Journal of Pediatric Gastroenterology and Nutrition
41:S1–S4 © November 2005 ESPGHAN. Reprinted with permission.

1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR)

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BACKGROUND

These *Guidelines for Paediatric Parenteral Nutrition* have been developed as a mutual project of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN; www.espghan.org) and the European Society for Clinical Nutrition and Metabolism (ESPEN; www.espen.org). The guidelines are addressed primarily to professionals involved in supplying and prescribing parenteral nutrition (PN) to infants, children and adolescents. Due to the scarcity of good quality clinical trials in children many of the recommendations are

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Chair/co-chair of working group on [5]home parenteral nutrition, [6]Vitamins, [7]carbohydrates, [8]introduction, [9]venous access, [10]lipids, [11]fluid and electrolytes, [12]organisation of PN in hospitals, [13]minerals and trace elements, [14]complications, [15]energy, and [16]amino acids.

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extrapolated from adult studies and are based on expert opinion. The document represents the consensus of view of a multidisciplinary working party of professionals, who are all actively involved in the management of children treated with PN.

Guidelines are intended to serve as an aid to clinical judgement, not to replace it, as outlined by the Scottish Intercollegiate Guideline Network (http://www.sign.ac.uk/guidelines/fulltext/50/section1.html). Guidelines do not provide answers to every clinical question; nor does adherence to guidelines ensure a successful outcome in every case. The ultimate decision about clinical management of an individual patient will always depend on the clinical circumstances (and wishes) of the patient, and on the clinical judgement of the health care team. These guidelines are not intended to be construed or to serve as a standard of medical care.

Parenteral Nutrition in Children

PN is used to treat children that cannot be fully fed by oral or enteral route, for example due to severe intestinal failure (1). Intestinal failure occurs when the gastrointestinal tract is unable to ingest, digest and absorb sufficient macronutrients and/or water and electrolytes to maintain health and growth. Children differ from adults in that their food intake must provide sufficient nutrients not only for the maintenance of body tissues but also for growth. This is particularly true in infancy and during adolescence when children grow extremely rapidly. At these times children are particularly sensitive to energy restriction because of high basal and anabolic requirements.

The ability to provide sufficient nutrients parenterally to sustain growth in infants and children suffering from intestinal failure or severe functional intestinal immaturity represents one of the most important therapeutic advances in paediatrics over the last three decades. Improvements in techniques for artificial nutritional support now ensure that children in whom digestion and absorption are inadequate or who are unable to eat normally no longer need to suffer from the serious consequences of malnutrition including death. Since the 1960s, the wider availability of intravenous amino acid solutions and lipid emulsions resulted in successful prescription of PN in small infants, which was followed by the development of more appropriate solutions and delivery systems. PN can now be used not only for patients who require short-term parenteral feeding but also on a long-term basis for patients with chronic intestinal failure. With PN children with prolonged intestinal failure have the potential to grow and develop normally and to enjoy a good quality of life within the constraints of their underlying disease, and selected patients with irreversible intestinal failure may thus become candidates for intestinal transplantation (2). Whilst advances in knowledge of nutrient requirements, improved methods of nutrient delivery and understanding of the prevention and management of complications ensure that paediatric PN can generally be delivered safely and effectively, areas of uncertainty and controversy remain.

PN is usually indicated when a sufficient nutrient supply cannot be provided orally or enterally to prevent or correct malnutrition or to sustain appropriate growth. Every effort should be made to avoid PN with the use of adequate care, specialised enteral feeds and artificial feeding devices as appropriate. PN is not indicated in patients with adequate small intestinal function in whom nutrition may be maintained by oral tube or gastrostomy feeding.

Malnutrition in children, in addition to the general effects of impaired tissue function, immuno-suppression, defective muscle function and reduced respiratory and cardiac reserve also results in impaired growth and nutrition. Whilst somatic growth exhibits a bi-model pattern being fastest in infancy, then dropping off and receiving a further spurt around puberty, other organs of the body may grow and differentiate only at one particular time. This is particularly true with respect to the brain for which the majority of growth occurs in the last trimester of pregnancy and in the first two years of life. Poor nutrition at critical periods of growth results in slowing and stunting of growth which may later exhibit catch-up when a period of more liberal feeding occurs. In adolescence the risk is of not achieving growth potential if severe and continuous disease occurs and adequate provision is not made for their nutritional needs. The sick child is at the greatest risk of growth failure and nutritional disorder.

Infants and children are particularly susceptible to the effects of starvation. The small preterm infant of 1 kg body weight contains only 1% fat and 8% protein and has a non-protein caloric reserve of only 110 kcal/kg body weight (460 kJ/kg). As fat and protein content rise with increase in size, the non-protein caloric reserve increases steadily to 220 kcal/kg body weight (920 kJ/kg) in a one year old child weighing 10.5 kg. If it is assumed that all non-protein and one third of the protein content of the body is available for caloric needs at a rate of 50 kcal/kg body weight (210 kJ/kg) per day in infants and children, estimates of the duration of survival during starvation and semi-starvation may be made. A small preterm baby, therefore, has sufficient reserve to survive only four days of starvation and a large preterm baby has enough for twelve days (3). With increased caloric requirements associated with disease this may be cut dramatically to less than two days for small preterm infants and perhaps a week for a large preterm baby. Recently it has become clear that small infants have special nutrition needs in early life and there is now a considerable body of evidence to suggest that nutrition at this age may determine various outcomes later in life, including both physical growth and intellectual development (4,5). Clearly infants are at a considerable disadvantage compared with adults and early recourse to PN is essential when impaired gastrointestinal function precludes enteral nutrition.

TABLE 1.1. *Form used for declarations on potential conflicts of interest that was completed by each contributor to the guidelines*

Declaration of competing interests for experts contributing to ESPGHAN and ESPEN guidelines paediatric parenteral nutrition

A competing interest exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry).

Please answer the following questions (all authors must answer)

1. Have you in the past five years accepted the following from an organisation that may in any way gain or lose financially from the results of your study or the conclusions of your review, editorial, or letter:

_____ Reimbursement for attending a symposium?
_____A fee for speaking?
_____ A fee for organising education?
_____ Funds for research?
_____ Funds for a member of staff?
_____ Fees for consulting?

2. Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the results of your study or the conclusions of your review, editorial, or letter?
3. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the results of your study or the conclusions of your review, editorial, or letter?
4. Do you have any other competing financial interests? If so, please specify.

We are restricting ourselves to asking directly about competing financial interests, but you might want to disclose another sort of competing interest that would embarrass you if it became generally known after publication.

1. Please insert ''None declared'' under competing interests or
2. Please insert the following statement under competing interests:

Date:_____ Signature:_____

(Print name too please)

Indications for PN

The time when PN should be initiated will depend both on individual circumstances and the age and size of the infant or child. In the small preterm infant starvation for just one day may be detrimental and where it is clear that enteral feeds will not be tolerated soon PN must be instituted shortly after birth. However in older children and in adolescence longer periods of inadequate nutrition up to about seven days may be tolerated, depending on age, nutritional status, and the disease, surgery or medical intervention.

Ethical Issues

PN enables the child with intestinal failure to survive even if there is little or no chance of intestinal recovery. However there are situations in which continuing to treat a child with PN might not be beneficial for the child even when medically possible. Ethical issues arise when the suffering imposed by administering PN is greater than any potential benefit. If treatment is continued it may place an intolerable burden of care on the child and family (6). For example a premature baby may start PN in a neonatal unit with the expectation that it will only be required for a few days or weeks. During the course of treatment the baby may go on to develop major organ failure whilst intestinal failure persists. If intestinal function is not improving and it is likely that long term home PN will be required in a child who also has failure of another major organ, it may be appropriate to change the aims and objectives of treatment. Another situation in which PN might not be beneficial is when a child is dying and other treatment is being withdrawn. It is particularly important to address this problem when parents are administering PN at home. They may find it more distressing to mentally prepare for their child's death when they are continuing to work hard to keep their child alive by administering PN infusions. It is important to address ethical issues by holding a multidisciplinary review

TABLE 1.2. *Grading of levels of evidence (LOE) according to the Scottish Intercollegiate Guideline Network (SIGN) 2000*

1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1−	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2−	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3	Non-analytic studies, e.g. case reports, case series. Evidence from non-analytic studies e.g. case reports, case series.
4	Evidence from expert opinion.

TABLE 1.3. *Grading of recommendations (GOR) according to the Scottish Intercollegiate Guideline Network (SIGN) 2000*

A. Requires at least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs, or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.
B. Requires a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.
C. Requires a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++.
D. Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.

meeting with all professionals involved in the child's care. The aim of the meeting is to make the best possible treatment plan for the individual child and to ensure that all professionals understand the reasons for any alteration in management. A smaller group of just two or three professionals can then discuss the issues with parents. Only then can an appropriate management plan be made. If treatment is to be withdrawn, it may be necessary to involve a palliative care team particularly since parents usually wish to take their child home.

METHODS

These guidelines have been developed by an international multidisciplinary working party of professionals actively involved in managing PN including dietitians, pharmacists, nurses and paediatricians specialising in gastroenterology, neonatology, nutrition, metabolism, intensive care, biochemistry and microbiology (see list of authors) on behalf of ESPGHAN and ESPEN. The project was coordinated by Berthold Koletzko (Univ. of Munich), Olivier Goulet (Hopital Necker Enfants Malades, Paris) and Raanan Shamir (Meyer Children's Hospital, Haifa) on behalf of the ESPGHAN Committee on Nutrition, who formed the Project Steering Committee jointly with the scientific organizers Joanne Hunt and Kathrin Krohn (Univ. of Munich). The project was financially supported by unrestricted donations of Baxter, Maurepas, France, B. Braun, Melsungen, Germany, and Fresenius-Kabi, Bad Homburg, Germany that were provided to and administered by the Charitable Child Health Foundation, Munich (www.kindergesundheit.de). All meetings and the writings of the manuscripts were performed without any participation of representatives or employees of commercial enterprises, and subjects and contents of the guideline were in no way influenced by the supporting companies.

For each section one or two authors acted as leaders and coordinators. Authors and their affiliation are listed at the front of the document. In order to ensure transparency every member of the working party completed a form disclosing possible conflicts of interests (Table 1.1), which were reviewed by the Project Steering Committee. While some authors reported institutional or personal scientific collaborations with commercial suppliers of products or services related to parenteral nutrition, the Project Steering Committee concluded that none of the project group members was dependant on such support, and the ability to provide independent judgement was not endangered in any case.

A systematic literature search was undertaken for each chapter. Evidence for practice was sought from publications from 1992 to the end of December 2003. Relevant publications from before 1992 could also be considered. In selected instances indicated in the respective chapters, chapter authors chose to extend the literature review to include references before 1992 or after 2004. The types of publication included were original papers, meta-analyses and reviews. Key words used for literature searches are shown in each chapter. All searches were performed in English. All groups prepared thorough, extensively researched documents, outlining their recommendations. A detailed analysis of the available data was performed and for each statement the level of evidence and grade of recommendation (Tables 1.2 and 1.3) was assessed. Literature from paediatric studies was used primarily. If only adult studies were available, they were graded according to the same scheme (not generally as expert opinion) but with the additional information that these were adult studies. A consensus conference was held in April 2004 in Munich, Germany, with several representatives from each group to review all the sections and agree on the statements made. Where good published evidence was unavailable, recommendations were discussed and if necessary voted upon. Opinions about omissions, inaccuracies and proposed changes were given by all attending participants. Chapter manuscripts were revised accordingly and agreed on by the respective groups, and reviewed and edited by the Project Steering Committee. The manuscripts were then made available in electronic form to all project participants for comments and suggestions for further revision, which were reviewed and decided on by the respective groups and the Project Steering Committee, and for final adoption by all project participants. Then the guidelines were made available to external scientific groups for review and comments, which were reviewed by the Project Steering Committee. By this process, these guidelines have been endorsed by the European Society for Paediatric Research.

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Journal of Pediatric Gastroenterology and Nutrition
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2. Energy

METHODS

Literature Search

Medline search, Pub-Med search.

