [23], [102] are based on the composition of available preparations. At this time there is no commercially produced vitamin supplement available on the market, which completely meets the current intake recommendations for premature infants as a supplement for long-term PN.
In the practical administration of PN it should be considered that vitamins can be degraded by oxygen, light and heat. Degradation reactions can be accelerated by catalytically active trace elements like copper and iron. Fat-soluble vitamins can be adsorbed on specific synthetic materials (infusion needles) in rare cases. Thus, the administered dose is uncontrolled and significantly reduced [103]. In Europe, combined preparations are available which, by dissolving the vitamins in a lipid emulsion, reduce absorption on plastic. Furthermore, the formation of peroxides in lipid emulsions can be reduced by adding multi-vitamin preparations [104]. Vitamin preparations should, if possible, be administered together with the lipid emulsion. The clinical impact of free radicals, which

can develop in intravenous multi-vitamin emulsions when exposed to light, is being currently discussed. They can result in an increase in peroxide excretion in urine of newborns [105]. Feed lines with light protection should be used when administering parenteral solutions with vitamins until the clinical significance of these results has been determined [106].

Vitamin D rickets prophylaxis: Oral vitamin D prophylaxis with 1000 IU Vitamin D/day per os from day seven of life is sufficient as a prophylaxis in extremely premature infants [107].

Vitamin K prophylaxis: Premature infants (<week 35 of pregnancy) and ill full-term infants should receive their first two doses of Vitamin K prophylaxis intramuscularly, subcutaneously or intravenously due to the unclear resorption from the gastrointestinal tract [108], [109]. The dose of intravenous Vitamin K prophylaxis is still being discussed at present. Vitamin K levels after one administration of 1 mg Vit K intramuscularly on the first day of life were higher in premature infants than in full-term infants [110].

Detailed specifications can be found in the "Guidelines on Paediatric Parenteral Nutrition" from ESPGHAN and ESPEN [1].

Trace element requirements

No age differentiation is indicated in literature on account of the limited data situation.

Neonatal patients, older children and teenagers

- The optimum time to begin with trace element supplementation in premature infants <1500 g birth weight is not clear. We recommend beginning supplementation to coincide with an increase in body weight (5th day of life) (C).
- The trace element requirements of premature infants and newborns as well as children have not undergone extensive testing (IV).
- A parenteral trace element supplement, which meets the current intake recommendations, is not available on the German market (II).
- Trace elements should be supplemented in long-term PN (C).
- Zinc deficiency has to be excluded in infants and children with unclear, poor development (especially linear growth) and/or skin efflorescences (typically on acra, mechanically burdened parts of the body or in the nappy region) or diarrhoea (II).

Commentary

Trace element requirements and optimum time to begin supplementation in premature and full-term infants, as well as infants and children, are not completely clear. The enteral absorption of trace elements in partial-parenteral nutrition mainly depends on the existing compound and the composition of the nutrition [111] such that it is extremely difficult to evaluate the remaining parenteral needs. Requirements for some trace elements have at least been narrowed down by controlled studies [102], [111], [112], [113], [114]. There is no trace element supplement for long-term PN which meets the current recommendations [102]. In long-term PN (>7 days), where enteral nutrition provides less than 50% of the energy intake, we recommend administering trace element supplements according to manufacturer instructions.

Premature and ill full-term infants have an increased risk of developing a trace element deficiency. Premature infants are born with lower trace element stores as the laying down of these stores occurs during the last trimester of the pregnancy. Rapid growth at unidentified requirement levels and variable resorption are further risk factors contributing to the development of a trace element deficiency in premature infants [115]. In ill full-term infants the requirements and intake vary according to the basic illness. The optimum time to begin supplementation is disputed.

Zinc: Zinc deficiency should be considered in newborns where the reason for unclear, poor development (especially linear growth) and/or skin efflorescences (acra, mechanically burdened parts of the body) are not clear [116], [117]. A multitude of case studies have been published on zinc deficiency in neonates [116]. Rare genetically-related trace element metabolic disorders are also to be considered in the case of unclear clinical symptoms [117].

Other supplements

- There is no documentation indicating a benefit from parenteral supplementation of glutamine or arginine in children (C).
- Carnitine supplementation should be considered in individual cases in premature and newborn infants on PE (B).

Commentary

Tests on *arginine* supplementation [118] in adult intensive care patients as well as some studies on enteral or parenteral *glutamine* administration in newborns show potential positive effects [119], [120] (II), although these are controversially discussed. There is no evidence from meta analyses to document the benefit of the parenteral supplementation of glutamine or arginine in premature and newborn infants [121].