Timeframe: publications from 1990–2003, in addition relevant publications from 1978 were considered.

Type of publications: original papers, meta-analyses, experts' recommendations, overviews.

Key Words: Energy expenditure, total parenteral nutrition, intensive care, critical care, prematurity, equations.

Language: English, French.

Key Words: Energy expenditure, resting energy expenditure, diet induced thermogenesis.

ENERGY IN PAEDIATRIC PARENTERAL NUTRITION (PN)

Introduction

Energy supply should aim at covering the nutritional needs of the patient (basal metabolic rate, physical activity, growth and correction of pre-existing malnutrition) including the support of anabolic functions (1). Excessive energy intake may result in hyperglycaemia, increased fat deposition, fatty liver and other complications (2). Underfeeding, on the other hand, may result in malnutrition, impaired immunologic responses and impaired growth (3). In general, infants require more calories when fed enterally than when fed parenterally. Energy supply can be divided into protein and non protein (carbohydrate and lipid) calories (see specific chapters on lipids, carbohydrates and amino acids). On a theoretical basis, energy needs can be calculated based on non protein calories as protein needs are calculated only for new tissue deposition, as well as for tissue renewal and not as an energy source. However, since the recommendations for energy needs in children usually include the protein contribution to energy expenditure, most of the statements in this chapter will include proteins as well as carbohydrates and lipids for assessment of energy needs.

This chapter provides a short overview on energy, but is not a substitution for a Nutrition Textbook. Some theoretical issues in energy supply will be mentioned but the intention is to provide a practical approach for clinical practice. In general, the total caloric requirements can either be estimated or directly measured. Measurement of energy expenditure is not routinely done and different equations were suggested for estimating energy needs. These equations (see below) can serve only as guidelines when commencing PN. Further aspects need to be taken into account according to clinical parameters:

1. Weight gain in regard to the target growth and required catch-up growth (see below).
2. Recommended intake of the different macronutrients (see specific chapters on lipids, carbohydrates and protein).
3. Tolerance to PN administration i.e. hyperglycaemia, hypertriglyceridaemia, liver enzyme abnormalities, cholestasis, tolerance of cyclic administration etc.

Components of Energy Needs

Total energy needs of a healthy individual are the sum of different components which can be divided into 4 main sub-groups: Basal metabolic rate (BMR), diet induced thermogenesis (DIT), physical activity (PA) and growth. Energy needs may be affected by nutritional status, underlying diseases, energy intake, energy losses, age and gender. No effect of gender on different components of daily energy expenditure was found in free-living prepubertal children (4). On the other hand, Goran et al (1991) found that fat free mass, gender and fat mass are important determinants of total energy expenditure (TEE) in prepubertal children (5). During puberty and adolescence, energy expenditure is affected by gender, body composition and season, but not by the stage of puberty (6).

Basal Metabolic Rate

Basal metabolic rate (BMR) is the amount of energy needed for maintaining vital processes of the body not including activity and food processing. It is measured in a recumbent position, in a thermo-neutral environment after 12 to 18 hours fast, just when the individual has awakened before starting daily activities. In practice, resting energy expenditure (REE) is usually measured instead of BMR. REE is similarly measured at rest in a thermo-neutral environment, after 8–12 hours fast and not immediately after awakening. REE doesn't differ by more than 10% from BMR (7). Sleeping energy expenditure, a component of BMR was shown to be equal to REE $\times$ 0.9 (8). BMR may be increased in conditions such as inflammation, fever, chronic disease (i.e. cardiac, pulmonary), or can decrease in response to low energy intake.

TABLE 2.1. *Equations for calculating REE and BMR (kcal/day) in infants from 0–3 years**

Source	Gender	Equation
WHO	male	REE = 60.9 × Wt − 54
	female	REE = 61 × Wt − 51
Schofield (W)	male	BMR = 59.48 × Wt − 30.33
	female	BMR = 58.29 × Wt − 31.05
Schofield (WH)	male	BMR = 0.167 × Wt + 1517.4 × Ht − 617.6
	female	BMR = 16.25 × Wt + 1023.2 × Ht − 413.5
Harris-Benedict	male	REE = 66.47 + 13.75 × Wt + 5.0 × Ht − 6.76 × age
	female	REE = 655.10 + 9.56 × Wt + 1.85 × Ht − 4.68 × age

*Wt = body weight in kilograms; Ht = Length in meters.

Diet Induced Thermogenesis

Diet induced thermogenesis (DIT) reflects the amount of energy needed for food digestion, absorption and part of synthesis and can, therefore, be affected by the route of substrate administration (oral, enteral or parenteral). DIT usually accounts for about 10% of daily energy needs. In orally fed healthy adult subjects the time of food consumption may affect DIT (9). During PN, DIT and the respiratory quotient are affected by the mode of PN administration (continuously vs. cyclic) (10–12).

Activity

Activity is the amount of energy spent for daily movements and physical activity. In older children, activity accounts for a large proportion of total energy expenditure. TEE of a hospitalized child lying in bed, on the other hand, is reduced. In contrast to most adults the activity of children on home parenteral nutrition, who can attend school, is not reduced (13).

To account for energy needs related to activity, different metabolic constants were suggested for multiplication of BMR (i.e. EE = BMR × constant). In patients on PN the more applicable constants are: × 1.0 for sleeping, × 1.2 for lying awake and for sitting quietly, and × 1.4–1.5 for standing quietly or sitting activities (14). Generally 1.1 or 1.2 are the constants used for patients.

Growth

The rapid changes in organ maturation and the higher growth velocity during the first 2 years of life and later on during adolescence imposes extra caloric needs as compared to adults. The energy needed to maintain accelerated growth represents 30–35% of the energy requirements in term neonates and is greater in preterm infants. Energy cost for 1gr of tissue deposition ranges between 4.9 kcal/g in premature infants and 6.4 kcal/g in adults recovering from anorexia nervosa (14). In patients fed parenterally over longer periods of time, growth and body composition should be assessed on a regular basis, and caloric intake adapted to allow normal growth.

Catch-Up Growth

Children recovering from malnutrition need extra calories to correct their growth deficits (weight, height). In such cases energy needs may be calculated based on the 50th percentile of weight and height for the actual age, rather than the present weight. This difference will provide extra calories (above daily needs) to achieve catch-up growth. Alternatively, calculation may be based on the actual weight multiplied by 1.2–1.5, or even by 1.5 to 2 times in severe cases of failure to thrive, to provide the extra calories needed for catch up growth. Further caloric needs should be adjusted according to weight and height gain.

Special Considerations

Energy needs are affected by the underlying disease and current nutritional status and should be met accordingly (1). Some diseases have been shown to increase or

TABLE 2.2. *Equations for calculating REE and BMR (kcal/day) in children from 3–10 years**

Source	Gender	Equation
WHO	male	REE = 22.7 × Wt + 495
	female	REE = 22.4 × Wt + 499
Schofield (W)	male	BMR = 22.7 × Wt + 505
	female	BMR = 20.3 × Wt + 486
Schofield-(WH)	male	BMR = 19.6 × Wt + 130.3 × Ht + 414.9
	female	BMR = 16.97 × Wt + 161.8 × Ht + 371.2
Harris-Benedict	male	REE = 66.47 + 13.75 × Wt + 5.0 × Ht − 6.76 × age
	female	REE = 655.10 + 9.56 × Wt + 1.85 × Ht − 4.68 × age

TABLE 2.3. *Equations for calculating REE and BMR (kcal/day) in children from 10–18 years**

Source	Gender	Equation
WHO	male	REE = 12.2 × Wt + 746
	female	REE = 17.5 × Wt + 651
Schofield (W)	male	BMR = 13.4 × Wt + 693
	female	BMR = 17.7 × Wt + 659
Schofield (WH)	male	BMR = 16.25 × Wt + 137.2 × Ht + 515.5
	female	BMR = 8.365 × Wt + 465 × Ht + 200
Harris-Benedict	male	REE = 66.47 + 13.75 × Wt + 5.0 × Ht − 6.76 × age
	female	REE = 655.10 + 9.56 × Wt + 1.85 × Ht − 4.68 × age

decrease energy needs, and some of these situations are discussed below.

ESTIMATING ENERGY NEEDS

Energy needs can be either measured or calculated based on acceptable equations. The best way to assess energy needs in children is to measure total energy expenditure or alternatively REE (15). Previous estimation of energy needs were based mainly on body size (i.e. weight, height, body surface area) (16), but it has been suggested that prediction of energy needs should be based on fat free mass, to account for differences in body composition (17) or even on organ tissue mass basis (18). Daily energy requirements are usually estimated by adding the increased energy expenditure associated with activity, stress, disease state, injury and growth to the calculated basal metabolic rate of healthy children (14). The differences in actual energy needs versus calculated needs based on general equations arise from the special status of the patient, i.e.: reduced physical activity during illness, energy losses from ostomies, malabsorption, diarrhoea, underlying disease or inflammation, infection, impaired body composition (decreased lean body mass due to increased catabolism) and different energy routes of supplementation (oral, enteral feeding, continuous vs. intermittent feeding and PN). In addition, the total energy expenditure of a child who is hospitalized and lying in bed is reduced.

As most of the children in need of PN suffer from one or more of the above, the estimated energy needs based on current equations may be incorrect.

Measuring Energy Needs

Different techniques are available for short and long-term measurement of energy expenditure:

BMR and REE can be studied by an open circuit indirect calorimetry.

Total energy expenditure (**TEE**) can be estimated by stable isotope techniques ($^{2}H_{2}^{18}O$ Doubly labelled water) and bicarbonate (^{13}C) (19) as well as by heart rate monitoring (20,21). Physical activity can be estimated by activity monitoring (22).

Calculating Daily Energy Needs

Different equations have been developed to calculate REE, BMR and TEE. These predicting equations were based on various studies that took place during the first 80 years of the 20th century. Of these, the WHO equations (WHO 1985), (Schofield (1985) and Harris Benedict (1919) equations are mostly used (14,23,24) (Tables 2.1–2.3). The main predictor for each component of energy expenditure is body weight (25) while height also accounts for some of the variability in energy needs. Apart from special considerations which will be discussed below, in most cases there is little need to provide more than 110–120% of energy expenditure to most of the hospitalized patients (7). This is not the case in patients on home parenteral nutrition where a recent study measuring total daily energy expenditure under free-conditions in stable subjects did not find any difference from healthy controls (13).

Some studies have recently suggested that the above currently used equations provide an inadequate estimation of REE in different age groups. Duro et al found that the 3 above equations (WHO, Schofield-W and Schofield-WH) underestimate REE in healthy infants <3 year old (25). Thompson et al measured healthy infants (0.43 ± 0.27 years) and found that all the equations overestimated REE. The worst estimation in this age group was obtained by using the H-B equations ((26) (LOE 2++)). These equations are specifically inadequate in children with altered growth and body composition (27). In cases like failure to thrive, the Schofield -WH was found to be the best predicting equation (28). When the WHO equation was used for estimating energy needs in healthy subjects of 2–12 years of age, the equation overestimated the measure of REE by 105 ± 12% (27). Overestimation by the H-B equations was also found in adult subjects (29). In another study

TABLE 2.4. *Parenteral energy needs*

Age (yr)	Kilocalories/kg body weight per day
Pre-term	110–120
0–1	90–100
1–7	75–90
7–12	60–75
12–18	30–60

which compared predicted to actual measurements in 7.8–16.6 years healthy controls, the Schofield -WH equation showed the best agreement with actual measurement (30). In a study of 199 subjects aged 5–16 years both the Schofield WHO and were comparable to the measured resting values, with the Schofield equations providing the best estimates (31). In various illnesses and related malnutrition, these prediction equations were not accurately estimating actual REE requirements ((27) (LOE 2++)). Of the four equations the Schofield equation using both weight and height measurements was the best at predicting REE. Nevertheless, all of these equations have been established in normal children and should be used with caution in sick children treated with PN. Average daily parenteral energy intakes per kg bodyweight considered adequate for a major proportion of patients are shown in Table 4.