Vitamin A is necessary for physiological lung growth (lung epithelial cells). A meta-analysis, which is based on seven randomised, controlled studies, documents the effectiveness of a supranutritive Vitamin A supplementation on reducing oxygen requirements and improving survival at one month of age in premature infants with a birth weight <1000 g. There is a tendency towards lower values regarding the incidence of retinopathy in premature infants [122], [123] (I). The authors of the systematic analysis

of the Cochrane database feel there is a need to carry out further studies on the effects of intravenous Vitamin A supplementation.

Carnitine is necessary for the transportation of long-chain fatty acids via the mitochondrial membrane and its oxidative metabolism. Carnitine is found in breast milk and baby foods, but is not usually added to conventional PN. Low carnitine levels have been measured in body tissues in premature infants on PN [124]. The clinical significance of this has not been determined. An impairment in fatty acid oxidation is only to be anticipated where a massive drop in serum carnitine concentrations occurs. For the metabolic availability of carnitine its free nonesterified percentage, is essential. The availability of free carnitine is reflected in the concentration and the acyl-carnitine/free carnitine (AC/FC) ratio. This ratio is in dynamic equilibrium with the intramitochondrial acyl-CoA/free CoA ratio. Lower intramitochondrial CoA-availability is assumed with an AC/FC ratio >0.4 (>0.7 when fasting) Carnitine supplementation results in a release of intramitochondrial CoA and should be considered in case of an explicit AC/FC ratio. A meta analysis (based on 14 randomised, controlled studies) showed there to be no effect of carnitine supplementation on the metabolism of lipids, lipogenesis or weight gain [125].

Practical procedure

Short, medium and long-term (partial) parenteral nutrition

- The utilisation of an adapted glucose/electrolyte solution (usually 10% glucose) with potassium and sodium supplementation in short-term (<48 h) intravenous intake is recommended in well-nourished toddlers and school children without specific metabolic or nutritional risks (IV).
- An adapted glucose/electrolyte solution (usually 10% glucose) with the required supplementation of sodium, potassium, amino acids, lipids and vitamins should be administered in medium-term PN (>2–7 days) (IV).
- An additionnal supplementation of magnesium, phosphate, and trace elements (where enteral nutritional provides 50% of the energy intake or less) should be administered in long-term PN (>7 days) (IV).

Commentary

If intravenous intake is required in well-nourished toddlers and school children without specific metabolic or nutritional risks, the following situations should be considered when anticipating duration:

I: short-term parenteral intake for less than 48 h.

II: medium-term parenteral nutrition for 2 to 7 days.

III: long-term PN for >7 days.

- It makes sense to differentiate between short, medium and long-term parenteral intake, because the procedure varies according to the duration of PN
- The utilisation of an adapted glucose/electrolyte solution (usually 10% glucose) with potassium and sodium supplementation in short-term (<48 h) intravenous intake is recommended in well-nourished toddlers and school children without specific metabolic or nutritional risks (IV).
- An adapted glucose/electrolyte solution (usually 10% glucose) with the required supplementation of sodium, potassium, amino acids, lipids and vitamins should be administered in medium-term PN (>2–7 days) (IV).
- An additional supplementation of magnesium, phosphate, and trace elements (where enteral nutritional provides 50% of the energy intake or less) should be administered in long-term PN (>7 days).

Newborns and infants

- There should be a written concept on the provision of PN in order to minimise errors (C).
- Newborns can be divided up into the following groups with regard to their nutrient requirements and PN-support in order to minimise errors:
  - premature infants <1500 g,
  - premature infants >1500 g,
  - ill full-term infants (C).
- The actual amount of PN administered must be calculated (not estimated) in neonates (avoid rounding error) (C).
- The use of PN standard solutions can reduce the the risk of errors.

Commentary

Due to the heterogeneity in pathophysiology and the differing maturity of patients it may be necessary to vary procedures during the neonatal period (e.g. fluid volumes, electrolyte substitution etc.). Classification according to, for example, birth weight is recommended for the calculation of PN in neonates:

- premature infants <1500 g,
- premature infants >1500 g, and
- ill full-term infants.

This differentiation makes sense with regards to variations in the administration of different nutrients. The described protocol can result in the procedures in (partial) parenteral nutrition being structured during the daily clinical routine and errors minimised.

A standardised questionnaire or electronic programme, which takes into account partial parenteral nutrition and enteral nutrition (see Table 3 for an example of a procedure questionnaire), should be used for prescribing PN to neonates.

The prescription of nutrition for neonates must be calculated and not estimated in order to ensure the nutrient

Table 3: Example of a procedure questionnaire in premature and ill full-term infants

Name:_____ First Name:_____ Birth Weight:_____ Sheet No.:_____

	Date			
	Day of life [n]			
	Corr. age [week of pregnancy]			
	Act. weight [g] difference to previous day [± g]			
Urine	Expulsion in [ml/day]			
	Expulsion in [ml/body weight/day]			
Fluid Req.	Fluid requirements [ml/day]			
	Deductions/Additions [± %]			
	Daily fluid requirements [ml/day]			
Enteral	Nutrition type [BM/PIM/Formula]			
	No. meals/ml/Meals			
	Daily volume [ml/day]			
	Protein content/day [g]			
	Lipid content/day [g]			
	Enteral supplements [ml]			
	Enteral supplement [ml]			
Proteins	Protein requirements/d [g/kg body weight/day]			
	Overall volume/d (requirements x weight)			
	IV prot. percentage (overall enteral requirements for protein)			
	Volume: AA solution 10 % [ml]			
Lipids	Lipid requirements/d [g/kg body weight/day]			
	Overall volume/d (requirements x weight)			
	IV lipid proportion (overall lipids – enteral)			
	Volume: lipid emulsion 20% [ml]			
Electrolytes	NaCl 5.85% [ml] 1ml ≈ 1mmol			
	KCl 7.45% [ml] 1ml ≈ 1mmol			
	Ca-Gluconate 10% [ml] 1ml ≈ 0.22mmol			
	Mg-Verla 10% [ml] 1ml ≈ 0.32mmol			
	Na-Glycero-phosphate [ml] 1ml ≈ 1mmol P+2mmol Na			
Supplements	Water soluble vit. [ml]			
	Fat soluble vit. [ml]			
	Trace elements [ml]			

(Continued)

Table 3: Example of a procedure questionnaire in premature and ill full-term infants

Vol.	Drug volume [ml]			
	Residual volume [ml/d]			
Glucose	Glucose 5% [ml]			
	Glucose 10% [ml]			
	Glucose % [ml]			
	Glucose intake/day [g/day]			
	Glucose intake in [mg/kg body weight/min]			
Kcal	Calories/d [kcal/day]			
	Calories/kg body weight/day [kcal/kg body weight/day]			
Flow rate	Speed of mixed infusion [mL/h]			
	Speed of lipid emulsion [mL/h]			
	Doctor's initials			

Breast milk (BM)*;	Formula;	+ Fortifier	*BM data after: Zuppinger K. Berner Datenbuch der Pädiatrie. 4th ed. Stuttgart: Fischer; 1992. p. 161
Lipid content	[g/100 ml]:	4.0	
Energy content	[kcal/100 ml]:	71.0	
Carbohydrate content	[g/100 ml]:	7.1	
Protein content	[g/100 ml]:	1.1	Procedure questionnaire from: Jochum F. Infusionstherapie und Diätetik in der Pädiatrie. Berlin: Springer Verlag; 2005. p. 516-7.
Lipid content	[g/100 ml]:	4.0	

intake in neonates and infants is adapted to their specific needs.

PN in premature infants and newborns

PN in the adaptation and stabilisation phase after birth

- There is no evidence-based data on the scale of post-partal weight loss required during the adaptation and stabilisation phase for long-term development (IV).
- Amino acid and lipid supply should begin on the first day of life (B).
- The fluid intake in premature infants <1500 g should only replace the estimated losses in the first days of life (mainly perspiratio insensibilis). Electrolyte supplementation is often not necessary (B).
- The incidence of hyperkaliaemia can be lowered by supplementing PN with 1 g amino acids from the first day of life in premature infants <1500 g (II).
- The maximum parenteral intake of amino acids should be between 2 and max. 4 g/kg body weight per day in premature infants and newborns (B).
- Max. lipid intake should not exceed 3–4 g/kg body weight per day in premature infants and newborns (B).
- Restricted fluid management with limited supply of sodium chloride results in a reduction in the amount of days with respiratory aids or respiratory therapy (II).
- The early enteral (re)establishing of solid foods (within <4 days after the birth) in premature infants lowers the incidence nosocomial infections, the duration of PN and the frequency in the utilisation of central venous catheters (I).