Recommendation

- Reasonable values for energy expenditure can be derived from formulae, e.g. Schofield. However, in individual patients measurement of REE may be useful. REE may be measured rather than calculated to estimate caloric needs due to a different individual variability and over or underestimation by the predicting equations. **GOR D**

Special Considerations

Premature Infants

Early nutrition support is advocated in extremely low birth weight and very low birth weight infants because of limited nutritional stores (32). A recent randomized controlled study compared the effect of PN on the first day of life as compared to PN started in the first few days and being advanced more slowly. Better growth was found with early PN (33). Energy intake affects nitrogen balance; minimal energy requirements are met with 50–60 kcal/kg per day, but 100–120 kcal/kg/d facilitate maximal protein accretion (34). A newborn infant receiving PN needs fewer calories (90–100 kcal/kg per day) than a newborn fed enterally because there is no energy lost in the stools and there is less thermogenesis (35).

In premature infants after surgery, one study of post surgical sick premature neonates did not find an increase in energy expenditure (36). However, in extremely low birth weight infants (ELBW), using doubly labelled water technique to measure energy expenditure, Carr et al found that ELBW (<1000 g birth-weight) with minimal respiratory disease but requiring mechanical ventilation appear to have significantly increased rates of energy expenditure (85 kcal/kg per day) in early postnatal life (37). Since foetal life energy accretion is approx. 24 kcal/kg per day between 24–48 weeks of gestation (38), an energy balance (energy intake-energy expenditure) of approximately 25 kcal/kg per day represents a reasonable goal for these small premature infants. Thus, on a theoretical basis sick children with high energy expenditure (85 kcal/kg per day) would require at least 85 + 25 = 110 kcal/kg per day to grow. Moreover, using the same doubly labelled water technique, it has been shown that ELBW infants may require even more energy intake at 3 to 5 weeks of age, when their measured EE ranges between 86–94 kcal/kg per day (39).

Intensive Care Unit (ICU)

In critically ill ventilated children, within-day variations in energy expenditure measurements are uncommon and a single 30-minute energy measurement can be an acceptable guide. Between-day variation on the other hand can, however, be large (40). Several studies did not observe hyper-metabolism in critically ill children and most of the recent data suggest that the predicting equations overestimate or nearly estimate the actual REE. Moreover, some studies found that measured EE was lower than predicted and was associated with a higher mortality risk (41). Using stress factors added to the predicted equations grossly overestimated the energy expenditure (42). It was suggested, therefore, to use only predicting equations without ''stress factors'' when calculating energy needs (42–44). In a study that found increased REE, the measurement was done alongside PN administration and was 20% higher than the predicted by the Talbot's tables (45). Similar results were obtained for the H-B equations with a stress factor of 1.3 (46). The catabolic process in critically ill subjects inhibits growth, thus reducing energy requirements on one hand, while increasing basal energy expenditure on the other (47).

A combined measurement of energy expenditure along with nitrogen balance or RQ may help in tailoring the right formulation (48).

White et al recently suggested a new formula for estimating energy expenditure in ICU patients with a close correlation between predicted and measured EE (R2 = 0.867) (44):

$$\begin{aligned}\text{EE (kcal/d)} = [&(17 \times \text{age in months})\\ &+ (48 \times \text{weight in kg})\\ &+ (292 \times \text{body temperature in °C})\\ &- 9677] \times 0.239\end{aligned}$$

This group has found that EE increased with time relative to the injury insult, which emphasizes the importance of serial measurements of EE in these patients. The changes were ascribed to the ''ebb'' and ''flow'' phases of the metabolic stress process. Resumption of anabolic (growth) metabolism may also contribute significantly to this phenomenon (47).

Post-Operative

Most of the studies indicate that major operations such as abdominal surgery are not accompanied by increased EE (49). REE peaks 2–4 hours after surgery and returns to baseline levels by 12–24 hours (50). The increase in postoperative REE is directly related to the severity of the operation and is greater in premature babies and in infants >48 hours of age. Because the increase in REE is of short duration and involves temporary metabolic changes there is no necessity to increase the energy intake of infants who have an uncomplicated operation (35). Pierro et al developed an equation for predicting basal energy requirements of stable surgical infants of less than 12 months (51).

$$\begin{aligned}\text{REE (cal/min)} &= -74.436 \\ &+ (34.661 \times \text{weight in kg}) \\ &+ (0.496 \times \text{rate in beats/min}) \\ &+ (0.178 \times \text{in days})\end{aligned}$$

Statement

- There is no support for increased energy needs after uncomplicated surgery. **LOE 2++**

Head Injury

REE is significantly increased after head injury (52,53). Energy expenditure varied markedly between and within children (mean 97% of predicted, range 60–137%) and was significantly lower in the children with poor outcome (52). Neuromuscular blockade (54) and hypothermia (55) reduce it to the predicted values.

Burn Injury

Recent studies suggest that previous studies overestimated energy needs (56). Goran et al (1991) compared measured REE to the predicted values based on Harris-Benedict equations and found that the energy required to ensure that 95% of patients achieve energy balance is approximately 2 × predicted REE (57).

Hematopoietic Transplantation

Measured energy expenditure post transplantation is significantly lower than the predicted by WHO equations (58) or Schofield equations (59).

Medications

Few studies have indicated changes in energy expenditure in response to different medications. Treatment with beta-blockers was found to reverse catabolism and attenuate hypermetabolism in children with burns (60).

Recommendations

- Reasonable parenteral energy supply can be estimated from calculated resting energy expenditure multiplied by a factor reflecting additional needs including physical activity, and from monitoring weight change. **GOR D**. Therefore, parenterally fed patients should be regularly weighed, usually on a daily basis during acute disease phases and in unstable patients. **GOR D**
- For calculating REE, WHO and especially Schofield (WH) equations should be used for children less than 10 years of age. For children aged 10 years and older, Harris Benedict, WHO and Schofield equations can be used. **GOR B**
- Measurement of resting energy expenditure by indirect calorimetry, and estimation of total energy expenditure from heart rate monitoring, might be used in selected patients to provide additional information. However, their general use is not recommended because of lack of data on outcome. **GOR D**
- Energy intake should be adapted in patients with disease states that increase resting energy expenditure, such as pulmonary (e.g. cystic fibrosis) and cardiac (e.g. some congenital heart disease) disorders. **GOR B**
- In most parenterally fed hospital patients energy needs are met by 100–120% of resting energy expenditure. **GOR D**
- Patients who are underweight and need to regain weight may need 130 to 150% of REE. **GOR D**
- Energy intake should not be increased after uncomplicated surgery. **GOR B**
- Total parenteral energy needs (including protein) of stable patients may be roughly estimated using Table 2.4. **GOR D**

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Journal of Pediatric Gastroenterology and Nutrition
41:S12–S18 © November 2005 ESPGHAN. Reprinted with permission.

3. Amino Acids

METHODS

Literature Search

Time frame: Publication search is 1992–2004 plus relevant publications before 1992.

Type of publications: Case control and cohort studies, randomised controlled studies and systematic reviews.

Language: English.

Key Words: Adolescents, children, neonates, preterm infants, parenteral nutrition, amino acids, requirements, toxicity, deficiency.

Patients

All children with age range from preterm to adolescent were considered in these guidelines.

Outcome

Recommendations were developed from a standpoint of nutrient adequacy. Depending on age groups, nutrient adequacy was based on intrauterine accretion rate, organ development, factorial estimates of requirements and amino acid interactions. Individual amino acids are discussed.

Minimal intakes of specific amino acids are those that meet the specific requirement of children in that age group. Maximal intakes are recommended to prevent excessive and potentially harmful intakes of amino acids.

AMINO ACIDS

Introduction

Proteins are the major structural and functional components of all cells in the body. They consist of chains of amino acid subunits joined together by peptide bonds. The chain length ranges from two amino acids to thousands, with molecular weights subsequently ranging from hundreds to hundreds of thousands of Daltons. From a nutritional perspective, an important aspect of a protein is its amino acid composition.

Some amino acids are classified as essential (indispensable). Those are amino acids that cannot be synthesized by humans and hence must be provided in the diet or parenteral solution. Non-essential amino acids can be synthesized from other amino acids or from other precursors. Some amino acids are categorized as semi-essential. These amino acids can be synthesized from other amino acids but their synthesis is limited under certain circumstances (1–6). These amino acids may be of particular importance for the preterm infant in whom a developmental delay in specific enzymes involved in amino acid synthesis have been demonstrated (7–11).

The essential, non-essential and conditionally essential amino acids are listed in table 1. Although everybody agrees on the concept that some none-essential amino acids are essential under certain circumstances, some debate exists about the conditional essentiality of arginine and proline.

METHODS FOR ESTIMATING TOTAL AND INDIVIDUAL AMINO ACID NEEDS

Amino acid requirements are mainly determined by the rate of net protein synthesis, which depends on the availability of rate limiting amino acids. There are several physiological and biochemical ways to determine whether the amino acid intake is sufficient or in excess of the needs of children. Different measurements in assessing adequacy of amino acid intake include anthropometry (weight and length), nitrogen balance, metabolic indices (e.g. amino acid concentrations, albumin, pre-albumin, total protein concentrations, blood urea nitrogen, metabolic acidosis), whole-body nitrogen kinetics, specific amino acid kinetics and the indicator amino acid method. The intake of each essential amino acid required to maintain nitrogen equilibrium in children and infants has been defined as the amount necessary to obtain growth and nitrogen balance.

In veterinary medicine the free amino acid concentrations were used to detect deficiencies and excesses of dietary amino acids. This principle works more rapidly than weight gain or growth studies (12–15). Most current amino acid solutions are developed in a similar fashion (16–18).

The amino acid indicator method seems to be an accurate and fast way to determine specific amino acid requirements. It has recently been developed to measure specific amino acid requirements (19–21) and has been validated in animal models of infancy (22–24). The technique is based on the partitioning of essential amino acid outflow under steady state conditions between oxidation and protein synthesis. When a single essential amino acid is deficient in the diet, the amount of protein that can be synthesized is limited. Since the limiting amino acid also limits the use of all other dietary amino acids for protein synthesis, the body must oxidize excess amounts of these amino acids. If one increases the dietary amount of the limiting amino acid, protein synthesis will increase and so will the utilization of the other dietary amino acids which in turn reduces their oxidation. Once the requirement for the limiting amino acid is reached, further increases in its dietary intake will cause no further increase in protein synthesis, nor decrease in the oxidation of the other essential amino acids.

The indicator amino acid oxidation method uses this relationship (19). Subjects are given a series of diets containing varying amounts of the amino acid for which the requirement is to be determined. The amounts vary below and above requirement. All other amino acids are furnished at constant

TABLE 3.1. *Essential, non-essential and conditionally essential amino acids*

Essential	Non-essential	Conditionally essential
Histidine	Alanine	Arginine
Isoleucine	Aspartic acid	Cysteine
Leucine	Asparagine	Glycine
Lysine	Glutamic acid	Proline
Methionine	Glutamine	Tyrosine
Phenylalanine	Serine	
Threonine		
Tryptophan		
Valine		

amounts *above* requirement. At the end of each diet period, a dose of another essential amino acid with a ^{13}C or ^{14}C label (the indicator amino acid) is given, and its oxidation is measured. The oxidation of the labelled indicator amino acid will decrease as the amount of test amino acid increases, until requirement is reached, and then the oxidation will plateau. Plotting the oxidation of the labelled indicator amino acid against test amino acid intake should show a breakpoint at the requirement level for the test amino acid. A slightly different approach is the use of the oxidation rate of the investigated amino acid or its direct metabolite. Such an approach has recently been used in the determination of the requirement of tyrosine in parenterally fed infants (25).

Most currently used parenteral amino acid mixtures contain amino acid amounts that result in a plasma amino acid pattern resembling the plasma amino acid patterns of normally growing, breast fed infants and children, or cord blood. These paediatric parenteral amino acid mixtures provide more essential and less non-essential amino acids than normally deposited by the infant or child.

The utilisation of the amino acid supply depends on a sufficient energy intake, and often an energy supply of 30 to 40 kcal per 1 g amino acids is recommended.