Commentary

In premature infants and full-term newborns there is a period of adaptation and maturation which occurs in the first seven days after birth (see "Physiological principles" above) which requires daily adjustments in the nutrient intake of ill full-term and premature infants. There is surprisingly little evidence-based data on physiology and nutrient requirements for this stage of life (optimum weight loss, optimum time to begin amino acid and lipid supply). Lipid (0.5–1 g/kg body weight/day) and amino acid intake (0.5–1 g/kg body weight/day) should begin on the first day of life [126], and a stepwise increase in amino acid intake to max. 2–3(–4) g/kg body weight/day and lipid intake to 3–4 g/kg body weight/day is widely practised and results in more rapid achievement of a positive nitrogen balance [52], [127]. Questions remain with regard to extremely small premature infants with a birth wieght <800 g with regard to potential adverse effects of early intravenous lipid intake on the first day of life [128]. A restricted fluid volume improves the outcome of neonates considerably by lowering the "perspiratio insensibilis" [129]. In premature infants a restrictive "dry" fluid management with sodium chloride restriction seems to have a favourable effect on the duration of respiratory aids / respiratory therapy [130], [131], [132]. Only the losses should be replaced in the first days of life in premature infants under 1500 g birth weight [17]. The incidence of hyperkaliaemia can be lowered by supplementing 1 g amino acids from the first day of life in this patient group. The early (re)establishing of enteral nutrition(<4 days after birth) lowers the incidence of nosocomial infections, the duration of (partial) parenteral nutrition and the utilisation of central venous catheters compared to later (re)establishing [133], [134].

PN in premature infants and newborns in the phase of continual growth

- Parenteral nutrition should be the exception in neonatal patients during the phase of continuous growth. If necessary, treatable reasons for delayed enteral (re)establishing of nutrition should be ascertained (C).
- The energy requirement shows great intraindividual and interintervidual variability (II).
- The energy intake can be adapted to the weight gain, whereby weight development should aim to be close to the intrauterine growth curve (C).

Commentary

The enteral (re)establishing of nutrition is usually completed in the first week of the continual growth phase (about the 2nd week of life) in premature infants and sick full-term infants. If PN is also required during this phase, treatable reasons for delayed enteral (re)establishing of nutrition should be ascertained. The energy requirements show great variability in this stage of life. They can be estimated according to weight development compared to intrauterine growth curves (if other reasons for growth not following percentiles have been excluded, it should be assumed that a too low energy intake will result in a decline and a too high energy intake will result in gains compared to intrauterine percentiles). The necessary energy to build up 1 g body tissue varies with the lipid content of the newly formed tissue (20–40%) but averages at approx. 5 kcal/g. The proportion of the newly formed fatty tissue is influenced by the nutritional regime. It should be considered with lesser fatty tissue built up, the energy required for growth is lower [135].

Methods of access

- Peripheral vein cannulae have a lower complication rate compared to central access points and should be used in infants whenever possible (II).
- A routine heparin supply to prevent thrombosis or to proling central venous catheter survival time has no proven benefit in infants and is not recommended (Ib).

Commentary

Peripheral commercial vein cannulae (PCVC) have a lower complication rate in infants (infection, thrombosis) than central venous catheters (CVC) [20]. Peripheral commercial vein cannulae (PCVC) can be used in partial or total parenteral nutrition if the osmolarity and state of the veins allow for this (risk of paravasatation/skin necrosis!).
Long-term total parenteral nutrition often cannot be applied safely in older children or teenagers without central venous catheters (CVC) due to the osmolarity. An individual decision is required on the choice of access while taking into consideration the underlying illness, therapy, osmolarity of the nutritional solution used or drugs and the expected duration.
Two meta-analyses showed no positive effect of heparin supply on central venous catheter lifetime or the formation of thromboses in neonates with percutanous central venous catheters [136], [137].

Use of standardised or individually tailored PN solutions

- After requirements have been calculated, standard solutions (e.g. produced by the hospital pharmacy), which are adapted to suit the specific nutrient needs of the respective age group, can be administered in short-term PN (B).

Commentary

Using ready-made standard solutions requires fewer personnel and allows for less risk regarding dosage errors or microbial contamination. Individually mixed infusions can be adapted to individual characteristics. Standard

solutions are suitable for short-term total and partial PN [138].

PN provision

A standardised procedure should be followed and the individual steps systematically documented in order to minimise errors. Computer programmes, which enable the fast and exact calculation of enteral and parenteral intake, are recommended (and in part commercially available). The fluid, glucose and electrolyte intakes and additional intakes with drugs can be calculated.
The following aspects should be considered: Estimation of the required duration of PN, enteral nutrition, fluid intake, protein and lipid intake, parenteral vs enteral/oral intakes, electrolyte/vitamin and trace element supply, concentration of the glucose solution, infusion speed, monitoring, and validation (see Table 3 "Example of a procedure questionnaire").

Neonatal patients

A practical example is shown in Table 4, which illustrates the (re)establishing of enteral food in newborns during the adaptation and stabilisation phase.

Measures to reduce side-effects of PN

- Procedures should be standardised wherever possible in order to minimise errors in the provision or preparation of partial (PPN) or total PN (TPN).
- Minimum enteral nutrition minimises the time until (re)establishing of total enteral nutrition and LOS (Length of Hospital Stay) (I).
- Non-nutritive sucking during PN reduces LOS (I).
- There is a specific risk of developing osteopenia due to the rapid bone growth in premature and full-term infants (III). Osteopenia prophylaxis should be started enterally once the (re)establishing of enteral nutrition has been completed without complications (C).
- In order to determine appropriate Ca and P intakes, the Ca and P excretion can be assesed in spot urine samples (B).
- The optimum duration of Ca and P supply is unclear (IV), but it appears reasonable to provide a Ca and P supply up to the corrected third month of life in premature infants with a birth weight <1500 g (C).

Commentary

Minimum enteral nutrition

Total PN reduces the functional and structural integrity of the gastrointestinal mucosa, the secretion of gastrointestinal hormones and the activity of mucosal enzymes like lactase [139], resulting in an intolerance to enteral nutrition and an extension of LOS (Length of Hospital Stay). A meta-analysis of eight randomised studies [134] investigated the effect of minimum enteral nutrition (<25 kcal/kg body weight/day for >5 days) on the development of food intolerance in at-risk premature infants (<1500 g birth weight, <week 33 of gestation) in comparison to total PN. The duration of (re)establishing of nutrition and LOS was significantly reduced. There was no effect on the incidence of necrotising enterocolitis. Side-effects of minimal enteral nutrition cannot be definitely excluded due to the inhomogeneity of the patients included and their low number [134].

Non-nutritive sucking

A meta-analysis (based on 14 randomised, controlled studies) documented a significant reduction in LOS through non-nutritive sucking in premature infants. No effects have been found on weight gain, energy intake, oxygen saturation, total intestinal transit or heart rate [140].

Osteopenia prophylaxis in premature infants <1500 g

Due to their high growth rate, premature infants have high calcium and phosphate requirements which cannot be met through breast milk or infant formula. Therefore, premature infants with a very low birth weight (<1500 g) are particularly at risk of developing osteopenia. Osteopenia in premature infants is linked to an increased incidence of fractures, prolonged respiratory therapy or requirement for respiratory aids and the development of a dolichocephalus [141], [142]. Premature infants under 1500 g birth weight should receive Ca/P supplementation depending on their individual requirements. The optimum duration of supplementation is unclear. We recommend supplementation in premature infants with a birth weight <1500 g up to corrected third month of life. The Ca and P excretion from spot urine specimens may be used to adapt the Ca and P supply to requirements, which vary according to growth [143], [144].

Monitoring

- Due to the low blood volume in infants, staff at facilities in which infants receive medium and long-term parenteral nutrition must have access to a special laboratory with micromethods (IV).
- Careful monitoring of the fluid volume must be carried out in premature infants due to their high fluid volume, high body water content in comparison to older patients and immature regulatory mechanisms (IV).
- Dehydration in premature infants, with immature kidneys, leads to hyperchloraemia prior to the development of acidosis as one of the first lab signs.
- The measurement of the specific weight or osmolarity of urine can only be drawn upon in premature infants and newborns in the first weeks of life when high values are measured. Low (normal) values can be due

Table 4: Example of the (re)establishing of nutrition in premature and ill full-term infants[1]