TOTAL AMINO ACID NEEDS DURING PARENTERAL NUTRITION

Differences Between Enterally Fed and Parenterally Fed Children

The amino acid requirement is lower in parenterally fed infants and children than in enterally fed infants because the supply bypasses the intestine. No human data are available but animal studies suggest that the equivalent of approximately 30–50% of the protein intake is used by the intestine in neonates (26–28). However, there is a wide variation in the intestinal uptake and utilization of specific amino acids that changes with age. First pass (intestinal and liver) leucine utilisation in older children is 24% (29), while it accounts for approximately 50% of the dietary intake in preterm infants (30). Intestinal utilisation of lysine accounts for approximately 20% of the intake (31) whereas 50% of glutamine is used (30) in preterm infants. Thus, the total needs of amino acids in parenterally fed children are lower than in enterally fed children, but there are huge differences in intestinal utilization of specific amino acids. Besides utilization by the intestine, a number of amino acids are also metabolized and converted into other amino acids within the intestine and/or liver upon first pass. Bypassing the intestine will lower systemic availability of these amino acids and thus increase the parenteral requirements. In addition, while ingested phenylalanine and methionine appear to be converted to tyrosine and cysteine, respectively. It seems that parenterally administered phenylalanine and methionine are converted to a lower extent. Systemically active peptides are produced within the intestine (e.g. sIgA) and animal studies show that the intestine uses predominantly dietary amino acids (more than amino acids that are offered to the intestine from the systemic circulation) for specific protein synthesis (32).

These metabolic considerations could not yet be taken into account during the development of currently available parenteral amino acid solutions for infants and children, which have been based on considerations of food protein composition (e.g. human milk proteins) and amino acid blood concentrations. However severe deficiencies will be detected by measuring plasma amino acid levels during 24 hours infusions of amino acids.

Preterm Infants

The most widely used method to estimate total amino acid requirements is the amount needed to achieve a positive nitrogen balance. Energy intake and substrate composition affect protein balance in parenterally fed neonates (33–37).

Optimal glucose and lipid intakes that maximize protein accretion and growth have not yet been determined at all amino acid intakes in neonates, particularly in those who are ill or extremely preterm. Preterm infants without amino acid supplementation excrete between 0.6 and 1.1 g protein/kg per day. (2,38–40). Supplementation of 0.85, 1.0 or 1.2 g amino acids /kg per day does not result in a positive nitrogen balance (40–42). Multiple regression analysis in the study of Thureen et al revealed that a mean intake of 0.9 g amino acids/kg per day is necessary to prevent significant protein loss (34). Van Toledo-Eppinga found a minimal catabolic state in preterm infants receiving 1.8 g/kg per day (43), whereas Rivera et al found a significant positive nitrogen balance at an intake of 1.5 g/kg per day (39). Positive nitrogen balances were also achieved with an intake of 2.3 g/kg per day and 2.65 g/kg per day (2,41). Parenteral intake of 3.2 g/kg per day results in a positive mean protein balance of 2 g/kg per day at a non-protein energy intake of 90 kcal/kg per day. No detrimental effects on plasma amino acid profiles were noticed (44). Very recently, Ibrahim et al showed that preterm infants are able to tolerate 3.5 g/kg per day from birth onwards (45). This amount resulted in a positive nitrogen balance already on the first day of life. Also high intakes such as 3.3 g/kg per day and 3.9 g/kg per day seem to be well tolerated (46).

No higher parenteral intakes were reported in the time frame of the literature search.

It seems safe to administer amino acids from birth onwards (40,45).

Recommendations

- Amino acid supply should start on the first postnatal day. **GOR B**
- A minimum amino acid intake of 1.5 g/kg per day is necessary to prevent a negative nitrogen balance. Higher intakes are needed to achieve physiological protein deposition. **GOR A**
- A maximum amino acid intake of 4 g/kg per day is recommended. **GOR B**

Term Neonates During the First Month of Life

At a parenteral supply of 2.4 g amino acids/kg per day, urinary nitrogen excretion ranges 0.10–0.12 g N/kg per day in stable, post surgical term infants (47) corresponding to 0.6–0.8 g protein/kg per day. This results in a positive nitrogen balance of approximately 1.8 g/kg per day.

Term neonates with a parenteral amino acid intake of 2.5 g/kg per day achieve a moderate but positive protein balance (0.27 g/kg per day) (48).

In a similar age group Zlotkin et al recommended a protein intake of 2.3–2.7 g/kg per day to achieve a similar weight gain rate as in full term infants who were fed human milk (49). No data are available on the minimum lower limit in this age group but presumably the lower limit is not different from that in preterm infants.

Recommendation

- A minimum amino acid intake of 1.5 g/kg per day is recommended to avoid a negative nitrogen balance while a maximum amino acid intake should usually not exceed 3 g/kg per day. **GOR D**

From 1st Month to 3rd Year of Life

The administration of 2.4 ± 0.3 g amino acids/kg per day to infants and children up to an age of 43 months (n = 40, median age 2.7 months) resulted in a mean positive nitrogen balance of 242 ± 70 mg/kg per day, with plasma amino acid levels within the reference range except for a low level of tyrosine (16). A positive nitrogen balance of 242 mg/kg per day corresponds to a positive protein balance of 1.5 g/kg per day. Infants (age 2–12 months) on the first day after cardiac surgery excrete 244 ± 86 mg N/kg per day corresponding to a negative protein balance of 1.5 ± 0.5 g protein/kg per day, whereas the supplementation of 0.8 g amino acids/kg per day resulted in a negative protein balance of −114 ± 81 mg N/ kg per day approx. 0.7 ± 0.5g protein/kg per day (50).

No more recent data, less than 20 years old, is available. Thus, based upon the knowledge that the amino acid needs gradually decline and that the above mentioned studies are all dealing with ill children, our minimum estimate of amino acid intake in this age group is 1 g amino acids/kg per day.

Recommendations

- A minimum amino acid intake of 1.0 g/kg per day is recommended to avoid a negative nitrogen balance. **GOR D**
- No firm recommendation can be made on the maximal intake although based on weight gain rates an intake higher than 2.5 g/kg per day seems not advisable. **GOR C**

3rd–5th Year of Life

A study by Coss-Bu shows that critical ill children at a mean age of 5 yrs have a negative nitrogen balance at a protein intake of 2.1 g/kg per day (51). The subjects with a positive nitrogen balance had a higher protein intake (2.8 ± 0.9 g/kg per day) than subjects with a negative nitrogen balance (1.7 ± 0.7 g/kg per day). No data is available on healthy children.

Recommendations

- There is a paucity of data in the age group 3rd–5th year of age, insufficient to draw any firm conclusions on as much the lower and upper limit of protein intake should be. Daily intakes of 1.0 to 2.0 g/kg per day are considered reasonable for stable patients. **GOR D**
- For critically ill patients the advisable amino acid intake may be higher (up to 3 g/kg per day). **GOR D**

6th–12th Year of Life

Critically ill children at a mean age of 8 years show a negative protein balance at an intake of 1.7 g protein/kg per day. Regression analysis showed a protein requirement of 2.8 g/kg per day in this study group (52).

Recommendations

- There is a paucity of data in the age group 6th–12th year of age, insufficient to draw any firm conclusions on defining the lower and upper limits. Daily intakes of 1.0 to 2.0 g/kg per day are considered reasonable for stable patients. **GOR D**
- For critically ill patients the advisable amino acid intake may be higher (up to 3 g/kg per day). **GOR D**

Adolescents

Young men, receiving an essentially protein free diet, excrete approximately 24–38 mg N/kg per day which corresponds to 0.15–0.24 g protein/kg per day (53,54).

Goulet et al administered different amino acid intakes to patients with a compromised gut function (55). The response of protein turnover to graded levels of amino acid intakes was assessed by using stable isotopes technology (leucine kinetics) in approximately 13 year old children in a stable nutritional status receiving home parenteral nutrition. Since the fat content of the body of adolescents changes very rapidly during this period, the estimates are based on lean body mass rather than body weight alone. Intakes ranged from 0.7 to 2.5 g amino acids/kg lean body mass per day. Positive nitrogen balance was achieved in these children at an intake of 1.5 g amino acids/kg lean body mass per day, whereas this was not the case at an intake 0.7 g amino acids/kg lean body mass per day. There was a significant positive difference in protein balance when the intake increased from 1.5 to 2.5 g/kg lean body mass per day.

Recommendations

- A minimum amino acid intake of 1.0 g/kg lean body mass per day is recommended to avoid a negative nitrogen balance. **GOR B**
- There is a paucity of data in the adolescent age group, insufficient to draw any firm conclusions on as much the upper limit of protein intake should be. An upper limit of 2.0 g/kg lean body mass per day is considered reasonable. **GOR D**

The recommendations are summarised in Table 3.2.

TABLE 3.2. *Parenteral amino acid supply considered adequate for most patients (g/kg body weight and day)*

Preterm infants	1.5–4.0
Term neonates	1.5–3.0
2nd month to 3rd year	1.0–2.5
3rd to 18th year	1.0–2.0

SPECIFIC AMINO ACID REQUIREMENTS DURING TOTAL PARENTERAL NUTRITION

Cysteine

Cysteine is considered a semi-essential amino acid in the newborn period, indicating that cysteine might need to be administered to circumvent low cysteine synthesis with subsequently low plasma levels and impaired protein synthesis. It is normally synthesized from methionine (S-donor) and serine (C-donor). Stability of cysteine is low in solution, making it hard to supply enough to the infant. However, it is possible to add cysteine-HCL to the amino acid solution just before the administration to the infant. Cystine (the oxidation product of two cysteine molecules combined) is stable but has a low solubility making it unsuitable as alternative to cysteine.

Cysteine is a major substrate for glutathione, a tripeptide (glutamic acid/cysteine/glycine) with important antioxidant properties, but also important in maintaining redox potential and calcium homeostasis. Appropriate levels of cysteine are therefore warranted. An intake of 170 μmol/kg per day (approx. 27 mg Cysteine-HCl/kg per day) resulted in plasma cysteine levels below the reference range whereas an intake of 345 μmol/kg per day) (≈54 mg Cysteine-HCl/kg per day) was enough to reach adequate plasma levels (56). The addition of 462 μmol/kg per day (72 mg/kg per day) resulted in normal plasma amino acid levels (57). Acetylation of cysteine prevents the instability but the bioavailability is low, approximately 50% (56).

In older children (age range 2–8 years) receiving an amino acid solution with varying doses of cysteine-HCl (0–40 mg/g AA, approx. 0–255 μmol/g AA), no changes were noted in free cysteine/cystine or methionine plasma levels were noted. Only plasma taurine levels varied with cysteine supplementation. (58)

Recommendations

- The minimum advisable intake lies between 200 and 350 μmol/kg per day (approx. 30–55 mg Cysteine-HCl/kg per day) in infants and young children. **GOR B**
- There is insufficient data in preterm infants to allow any firm conclusions to be made on the upper limit of cysteine intake. **GOR D**

Tyrosine

Like cysteine, tyrosine is considered a semi-essential amino acid in the neonatal period (59). The hydroxylation of phenylalanine to tyrosine is argued to be limited although Denne showed significant hydroxylation in even very preterm infants (60). However, many studies show low plasma concentrations of tyrosine in unsupplemented infants.

Supplementation of 55–90 μmol tyrosine/kg per day (≈10–16 mg/kg per day) resulted in plasma levels below reference range in preterm infants (56). Acetylation of tyrosine increases the solubility, but the bioavailability is low. In two studies only 60% of N-acetyl-Tyrosine is retained (17,56). An intake of approximately 700 μmol/kg per day which corresponds to a net intake of 126 mg tyrosine as NAT/kg per day resulted in adequate tyrosine levels. An intake of less than 200 μmol/kg per day (corresponds to a net intake of 36 mg tyrosine as NAT/kg

per day) did not. However, plasma levels of N-acetyl-tyrosine exceeded the plasma levels of tyrosine.

Due to the immaturities in the neonatal tyrosine catabolic enzyme pathway, tolerance of tyrosine intakes at levels greatly over requirement is limited (61). In addition, due to the known neurologic impairment caused by hypertyrosinemia to the developing brain as assessed by lower IQ and psychologic tests, excess intakes must be avoided (62,63).

Recently, a dipeptide, glycyl-L-tyrosine was used to determine the tyrosine requirement in parenterally fed term neonates (25). Using the elegant technique of the indicator amino acid method, the tyrosine mean requirement and safe level of intake (at which 95% of the infants will have sufficient intake) were found to be 74 mg/kg per day and 94 mg/kg per day respectively.

Recommendations

- There is a paucity of data in preterm infants, insufficient to draw any firm conclusions on as much the upper and lower limits of tyrosine intake should be. The lower limit should be more than 100 μmol/kg per day (≈18 mg/kg per day). **GOR C**
- The advisable intake in term infants is 520 μmol/kg per day (≈94 mg tyrosine/kg per day). **GOR C**
- There is insufficient data in term infants to allow any firm recommendations to be made on the upper limit of tyrosine intake. **GOR D**

Glutamine

In critically ill adult patients, glutamine supplementation may reduce sepsis and mortality (64). In 2005, a systematic review stated that there is no evidence from randomised trials to support the routine use of glutamine supplementation in preterm babies (65). In 4 day old preterm infants, additional glutamine did not have an effect on leucine balance (66). Ten days of glutamine supplementation in very-low-birth weight infants resulted in higher plasma glutamine levels but ammonia levels were not increased (67). No effect of glutamine supplementation on sepsis incidence or mortality was observed. Neither had glutamine an effect on tolerance of enteral feeds, necrotizing enterocolitis, or growth. (68). Thus, there is no new evidence that glutamine should be added to parenteral mixtures for preterm infants. No data are available in older children.

Recommendation

- There is no conclusive evidence for the need to provide glutamine supplementation to the preterm infant. **GOR A**

Taurine

Taurine is not a typical amino acid because, although it contains an amino group, it does not have the requisite carboxyl group. Despite this, it is being discussed here. Taurine deficiency may increase glyco-conjugates of bile acids and result in cholestasis. Although the cause of neonatal cholestasis probably is multifactorial, there are data indicating that adequate taurine may prevent cholestasis in neonates. In addition, taurine deficiency may result in retina dysfunction (69). Taurine is synthesized from methionine and cysteine and studies show that prolonged parenteral nutrition in children with a cysteine and taurine free parenteral solution resulted in reduced plasma taurine levels (70,71). Taurine supplementation (3 mg/g AA) maintained plasma taurine concentrations within the reference range in term infants but not in very low birth weight infants (18). Cysteine supplementation (50–100 mg/kg per day) normalizes taurine concentrations in 7 year old children with short bowel syndrome (58).

Taurine supplementation results in a slightly higher nitrogen retention in newborn babies. The amino acid solution used was based on human milk.

Recommendations

- There is no conclusive evidence to support the supplementation of the preterm infant with taurine. However it is advised that taurine is supplemented in the same amount as it is present in human milk, approx. 22 μmol/gram amino acids or 2.8 mg/g amino acids. **GOR D**
- No firm recommendation can be made upon advisable lower or upper limits. **GOR D**

No other amino acids are discussed as there is insufficient data available to recommend any intake ranges.

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Journal of Pediatric Gastroenterology and Nutrition
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4. Lipids

METHODS

Literature Search

Timeframe: publications from 1992–2003, in addition relevant publications from 1971 and after 2003 were considered.

Type of publications: original paper, meta-analyses and overviews.

Language: English.

Key Words: parenteral nutrition, lipid/fat emulsions, paediatrics, lipoprotein lipase, free fatty acids.

LIPIDS

Background

Lipid emulsions are used in paediatric parenteral nutrition (PN) as a non-carbohydrate source of energy in a low volume and with low osmolarity. In addition they provide essential fatty acids. The use of lipid emulsions decreases CO_2 production compared with parenteral nutrition containing a high carbohydrate content (1–3). Net-nitrogen balance can be improved by the addition of lipid emulsions to PN solutions (1,4,5).

Recommendation

- Lipid emulsions are an integral part of paediatric parenteral nutrition providing high energy needs without carbohydrate overload and supplementing essential fatty acids. **GOR D**

Composition of Macronutrients

Fat oxidation depends on the total energy intake and expenditure, the total intake of carbohydrates and triglycerides and the carbohydrate/fat ratio administered ((1,2) (LOE 1)). As carbohydrate intake increases fat oxidation diminishes in favour of lipid storage. In infants net lipogenesis occurs at glucose intakes above 18 g/kg per day, whereas it occurs at lower glucose intakes in older children (1,6). Maximum fat oxidation occurs when intravenous lipid emulsions provide 40% of the non-protein PN calories in newborns (3) and 50% in infants (1). Generally a lipid intake of 25 to 40% of non-protein calories is recommended in fully parenterally fed patients.

Recommendations

- Lipid intake should usually provide 25–40% of non-protein calories in fully parenterally fed patients. **GOR D**
- Glucose intakes above 18 g/kg per day, which tend to induce net lipogenesis in infants, should usually be avoided in infants. **GOR B**

Fat Intake

Omission of lipid emulsions from total parenteral nutrition may lead to biochemical evidence of essential fatty acid deficiency within a few days in preterm infants (7–9).

In order to prevent biochemical evidence of EFA (essential fatty acids) deficiency, 0.25 g/kg per day linoleic acid should be given to preterm infants (7,9). In term infants and older children the supply of 0.1 g/kg per day linoleic acid may be sufficient to prevent EFA deficiency. When prescribing lipid emulsions the different LA content of the available lipid emulsions needs to taken into account (see annex).

Minimum requirements of plasma alpha-linolenic acid are difficult to define. Most of the data about alpha-linolenic acid deficiency is derived from animal studies (10). In children there is one case report of alpha-linolenic acid deficiency in a 6 years old girl (11). In Europe, all lipid emulsions used for children contain alpha-linolenic acid.

The upper limit of lipid administration is difficult to determine. In preterm infants a lipid supply of 3 g/kg per day as continuous infusion was tolerated well based on measurement of serum triglycerides, cholesterol and molar ratios of free fatty acids/albumin (12–14). However preterm infants weighing less than 1000 g deserve special attention because their tolerance to intravenous lipids may be limited (15) (LOE 2–3).

In term infants fat oxidation reaches a maximum at 4 g/kg per day, given that the maximum glucose intake does not exceed maximal oxidative glucose disposal of about 18 g/kg per day (1,2). However, especially in premature and VLBW infants, a lipid supply exceeding fat oxidation may be desirable to achieve fat deposition. The metabolic utilisation of intravenous lipids varies with gestational and postnatal age, severity of disease and other factors. Therefore, monitoring of indicators of

lipid utilisation such as plasma triglycerides (or ideally lipid oxidation) may help in defining adequate intakes (LOE 3–4).

Recommendations

- In order to prevent EFA deficiency a minimum linoleic acid intake of 0.25 g/kg per day should be given to preterm infants and 0.1 g/kg per day to term infants and older children. **GOR D**
- Parenteral lipid intake should usually be limited to a maximum of 3–4 g/kg per day (0.13–0.17 g/kg per hour) in infants (**GOR B**) and 2–3 g/kg per day (0.08–0.13 g/kg per hour) in older children. **GOR D**

Application

The triglyceride portion of lipid emulsion particles is hydrolyzed by endothelial lipoprotein lipase (LPL). The liver rapidly removes lipid emulsion particle-remnants. Free fatty acids (FFAs) and glycerol are metabolized in a similar way to enteral lipids (16–18). FFAs can be captured by the adjacent tissues or circulate bound to albumin, for use in other tissues or uptake by the liver. The rate of hydrolysis varies according to the type of the triglyceride substrate (i.e., length of the fatty acid, degree of saturation, position of the fatty acid on the glycerol) (19). The amount and type of phospholipid emulsifier may also interfere with the rate of hydrolysis of the lipid particles of intravenous emulsions.

If the lipid emulsion is infused at a rate that is equal to or less than the rate of hydrolysis, a marked change in plasma triglyceride concentration reflecting accumulation of the infused triglyceride emulsion is unlikely. However, if the rate of infusion exceeds the rate of hydrolysis, plasma triglyceride concentration will rise and may cause adverse effects. Furthermore, if the rate of hydrolysis exceeds the rate at which the released free fatty acids are taken up and oxidized, the plasma concentration of free fatty acids will also increase. There were case reports about a condition called ''fat overload syndrome'', which may appear with rapid infusion of high dosages of lipid emulsions and may present with coagulopathies, hepatomegaly, elevated liver enzymes, hyperbilirubinaemia, respiratory distress and thrombocytopenia (20,21).

In preterm infants tolerance of lipid emulsions is improved by continuous infusion over 24 hours versus an intermittent regimen with lipid-free intervals (12,14,22). Although there are no comparable studies in older children, continuous infusion of lipid emulsions is recommended whenever possible. However, under stable conditions, lipid emulsions may also be well tolerated when given intermittently as part of cyclic home PN (LOE 4). There is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance (22). An incremental increase in lipid infusion of 0.5 to 1 g/kg per day may help to monitor for possible hypertriglyceridaemia.

Clearance of lipid emulsions from the blood depends on the activity of LPL. Post heparin lipoprotein lipase activity can be increased by relatively high doses of heparin (23,24). However, heparin does not improve utilization of intravenous lipids. The increase in LPL activity by heparin leads to an increase in FFAs, which may exceed the infants ability to clear the products of lipolysis and may weaken the binding of LPL to the endothelium (24–26).

Lipid metabolism results in lipid peroxidation and free radical formation (27–29). The enhancement of fat utilisation by reducing the carbohydrate-fat ratio, at stable lipid intakes, and thus reducing energy intake reduces lipid peroxidation and free radical production (30). Soybean oil based lipid emulsions contain only small amounts of alpha-tocopherol (biologically active form of vitamin E), unless they are supplemented (31), whereas olive oil based lipid emulsions are higher in alpha-tocopherol content (32). Patients on PN should be supplemented with a multi-vitamin preparation that includes vitamin E (alpha-tocopherol) which acts as a free radical scavenger and anti-oxidant (33–35).

Recommendations

- Dosage of lipid emulsions should not exceed the capacity for lipid clearance and should be adapted if marked hyperlipidaemia occurs. **GOR B**
- In infants, newborns and premature babies lipid emulsions should usually be administered continuously over about 24 hours. **GOR B**. If cyclic PN is used, for example in home PN, lipid emulsions should be given over the same duration as the other PN components. **GOR D**
- There is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance. If lipid infusion is increased in increments of 0.5 to 1 g/kg per day, it may be possible to monitor for hypertriglyceridaemia. **GOR D**
- Heparin does not improve utilisation of intravenous lipids and should not be given with lipid infusion on a routine basis, unless indicated for other reasons. **GOR B**

Monitoring

Plasma clearance of infused triglycerides can be assessed by measurement of plasma triglyceride concentrations. However, it is unclear at what serum level of triglycerides adverse effects may occur (36). In infants fed human milk or formula, triglyceride concentrations

of 150 to 200 mg/dl are frequently encountered (14,37). However, it seems reasonable to accept slightly higher triglyceride levels of 250 mg/dl during lipid infusion as the upper limit in newborns, premature and term infants (LOE 4). For older children, serum levels of triglycerides of 300–400 mg/dl may be acceptable based on the fact that lipoprotein lipase is saturated at around 400 mg/dl (38) (LOE 4). Checking serum triglyceride levels should be considered with each increase of 1.0 g/kg per day of intravenous lipids and weekly after the maximum dose is achieved.