		Requirement		Infusion Requirement Requirement with total PN[1]					Enteral
		Fluid	Energy	Glu	AA	Lipids	NaCl	KCl	Nutrition
	Birth Weight	[ml/kg body weight/ day]	[kcal/kg body weight/ day]	[g/kg body weight/day]			[mmol/kg body weight/day]		[ml/d]
Day 1:	PI <1000 g	90		4–8	1,0 (–3.0)	1.0	0	0	0
	PI 1–1.5 kg	80		4–8	1.0 (–3.0)	1.0	0	0	0
	NB ≥1.5 kg	60		4–10	1.0 (–3.0)	1.0	2–5	1–3°	8/6x5–10 BM/SN
Day 2:	PI<1000g	110		4–8	1.0 (–3.0)	1.0	0	0	6x0.5 BM/PIF
	PI 1–1.5 kg	100		4–8	1.0 (–3.0)	1.0	0	0	12x0.5 BM/PIF
	NB ≥1.5 kg	80		4–10	1.0 (–3.0)	1.0	2–5	1–3	8/6x10–20BM/SN
Day 3:	PI < 1000 g	130		5–9	1.0 (–3.0)	1.0	0	0	12x0.5 BM/PIF
	PI 1–1.5 kg	120		5–9	1.0 (–3.0)	1.0	{2–5}	{1–3}	12x1.0 BM/PIF
	NB ≥1.5 kg	100		5–10	1.0 (–3.0)	1.0	2–5	1–3	8/6x15–30 BM/SN
Day 4:	PI <1000	150		5–10	2.0 (–3.0)	1.0	{2–5}	{1–3}	Increase by 10–15
	PI 1–1.5 kg	140		5–10	2.0 (–3.0)	1.0	2–5	1–3	15–20
	NB ≥1.5 kg	120		6–12	2.0 (–3.0)	1.0	2–5	1–3	15–25 ml/kg body weight/day
Day 5:	PI <1000 g	160		6–12	2.5 (–3.0)	2.0	2–5	1–3	Increase by 10–15
	PI 1–1.5 kg	160		6–12	2.5 (–3.0)	2.0	2–5	1–3	15–20
	NB ≥1.5 kg	140		7–15	2.5 (–3.0)	2.0	2–5	1–3	15–25 ml/kg body weight/day
Day 6:	PI <1000 g	160	80–160	7–14	2.5 (–3.0)	3.0	2–5	1–3	Increase by 10–15
	PI 1–1.5 kg	160	70–140	7–14	2.5 (–3.0)	3.0	2–5	1–3	15–20
	NB ≥1.5 kg	160	60–120	7–16	2.5 (–3.0)	3.0	2–5	1–3	15–25 ml/kg body weight/day
Day 7:	PI ≥1.5 kg	160	80–160	7–16	2.5 (–3.0)	3.5	2–5	1–3	Increase by 10–15
	PI 1–1.5 kg	160	70–140	7–16	2.5 (–3.0)	3.5	2–5	1–3	15–20
	NB ≥1.5kg	160	60–120	7–16	2.5 (–3.0)	3.5	2–5	1–3	15–25 ml/kg body weight/day
Day 14:	PI <1000 g	160	80–160	7–16	2.5 (–4.0)	3.5	2–5	1–3	Target: 160 ml/kg body weight/day
	PI 1–1.5 kg	160	70–140	7–16	2.5 (–4.0)	3.5	2–5	1–3	Divided up into
	NB ≥1.5kg	160	60–120	7–16	2.5 (–4.0)	3.5	2–5	1–3	N meals:
Day 28:	PI <1000 g	160	80–160	7–16	2.5 (–4.0)	3.5	2–5	1–3	<1500 g 12 meals
	PI 1–1.5 kg	160	70–140	7–16	2.5 (–4.0)	3.5	2–5	1–3	≥1500 g 8 meals
	NB ≥1.5 kg	160	60–120	7–16	2.5 (–4.0)	3.5	2–5	1–3	≥2000 g 6 meals

- [1]Cave: The demand for nutritional substrates varies greatly and has to be adapted to suit each individual patient. Specifications apply to eutrophic newborns. The proportion of enteral nutrition (cave: intestinal resorption rate!) is to be deducted from the nutrient requirements. The result provides the parenteral proportion.
- {} start Na/K supplement depending on plasma levels.
- [F]= human milk fortifier. Supplement only if proportion of enteral nutrition is at least 75% and age > 7th day of life, PIF="premature infants formula"; SN="starter nutrition".
- °only add after first miction

to low renal concentrating ability in premature infants and newborns as a result of immature kidneys (II).

- Daily clinical tests, fluid balances, acid-base status, electrolytes and blood sugar are required during the initial phase of PN, depending on the maturity and illness of neonates, (C).
- In medium and long-term PN, routine clinical tests should also be accompanied by the following: documentation of weight, length and head circumference

development (in percentile questionnaires), weekly evaluation of acid base status, blood sugar, electrolytes, haematocrit, urea, creatinine, at least one transaminase, Y-GT, urine osmolarity or specific weight (alkaline phosphatase every two weeks) (C).