Recommendations

- Triglyceride levels in serum or plasma should be monitored in patients receiving lipid emulsions, particularly in cases with a marked risk for hyperlipidaemia (e.g. patients with high lipid dosage, sepsis, catabolism, extremely low birthweight infants). **GOR D**
- Reduction of the dosage of lipid emulsions should be considered if serum or plasma triglyceride concentrations during infusion exceed 250 mg/dl in infants or 400 mg/dl in older children. **GOR D**

Available Lipid Emulsions

The lipid emulsions currently used contain soybean oil with egg yolk phospholipid as the emulsifier and glycerol to make the emulsion isotonic (see annex). Recently, the use of a new olive oil/soybean oil based lipid emulsion was studied in children, infants and premature newborns with encouraging results (32,39). The suggested advantages include prevention of lipid peroxidation, supply of less PUFA (polyunsaturated fatty acids) and thus enhancement of linoleic acid conversion and provision of higher antioxidant intake which results in an improved vitamin E status which is important especially in premature infants. However, there is currently not enough data to justify a recommendation towards any specific product (40) (LOE 1–2).

Soybean and olive oil based lipid emulsions contain LCT (long-chain triglycerides). Fat emulsions containing equal proportions of LCT and MCT (medium-chain triglycerides) are available. They contain less PUFA (polyunsaturated fatty acids) and their MCT part is oxidized more rapidly (19). Another possible advantage is that the oxidation of MCT is much less dependent on carnitine than oxidation of LCT. Adult and paediatric studies suggested that MCT/LCT emulsions lead to higher net fat oxidation, reduced liver derangement, improved white blood cell function, and less effects on pulmonary haemodynamics and gas exchange than LCT emulsions (41–45), while there were no major differences for plasma lipids and fatty acids (41,46–48). There are conflicting data about the effect of mixed MCT/LCT emulsions on nitrogen retention with some studies finding an increase in nitrogen retention (49,50), while another study found less positive leucine balance when compared to LCT emulsions (51). The available data in children and neonates (41,47,52–54) does not justify the preferential use of MCT/LCT emulsions over LCT emulsions (40,48).

There is insufficient data on the use of fish oil or structured lipid containing intravenous fat emulsions in paediatric patients, and thus their routine use is not recommended until further evidence may become available.

Standard 20% emulsions contain a lower ratio of phospholipid emulsifier/triglycerides than standard 10% lipid emulsions (55) and should preferably be used for intravenous PN (56,57). Higher amounts of PL (i.e. particles rich in PL) impede the removal of triglycerides from plasma, leading to an increase in plasma triglyceride concentration and accumulation of cholesterol and phospholipids in low-density lipoproteins (57). When the clearance mechanism of the exogenous phospholipids is exceeded, formation of lipoprotein X occurs (58). A 10% lipid emulsion with the same phospholipid/triglyceride ratio as the standard 20% emulsion did not show increased triglyceride and cholesterol concentrations (59).

Statement and Recommendations

- The use of commercial lipid emulsions based on LCT (soybean oil or olive oil/soybean oil), or physical mixtures of MCT and LCT can be considered generally safe in infants and children. **LOE 1**
- There is currently no evidence (based on clinical outcome data) supporting the advantage of any of the lipid emulsions that are currently available. **GOR D**
- Lipid emulsions used should not contain a higher phospholipids/triglyceride ratio than standard 20% lipid solutions to decrease the risk of hyperlipidemia. **GOR B**

Lipid Emulsions in Special Disease Conditions

Critical Illness and Infection

There is very little data concerning the use of lipid emulsions in critically ill and septic children. To our knowledge there are no outcome studies investigating the effect of lipid emulsions in this group of patients. One study in critically ill children showed that

hypermetabolic patients mainly used fat for oxidation. In these patients fat oxidation was reduced by increasing carbohydrate intake (60). Similarly, an adult study suggested that the administration of fat may be beneficial in critically ill patients to decrease de novo lipogenesis from glucose and CO_2 production associated with a high carbohydrate intake (61).

There is conflicting data about lipid clearance during infection. Some studies state that lipid clearance is reduced (62–64) whilst another found no association between hypertriglyceridemia and infection (65). In septic premature infants triglyceride levels tended to be higher and fatty acid oxidation was lower than in non-septic patients (63,64). However, it is difficult to define an upper limit of lipid intake based on these data, since high doses of heparin were applied and 10% lipid emulsions were used, which lead to increased plasma triglyceride concentrations when compared to the standard 20% lipid emulsions.

In addition to alterations in the metabolism of lipid emulsions in critically ill and septic patients, hyperactivation of the reticuloendothelial system has been described in children on long-term PN at the time of septic episodes (66). However, the use of lipid emulsions may be important in such patients to avoid excessive carbohydrate intakes and to provide essential fatty acids. In critically ill and in septic patients, close monitoring of plasma triglycerides and adjustment of lipid infusion rate if necessary is recommended.

Recommendation

- In critically ill or infected patients receiving lipid emulsions, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. **GOR D**

Respiratory Failure

Concerns have been raised regarding the possible adverse effects of intravenous lipid emulsions on pulmonary function (67), especially in premature neonates and those with acute lung injury. Severe adverse oxygenation effects are considered as part of the ''fat overload syndrome'' (68). While it has been thought that impaired pulmonary function (e.g. decreased pulmonary diffusion capacity with increased alveolar-arterial oxygen gradient, reduced oxygenation) was attributable to hypertriglyceridaemia, it has recently been hypothesized that it is actually due to the conversion of polyunsaturated fatty acids in the emulsion to prostaglandins causing changes in vasomotor tone with resultant hypoxemia (36,67,69). The production of hydroperoxides in the lipid emulsion might also contribute to untoward effects by increasing prostaglandin levels (29,70,71).

Recent evidence from studies in adults with acute respiratory failure suggests that infusion of an MCT/LCT emulsion in very high dosage induces significant alterations in lung function and haemodynamics, with inflammatory changes, oedema and surfactant alterations (72), which may depend on the rate of infusion (73) and on the type of lipid emulsion used (44). Other studies suggested that a mixture of MCT/LCT has less adverse effects in patients with respiratory failure than LCT lipid emulsions (42,44). Although there are no studies in children with acute respiratory failure, it might be prudent to limit lipid intake during the acute phase of respiratory failure.

Recommendation

- Although there is no firm evidence of the effects of lipid emulsions in children with severe acute respiratory failure with or without pulmonary hypertension, it appears prudent to avoid the supply of lipid emulsions in high dosages. However, lipid supply should generally be continued at least in amounts supplying the minimal essential fatty acids requirements. **GOR D**

Premature and Newborn Infants

Administration of lipids is important in premature infants requiring PN to provide essential fatty acids and increase caloric intake with a low volume. Premature infants fed parenterally without lipids may develop biochemical evidence of essential fatty acid (EFA) deficiency within 2–3 days (7,8). Intravenous lipids may be well tolerated from the first day of life onwards (74).

However, early administration of lipid emulsions remains controversial because the possibility of adverse effects on subsequent CLD (chronic lung disease) and mortality was raised. A study performed by Sosenko et al. (75) suggested that early administration to premature infants weighing less than 800 g at the age of less than 12 hours increases mortality rate and the risk of pulmonary hemorrhage. However, the number of infants whose mothers had received antenatal corticosteroids was significantly higher in the control than in the Intralipid group, possibly introducing a bias. There was no significant difference between the two groups concerning the incidence of CLD.

A study investigating the effect of early administration of intravenous lipid emulsions found an increased risk of CLD (76), whereas other studies showed no increase in the risk of respiratory impairment (74) or development of CLD (77,78). A meta-analysis, published only in abstract

form, of six randomized clinical trials designed to assess the effect of early (day 1 to 5) versus late (day 5 to 14) introduction of intravenous lipids reported no effect on the incidence of death or CLD at 28 days or at 36 weeks post conception (79).

Although this issue has not been settled conclusively, it appears that the benefits of intravenous lipid administration in premature infants weighing more than 800 g outweigh this potential risk, especially if 20% lipid emulsions are infused slowly (over 24 hours) (22) and serum triglyceride levels are monitored to identify intolerance ((74) (LOE 1–2)).

FFA (free fatty acids) compete with free bilirubin for albumin binding sites (80). A high FFA/albumin ratio may be associated with an increased risk of hyperbilirubinemia. High levels of FFA released from triglycerides may thus increase the risk of bilirubin toxicity especially in very premature infants. However, there is evidence that intravenous lipid emulsions do not have a significant effect on indirect hyperbilirubinemia in populations of newborn infants (81,82). To limit the risk of increasing hyperbilirubinemia lipid emulsions should be administered as continuous infusion (81). Serum triglyceride and bilirubin levels should be monitored and lipid infusion rate be adjusted accordingly. The exposure of lipid solutions to phototherapy light may result in the formation of triglyceride hydroperoxides that may be harmful, especially to premature infants. Thus, lipid emulsions should always be protected from phototherapy light by special light-protected dark tubing (83) (LOE 2). In addition, some authors recommend light-protected tubing for ambient light as well (83,84). In vitro studies have suggested that administering multivitamins containing ascorbic acid with the lipid emulsions via dark delivery tubing provides the most effective way of preventing peroxidation of the lipid and also limiting vitamin loss (84).

Recommendations and Statement

- In newborn infants who cannot receive sufficient enteral feeding, intravenous lipid emulsions should be started no later than on the third day of life, but may be started on the first day of life. **GOR B**
- Early administration of intravenous lipids in the first days of life does not increase the incidence of chronic lung disease or death in premature infants when compared to late administration of intravenous lipids (LOE 1). However there are concerns about potential adverse effects of early administration of lipid emulsions in VLBW (very low birth-weight) infants weighing less than 800 g. **LOE 2**
- Lipid emulsions have not been demonstrated to have a significant effect on hyperbilirubinaemia in populations of premature infants (LOE 2). It is unclear which level of bilirubin can be considered as safe in premature infants. In parenterally fed infants at risk of hyperbilirubinaemia, serum triglyceride and bilirubin levels should be monitored and lipid infusion rate be adjusted if deemed necessary. **GOR D**
- Lipid emulsions should be protected by validated light-protected tubing during phototherapy to decrease the formation of hydroperoxides. **GOR B**

Thrombocytopenia

Intravenous lipid emulsions do not seem to affect platelet number or function (85–87). However, some concerns were raised regarding the effect of lipid emulsions on platelet aggregation (88). Long-term administration of PN with lipid emulsions induced hyperactivation of the monocyte-macrophage system with haematologic abnormalities, including recurrent thrombocytopenia due to reduced platelet lifespan and haemophagocytosis in bone marrow (66). Therefore, it seems advisable to monitor serum triglyceride levels (20), and consider decreasing parenteral lipid intake in conditions of severe thrombocytopenia or coagulopathy (e.g. sepsis, DIC). A supply of essential fatty acids meeting minimal requirements is necessary to maintain normal platelet function (89) (LOE 2–3).

Recommendations

- In patients with severe unexplained thrombocytopenia serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage be considered. **GOR D**
- Lipids in amounts supplying at least the minimal essential fatty acids requirements should always be given to maintain normal platelet function. **GOR B**

Adverse Effects

Cholestasis

Concerns have been raised regarding possible adverse effects of intravenous lipid emulsions on liver function. Liver dysfunction was associated with lipid intolerance in newborns who received intravenous fat (65) (LOE 3). Among other factors, intravenous lipids are also

considered as one of the risk factors for PN-associated cholestasis (90) (LOE 3) (see also chapter on complications). Thus it is important to monitor liver function tests when lipid emulsions are given. If there is evidence of progressive hepatic dysfunction or cholestasis a decrease in lipid supply should be considered, especially if there are other concurrent morbidities (e.g. sepsis, thrombocytopenia).

Recommendation

- In patients with marked progressive cholestasis associated with PN, unrelated to acute infection, potential causes should be explored and a decrease or even a transient interruption in intravenous lipid supply should be considered. **GOR D**

Effects on Immune System

The effects of intravenous lipids on the immune system are controversial. Interpretation of available data is complicated by the use of inappropriately high lipid doses in some studies, the use mostly of only soybean emulsions, and of different in vitro models.

In vitro studies showed adverse effects of lipids on the survival of monocytes derived from children (91) and binding of IL-2 to its receptors (92). On the other hand, in vivo studies in paediatric patients did not reveal adverse effects of lipid emulsions on complement factors (93) or polymorphonuclear leukocyte function (94,95).

Whereas Dahlstrom et al. (62) did not find an impairment of monocyte activation and complement factors in children on long term PN, Okada et al. found decreased whole blood bactericidal activity in infants on long term PN (96). However, it was not possible to differentiate between the effect of lipid emulsions and other components of the PN solution.