Commentary

Daily clinical tests, to include the monitoring of the fluid balance, checks of the acid base status, electrolytes and blood sugar, are usually required in the initial phase of PN depending on the age and maturity of the children and their underlying illness. In medium and long-term PN, routine clinical tests should also be accompanied by the following: documentation of weight, length and head circumference development (in percentile questionnaires), weekly evaluation of acid base status, blood sugar, electrolytes, haematocrit, urea, creatinine, at least one transaminase, Y-GT, urine osmolarity or specific weight (alkaline phosphatase every two weeks).

Lipids

The concentration of plasma triglycerides at which undesirable effects occur is not known [145]. Average triglyceride concentrations of 150 to 200 mg/dl and above are often specified in infants fed with breast milk or infant formula [86], [146]. Values of 250 mg/dl in healthy infants are not unusual. In older children higher concentrations of up to 300 and 400 mg/dl can also be acceptable as the lipoprotein lipase doesn't become saturated until approx. 400 mg/dl [147]. When gradually introduced, plasma triglycerides should be initially checked on a weekly basis for every 1 g/kg lipid intake increase and after reaching maximum intake levels.

Newborns

Monitoring the fluid balance in premature infants and sick newborns is extremely important due to their high fluid volume, high body water content in comparison to older patients and immature regulatory mechanisms (see above). Monitoring must take the special physiological features of neonates into consideration to be efficient:

- The measurement of the specific weight or osmolarity of urine are only indicative in premature infants and newborns in the first weeks of life when high values are measured. Low (normal) values can be due to low renal concentrating ability in premature infants and newborns because of immature kidneys.
- The immaturity of the kidney in premature infants in case of dehydration leads to hyperchloraemia prior to the development of acidosis as one of the first lab-chemical signs.
- Due to the low blood volume in neonates, staff at facilities in which neonates can receive medium and long-term parenteral nutrition must have access to a special laboratory with micro methods.

Attachment

Information on the selection and production of amino acid solutions

- Several metabolic pathways involved in the synthesis of amino acids are still immature in newborn and premature infants. As a result, some amino acids, which are regarded as non-essential for adults, may become conditionally essential (e.g. cysteine, tyrosine, histidine, taurine, and glutamine). In addition, individual plasma amino acids reach clearly increased levels because significant degradation enzymes are still immature. Amino acid imbalances occur more rapidly in comparison to adults (I).

Commentary

Increased phenylalanine concentrations are toxic for the central nervous system and can result in serious developmental disorders. Both hepatic phenylalanine hydroxylase activity and the enzymatic system of the metabolism of tyrosine are still immature in premature infants. Premature infants (<week 30 of pregnancy) with high amino acid intakes therefore have a tendency to develop hyperphenylalaninaemia and hypertyrosinaemia.
The enzyme activities in full-term infants result, however, in a rapid amino acid metabolism, causing low phenylalanine and tyrosine concentrations. Attempts are made to increase the low plasma tyrosine concentrations in infants receiving parenteral nutrition by supplementing with N-acetyl tyrosine, which is more soluble. Newborns and premature infants do still, however, have a reduced deacetylation capacity such that tyrosine may not be sufficiently utilised in this more soluble form [148], [149], [150], [151].
There is an interaction between the branched-chain and aromatic amino acids: Leucine supports the phenylalanine and tyrosine metabolism [152].
Methionine is a sulphurous, essential amino acid and is regarded as the precursor to cysteine and taurine. Methionine is the major methyl group donator in the hepatic intermediary metabolism. It is converted to homocysteine through demethylation, which remethylates to methionine when tetrahydrofolic acid is introduced or which is finally converted to cysteine via a transsulfuration pathway forming cystathionine.
Cysteine is a *largely essential amino acid* in both premature infants and full-term newborns due to its immature cystathionase activity. Plasma cysteine concentration is already a function of methionine intake in premature infants. It is often observed that normal *plasma cysteine concentrations* only occur if plasma methionine concentrations are raised. As a result cysteine supplementation of amino acid solutions is recommended in young infants [153], [154].
Supplementation with cysteine-HCl is not usually applied because of its low solubility and risk of acidosis. The

available N-acetyl cysteine may not be effectively metabolised due to limited deacetylation and immature metabolic rates in premature infants. Procysteine, a preliminary stage of glutathione, has also been tested [155].

Taurine is formed through decarboxylation of cysteine sulfinic acid, an enzyme stage that is still immature in premature infants. The foetus accumulates approx. 50–60 µmol taurine/day during the last trimester of pregnancy [156].