There are concerns that the administration of lipid emulsions may increase the risk of coagulase-negative staphylococcal bacteraemia in premature infants (97,98), possibly by a contribution of lipid emulsions to survival and growth of coagulase-negative staphylococci on contaminated catheters (99). Although this issue has not been settled conclusively, it appears that the nutritional benefits of intravenous lipid administration outweigh the potential risks.

Statement

- The nutritional benefits of the use of lipid emulsions seem to outweigh the potential risks of adverse effects on the immune system. **LOE 4**

Carnitine

Carnitine facilitates the transport of long-chain fatty acids across the mitochondrial membrane, and thus makes them available for beta-oxidation (100). Carnitine is present in human milk and cows' milk formulae, but currently PN solutions do not contain carnitine. Carnitine is synthesized in the liver and kidney from lysine and methionine, both of which are essential amino acids (101). Controversy exists as to the need to provide a source of carnitine to infants receiving total PN. Tissue carnitine stores of newborn infants fewer than 24 hours of age show a positive correlation with gestational age (102). It has been calculated that the skeletal muscle carnitine pool in the adult is four times larger than that of a term infant, and 10 times larger than that of the very premature infant, on a per kilogram body weight basis (103,104). Both gestational age and exogenous carnitine supply affect tissue carnitine reserves, and infants receiving carnitine-free PN are not able to synthesize enough carnitine to maintain body stores (105,106). Studies evaluating carnitine supplementation in infants and children have yielded controversial results. Carnitine levels decrease during prolonged carnitine-free PN, especially in small preterm infants (103) (LOE 1). However, a Cochrane-based meta-analysis showed no benefit of parenteral carnitine supplementation on lipid tolerance, ketogenesis or weight gain in neonates requiring PN (53) (LOE 1). Carnitine supplementation should be considered on an individual basis in infants exclusively on PN for more than 4 weeks (107,108).

Statements and Recommendations

- Decreased levels of carnitine occur during prolonged PN without carnitine supplementation. **LOE 1**
- There is no documented benefit of parenteral carnitine supplementation on lipid tolerance, ketogenesis or weight gain of neonates requiring PN. **LOE 1**
- Carnitine supplementation should be considered on an individual basis in patients receiving PN for more than 4 weeks. **GOR D**

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5. Carbohydrates

METHODS

Literature Search

Medline search, Pub-Med search.

Timeframe: publications from 1983 to February 2004.

Type of publications: e.g. *original papers, meta-analyses and overviews.*

Key Words: children, PN, Glucose, carbohydrate, energy-resource, insulin.

Language: English and French.

CARBOHYDRATES

Introduction

Carbohydrates are the main source of energy in nutrition and usually provide 40–60% of the energy supply in western diets. The majority of the carbohydrate derived from a normal diet reaches the body's peripheral tissues as glucose. Glucose is utilised by all cells and serves as metabolic fuel for muscle, liver, heart, kidneys and gut and as the obligate energy source for brain, renal medulla and erythrocytes. Glucose is the main carbohydrate utilised during foetal life; about 7 g/kg per day (approximately 5 mg/kg per minute) of glucose crosses the placenta in the last trimester of pregnancy.

The major source of non-protein calories in parenteral nutrition (PN) is D-Glucose (dextrose), which is provided in the monohydrate form for intravenous use. Dextrose usually contributes most of the osmolality of the PN solution.

By considering the consequences of excessive glucose intake during PN, and by taking into account the rate of glucose production and oxidation, it is possible to establish recommendations. Energy provision during PN includes the use of intravenous fat emulsions (IVFE) (see Lipids chapter). IVFE provide a concentrated source of calories with a low osmotic load (2.0 kcal/ml for a 20% emulsion, compared to about 0.8 kcal/ml for a 20% dextrose solution). The optimal glucose/lipid ratio remains to be defined. Glucose tolerance may be influenced by cyclical PN, metabolic status, acute illness and always requires careful monitoring.

Consequences of Overfeeding with Glucose

In the past, PN for adults, children and infants provided most of the energy as glucose, although it was not precisely known how much of the intravenously-administered glucose was oxidized.

When glucose is administered in excess of the amount that can be directly oxidized for energy production and glycogen, the excess is directed to lipogenesis thus promoting fat deposition (1,2). Restoration of fat stores may be a nutritional goal in patients with severe malnutrition, however excessive fat deposition may be deleterious. Whatever the situation, this conversion into lipids accounts, in part, for the increase in energy expenditure observed with high rates of glucose infusion (3).

Excessive glucose intake is thought to increase CO2 production and minute ventilation but few relevant data are available to support the clinical relevance (4–6). Total energy delivery as well as amino acid intake also contribute to increased CO2 production and minute ventilation (5,6).

Excessive glucose intake may also impair liver function especially by inducing steatosis, while its contribution to the development of cholestasis is not clearly established (7–9). Studies in normal adult volunteers suggest that high carbohydrate feeding leads to an increase in total VLDL triglyceride secretion rate from de novo synthesis, primarily due to stimulation of the secretion of preformed fatty acids (FA) (10). These results imply that the liver derives it's energy from carbohydrate oxidation rather than from FA oxidation, while FA taken up by the liver are channelled into VLDL triglycerides (10). Hepatic steatosis results when export of the VLDL triglycerides does not keep pace with triglyceride production (10,11). PN may be associated with insulin resistance, due to both the substrate infusion and the underlying disease (12,13).

Protein metabolism is influenced by the composition of energy intake in patients on PN (14–17). Lipid emulsion allows the energy input to be diversified, with a reduction in the consequences of excessive glucose supply. In adults, as well as in paediatric patients, the use of IVFE and/or the reduced glucose intake was shown to improve net nitrogen balance (14–17).

PN is associated with an increased risk of infectious complications compared with enteral feeding or no nutritional support. The most recent and largest meta-analysis of 27 studies in 1828 adult surgical patients confirmed that enteral feeding does carry a lower infective risk than PN, but at the cost of a non-significant trend towards increased complications. Overall, enteral feeding did not reduce mortality compared to PN (18). However,

failure to prescribe PN for malnourished patients who are unable to tolerate enteral feeds triples their risk of death (19).

Animal data suggests that hyperglycaemia might be a risk factor for infection. Hyperglycaemia in an animal model reduces the ability of lung macrophages to fight infection (20). Animal data suggests that infection reduces non-hepatic glucose utilisation and causes hyperinsulinism (21). High blood glucose levels in adult ICU patients are associated with increased infectious-related mortality (22).

Statements

- Excessive glucose intake may be responsible for hyperglycaemia. **LOE 1**
- Excessive glucose intake causes increased lipogenesis and fat tissue deposition together with subsequent liver steatosis and enhanced production of VLDL triglycerides by the liver. **LOE 2-3**
- Excessive glucose intake causes increased CO2 production and minute ventilation. **LOE 3**
- Excessive glucose intake causes impaired protein metabolism. **LOE 2-3**
- High blood glucose levels have been shown, in adult ICU patients, to be associated with increased infectious-related mortality. **LOE 2-3**

Rate of Endogenous Glucose Production and Rate of Glucose Oxidation

The efficiency with which glucose is used to meet energy needs should guide its relative contribution to PN regimens. Exogenous glucose delivered in excess of the rate of glucose oxidation may enter non-oxidative pathways and is unlikely to improve energy balance.

The majority of quantitative estimates of production and oxidation of glucose have been performed using stable isotopic tracers and indirect calorimetry in newborns, while only few studies are available for infants and children. Basal rate of glucose production (RGP) varies from 2 mg/kg per min in adults, to 8 mg/kg per min in preterm infants (or from 3 g/kg per day to 11.5 g/kg per day) (23–26). The RGP is maximal during the post natal period and decreases gradually with age.

Gluconeogenesis provides a significant amount of glucose, and is responsible for about 31% rate of glucose appearance in healthy full term newborns (23). A clinical trial of 20 preterm infants on PN (25) showed that these infants maintain normoglycaemia by glucose produced via gluconeogenesis as a result of glycerol delivery from fat metabolism. This suggests that not all the glucose has to be provided exogenously (25).

During PN, the rate of parenteral glucose delivery must be kept constant without exceeding the maximum rate of glucose oxidation (RGO), which differs significantly among patients according to their age and clinical status. During high rates of glucose infusion, there is a complete suppression of endogenous production of glucose, accompanied by hyperinsulinism and a respiratory quotient equal to 1.0. A linear relationship was shown in newborns between glucose intake and glucose utilization, measured by indirect calorimetry and glucose oxidation measured by stable isotopic tracers (24).

In appropriate for gestational age-preterm infants, the RGO does not exceed 6 to 8 mg/kg per min (9.5 g/kg per day) after birth (27,28) while in term surgical infants or infants on long-term PN, the maximal RGO is about 12 mg/kg per min (18 g/kg per day) (29,30). A study in critically burned children, demonstrated the maximal RGO to be 5 mg/kg per min, which is below caloric requirements (31). The clinical approach is probably to exercise restraint in the delivery of glucose in critically ill children. While estimations of caloric requirement for children often include a component to support growth, this may not be a reasonable goal in a child receiving acute care for severe injury or illness. Except for preterm infants, one could consider that maximal RGO is continuously decreasing from birth to adulthood taking into account the brain to total body weight ratio and the brain glucose consumption.

Thus glucose intake should be adapted to age and clinical situation e.g. premature babies, infants and children, critically ill patients and severe malnutrition.

Statements and Recommendations

- Production of glucose varies from 2 mg/kg per min in adults to 8 mg/kg per min in preterm infants (or from 3 g/kg per day to 11.5 g/kg per day). **LOE 2**
- In preterm infants glucose infusion should be started with 4–8 mg/kg per min. **GOR C**
- Maximal glucose oxidation in preterm infants is 8.3 mg/kg per min (12 g/kg per day) after birth. **LOE 2-3**
- In critically ill children glucose intake should be limited to 5 mg/kg per min (7.2 g/kg per day). **GOR D**
- Glucose administration to full term neonates and children up to 2 years of age should not exceed 18 g/kg per day (13 mg/kg per min). **GOR C**
- Variations in glucose intake according to age and clinical situation (e.g. malnutrition, acute illness, drug administration) should be considered. **GOR D**
- Glucose intake should be adapted in case of simultaneous administration of drugs known to impair glucose metabolism such as steroids, somatostatin analogs, tacrolimus. **GOR C**
- The recommended glucose supply is shown in Table 5.1. **GOR D**

TABLE 5.1. *Recommended parenteral glucose supply (g/kg body weight and day)*

	Day 1	Day 2	Day 3	Day 4
Up to 3 kg	10	14	16	18
3–10 kg	8	12	14	16–18
10–15 kg	6	8	10	12–14
15–20 kg	4	6	8	10–12
20–30 kg	4	6	8	<12
>30 kg	3	5	8	<10

- These recommendations need to be adapted to the clinical situation (e.g. refeeding syndrome in severe malnutrition) to oral and/or enteral energy intake and to the required weight gain for normal or catch up growth. **GOR C**
- It is important, especially when prescribing PN for infants, to accurately evaluate the carbohydrate load provided by concurrent infusion therapy. **GOR C**
- In critically ill and unstable patients, it is reasonable to start with lower amounts of carbohydrates and increase the amounts according to the patient's condition. Metabolic complications associated with a more rapid introduction of carbohydrate may be uncommon in more stable patients, and this approach can be an exercised if blood glucose is closely monitored. **GOR C**

Glucose/Fat Ratio

Substitution of part of the glucose calories with fat derived calories avoids the undesirable effects reported with glucose-based PN. Studies performed in infants or neonates have assessed glucose and fat utilization (32–35). In infants, it was possible to study the optimal glucose infusion rate by using five isocaloric PN regimens differing in their glucose/lipid ratio (32). Fat infusion aiming at a significant contribution to the coverage of energy expenditure requires that glucose oxidation be equal to or lower than maximal oxidative glucose disposal. For maximal lipid infusion rates see chapter on Lipids.