Taurine has many functions, not all of which are completely understood, although it is of importance to the central nervous system, retina and gastrointestinal tract. The proven relevance of the maturing of acoustically evoked potentials points to the clinical significance of taurine [157], [158]. Young infants on PN are, therefore, dependent on exogenous taurine intake in order to maintain plasma concentrations [157], [159].

Threonine: The plasma threonine concentration is directly proportional to the intake as well as inversely proportional to the gestational age in PN for premature infants [160]. A toxicity of raised plasma threonine concentrations has not yet been proven, although it is kown that concentration levels in the brain increase proportionally to plasma concentrations.

Lysine: Of all amino acids the materno-foetal gradient is most prominent in lysine. Plasma lysine concentrations in the foetus are approx. four times higher than those of the mother. Both lysine deficiency and surplus have negative effects on growth, brain DNA concentration and the dynamics of urea synthesis [161].

Leucine influences the speed of protein synthesis in the muscles. The demand for *branched-chain amino acids* is greater in premature infants than in full-term infants, and thus they easily tolerate amino acid solutions with a higher concentration of branched-chain amino acids.

Histidine: Of all essential amino acids, the plasma concentration of histidine is least influenced by the intake. Histidine is therefore regarded as a conditionally essential amino acid in young infants.

Arginine: The arginine concentration in an amino acid solution contributes to preventing hyperammonaemia. Premature infants with asymptomatic hyperammonaemia show lower plasma concentrations of urea cycle intermediates, which can be normalised by raising the arginine intake. Part of the arginine requirement can also be met by ornithine, which is taken into consideration in some amino acid solutions [162].

N-acetyl amino acids

- Based on recent data, it is assumed that N-acetyl amino acids are only metabolised to a limited extent in humans and therefore are only of limited significance as alternative amino acid sources in clinical nutrition (IV).

Commentary

There are no documented benefits of additionally administering N-acetyl cysteine due to limited deacetylation and immature metabolic rates in premature infants.

Notes on differences between lipid emulsions

- PE with a low phospholipid triglyceride ratio (e.g. in 20% lipid emulsions) results in less elevated phospholipid and cholesterol levels (II).
- The use of lipid emulsions on the basis of soy bean oil, an olive oil-soy bean oil mixture as well as a coconut oil (MCT)-soy bean oil mixture have been tested in paediatric patients and their use is well established (I).
- None of these lipid emulsions have a documented benefit regarding the attained clinical end points (C).

Commentary

Apart from the long established use of lipid emulsions based on soy bean oil, a new emulsion based on an olive oil and soy bean oil mixture has been available for some time and studies with this new mixture have already shown promising results in children, infants and premature infants [163], [164]. Postulated benefits of the olive oil-based lipid emulsions are reduced lipid peroxidation, lower PUFA intake and higher intake of antioxidative substances. Currently data are insufficient to propose a recommendation for olive oil-based emulsions [165].

Soy bean and olive oil-based lipid emulsions contain long chain triglycerides. There are also lipid emulsions with the equal proportions of LCT and MCT from coconut oil. They contain less PUFA, and the MCT proportion is oxidised more rapidly [166]. A further potential benefit is that oxidation of MCT is less dependent on carnitine that of LCT. The energy content of MCT per g fat is, however, approx. 16% lower than that of LCT. Studies in adults and children show a higher lipid oxidation, less influence on the parameters of the liver function, improved leukocyte function and less influence on pulmonary haemodynamics and the gas exchange than with LCT emulsions [167], [168], [169], [170], [171]. There were no significant differences in regard to the plasma lipids and fatty acids [167], [172], [173], [174]. There is differing data concerning a nitrogen-saving effect when administering a MCT/LCT mixture. One study describes increased nitrogen retention [175], [176], while another study describes a more unfavourable leucine metabolism than when on LCT intake [177]. The current studies in children and newborns [125], [167], [173], [178], [179] do not justify any generally favoured utilisation of MCT/LCT emulsions compared to pure LCT emulsions at present [165], [174].

The ratio between phospholipids (PL) and triglycerides (TG) is lower in 20% lipid emulsions than in standard 10% lipid emulsions [180]. Lipid emulsions with a low PL/TG

ratio as in the standard 20% emulsions, should be favoured in PN [98], [125], [181], [182]. Higher amounts of phospholipids impair the clearance of triglycerides from the plasma, resulting in an increase in the plasma triglyceride concentration and of cholesterol and phospholipids in Low-Density-Lipoproteins [98]. The emulsion characteristics (dispersity, stability) and various incompatibilities are of great significance in the parenteral intake of lipids.

Notes

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