Recommendation

- Glucose intake should usually cover 60–75% of non-protein calories. **GOR C**

Cyclical Parenteral Nutrition

The term cyclical PN refers to the administration of intravenous fluids intermittently with regular discontinuation of infusion (36). Most available data comes from studies performed in stable adult patients on long-term PN (37–40). Cyclical PN is well established with documented tolerance in children (41–44). However cyclical PN may lead to high glucose infusion rates with subsequent hyperglycaemia, and an increased risk of hypoglycaemia upon discontinuation.

In clinical practice, cyclical PN may be performed as soon as clinical status permits. Maximal glucose infusion rate should not exceed 1.2 g/kg per hour, and the rate of infusion should be increased in a stepwise manner. Such a stepwise adaptation of infusion rate will not only avoid glucose overload but also hyperosmotic load from electrolytes. A similar stepwise reduction of infusion rate is also recommended at PN discontinuation to avoid hypoglycaemia (45).

Advantages of cyclical PN include:

1. Alternating fasting and feeding periods allows for changes in the insulin/glucagon balance and reduces lipogenesis in both adipose tissue and liver.
2. Physical activity during the day that is beneficial for protein synthesis and growth as well as psychologic behaviour (46). In that regard, advantages in terms of nitrogen balance were never shown in the conditions of the experiments in humans.
3. Cyclic PN might lower the risk for the development of liver disease. In a prospective study (47), involving adults on PN exhibiting various degrees of presumed PN-associated liver disease, patients who developed hyperbilirubinemia were randomized to either remain on continuous PN or were placed on cyclic PN. Patients with initial serum bilirubin less than 20 mg/dl, who remained on continuous PN, had a significant rise in serum bilirubin compared with the cyclic PN groups. There was no apparent advantage of cyclic PN in patients with serum bilirubin greater than 20 mg/dl. Similar studies in paediatric patients are not available.

Recommendations

- Cyclical PN is well tolerated and may be used from 3–6 months of age. **GOR C**
- In cyclical PN the maximal rate of glucose infusion may exceed glucose oxidation rate. The maximal infusion rate should not exceed 1.2 g/kg per hour (20 mg/kg per min). **GOR C**
- A stepwise increase and decrease of glucose infusion rates at onset and at discontinuation of the infusion respectively should be considered to avoid hyper- and hypoglycaemia. Glucose tolerance should be monitored. **GOR D**

Monitoring and Use of Insulin

PN may be associated with insulin resistance, due to both the substrate infusion and the underlying disease. Animal studies suggest that a PN adapted state is reached

in long term PN, where liver glucose uptake is unresponsive to rises in insulin above basal level (21).

Particular attention must be paid to glucose tolerance (hyperglycaemia, glycosuria) at the time of starting cyclic PN, since decreasing the duration of infusion may lead to excessive increase in the glucose rate of delivery. Osmotic diuresis may cause water and electrolyte depletion. In patients on stable long-term PN, glycosuria may indicate a stressful event, particularly infection, which impairs sensitivity to insulin (48).

Some children receiving PN have abnormal glucose tolerance (13). Insulin secretion and sensitivity were measured in 12 patients; the insulin response to sustained hyperglycaemia was stronger in children with normal glucose tolerance while receiving cyclic PN. Two patients with abnormal glucose tolerance showed decreased capacity to release insulin. Whole body glucose disposal was greater in younger than older children (range 7.1–25.2 mg/kg per min) ($p < 0.01$) (13).

A study in adult ICU patients showed that by using insulin to control blood glucose between 80–110 mg/dl, mortality in the ICU was reduced from 8 to 4.6%, overall in-hospital mortality was reduced by 34% and bloodstream infections by 46% (49). The message in adults, in ICU, is to keep glucose infusion below 4 mg/kg/min and manage hyperglycaemia with insulin. However, these data have to be confirmed in children, and therefore no firm recommendation can be made. Also, pre-term infants given insulin respond variably to insulin and may develop profound hypoglycaemia.

Recommendations

- Hyperglycaemia causing marked glycosuria should be avoided. **GOR D**
- Hypoglycaemia (<2.5 mmol/l, [<50 mg/dl]) should be avoided. **GOR D**
- Insulin infusion may be used in VLBW infants with hyperglycaemia while on PN, but the safety and the effects on clinical outcome are presently unknown. **GOR D**
- The use of insulin should be restricted to conditions where reasonable adaptation of glucose infusion rate does not control marked hyperglycaemia. **GOR D**

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Journal of Pediatric Gastroenterology and Nutrition
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6. Fluid and Electrolytes (Na, Cl and K)

METHODS

Literature Search

Timeframe: publications from 1969 until 2004.

Type of publications: original articles, case series, case-control studies, and overviews.

Key Words: Neonate, Preterm infants, Infants, Children, Fluids, Sodium, Potassium, Chloride.

Language: English, German.

BACKGROUND

Water is an essential carrier for nutrients and metabolites, and it comprises the major part of human body mass at any age. Water and electrolyte requirements per unit body mass are very high after birth and decrease with age until adulthood. Most published studies on the adaptation processes of water and electrolyte metabolism relate to the preterm neonate, while studies on water and electrolyte metabolism in older paediatric patients are limited. Therefore, recommendations for children are often based on extrapolations from data in neonates and adults.

Neonatal Period

The amount of total body water (TBW) decreases markedly from intrauterine life to adulthood: water contributes to 90% of body weight in the 24 weeks old foetus, 75% in term infants, and 50% in adults (1,2). During intrauterine life body water content decreases along with the relative increase of fat mass particularly during the third trimester of gestation (3). Water turnover is high in neonates and decreases with increasing age and the concomitant decreases of metabolic rate and growth velocity (4–6).

Water turnover, like energy turnover, is related to lean body mass (LBM) but has no close relationship to body fat mass (FM). Extremely low birth weight infants (ELBW) and very low birth weight (VLBW) infants have relatively low body fat contents and a higher percentage of LBM and of body water than older infants, which is related to high water turnover.

Total body water is divided into two compartments: intracellular fluid (ICF) and extracellular fluid (ECF). Potassium (K+) is the major ion of the ICF, and its intracellular concentration depends on the Na/K-ATPase activity which is impaired at insufficient supplies of oxygen and energy (7). Premature infants are vulnerable to imbalances between intra- and extracellular compartments. The total volume of intracellular water increases with the number and size of body cells during body growth. ECF is subdivided into intravascular and extravascular components as well as a "third space" which characterises free fluid in preformed body compartments under physiological (like urine in the bladder, cerebral spinal fluid, etc) and pathological conditions (like ascites, or pleural effusions). The major ion of ECF is sodium (Na^+). ECF decreases during growth. Blood volume in neonates is 85–100 ml/kg body weight compared to 60–70 ml blood volume/kg body weight in adolescents and adults (8).

In the assessment of fluid balance, metabolic water production may be of particular importance in paediatric patients because of their high metabolic rates. Endogenous water production equals 0.6 ml H_2O per gram of carbohydrates, 1.0 ml H_2O per gram of fat and 0.4 ml H_2O per gram of protein oxidised (9). A daily weight gain of 15 g/kg in a neonate results in a net storage of about 12 ml of water and approx. 1.0–1.5 mmol Na^+ per kg body weight per day.

Immediate adaptation processes after birth affect the metabolism of water and electrolytes as a result of discontinuation of placental exchange and the onset of considerable insensible water loss and thermoregulation. Subsequent adaptation includes the onset of autonomic renal regulation of fluids and electrolytes, and intake of fluids and other nutrients.

The time course of adaptation may be divided into three major phases:

- Phase I: transition. The immediate postnatal phase is characterised by a relative oliguria (10) followed by a diuretic phase, during which body fluid compartments are rearranged by isotonic or hypertonic (i.e. hypernatraemic and hyperchloremic) contraction (duration hours to days). These changes are caused by considerable evaporative water loss via the immature skin as well as by continuing natriuresis (as present during foetal life) (11). Phase I usually ends when maximum weight loss has occurred. The generally accepted water loss is up to 10% of body weight.
- Phase II: the intermediate phase is characterized by diminished insensible water loss along with increasing cornification of the epidermis, a fall in urine volume to less than 1–2 ml/kg per hour, and a low sodium excretion.
- Phase III: stable growth is characterized by continuous weight gain with a positive net balance for water and sodium.

Many of the regulatory processes involved have limitations in paediatric patients because of immaturity or limited efficacy in infants and children. The renal glomerular surface area available for filtration is small in preterm and term neonates compared to that in older infants and adults (12). In term infants, GFR increases significantly during the first week of life (13) and continues to rise over the first two years of life (14). Immaturity of the distal nephron with an anatomically shortened loop of Henle lead to reduced ability to concentrate urine (15). Maximum urinary concentrations are up to 550 mosm/l in preterm infants, and 700 mosm/l in term infants, compared to 1200 mosm/l in adults (16). Neonates may be placed at risk for volume depletion when a high renal solute load cannot be compensated for by the ability to produce concentrated urine. Although hormonal factors i.e. renin-angiotensin-aldosterone system (RAAS), and arginine-vasopressin (AVP) are mature early in gestation, the effects are limited by renal immaturity (17). A lower plasma oncotic pressure and higher permeability of the capillary wall in preterm infants compared to term infants and adults (18) enhances the shift of water from the intravascular to the interstitial compartment, with an increased risk of oedema especially under pathologic conditions such as sepsis (19).

Sodium (Na^+) is the principal cation of the extracellular fluid and modulates the maintenance of the intravascular and interstitial volumes. Sodium intake can influence the ECF volume. Sodium excretion occurs primarily through urine, but also through sweat and faeces.

Chloride (Cl^-) is the major anion of the extracellular fluid occurring in plasma, lymph, connective tissue, cartilage and bone. The exchangeable chloride remains relatively constant per unit of body weight at different ages. The intake and output of chloride usually parallels that of sodium, but external losses and excretion can occur independently, mainly in equilibrium with bicarbonate status. The daily turnover of chloride is high. Renal conservation occurs with tubular reabsorption of 60–70% of the filtrated chloride.

Potassium (K^+) is the major intracellular cation, and the potassium pool correlates well with the lean body mass. Ten percent of the potassium body pools are not exchangeable (bone, connective tissue, cartilage). The potassium intake varies widely. Extracellular potassium concentration is not always related to intracellular concentration.

In neonates, faecal sodium losses depend on gestational age and amount to about 0.1 mmol/kg body weight per day in premature infants and 0.02 mmol/kg per day in term infants. Faecal potassium losses are about twice as high as sodium losses, but show no relation with gestational age (20). Additional losses may occur under pathological conditions e.g. bowel obstruction, ileostomy, pleural effusions, peritoneal drainage, and external cerebrospinal fluid drainage. In these circumstances the electrolyte content of lost fluids cannot be predicted precisely. In the clinical setting it is a good routine to measure at least once the sodium concentrations of such fluid losses in order to replace them (chloride usually correlates with sodium losses). Potassium losses are usually much smaller because of the mainly intracellular distribution.

Extra needs for accretion of body mass during growth periods require an adequate supply of electrolytes. A mean growth rate of 15 g/kg body weight per day results in a net storage of about 1.0–1.5 mmol Na^+/kg body weight per day in neonates. It has been shown that restricted administration of sodium impairs longitudinal growth and weight gain in otherwise healthy preterm infants (21). The growth rate decreases with age. There are limited experimental data about the water and electrolyte needs in older children. In a balance study, Fusch et al. estimated a sodium requirement of 2.7 mmol/kg body weight per day. The authors expected an overestimation of sodium requirement in the investigated paediatric patients and assumed an even lower requirement (22). It may be of importance that some drugs (benzylpenicillin) and mineral salts (phosphates) may contain considerable amounts of cations because they are prepared as the sodium or potassium salts.

Phase I/Transition

The goals for fluid and electrolyte administration during this period are to:

- allow contraction of ECF (without compromising intravascular fluid volume and cardiovascular function) with negative water balance of not more than 10%.
- allow a negative net balance for sodium of 2–5 mmol/kg per day for the first postnatal days, to maintain normal serum electrolyte concentrations.
- secure a sufficient urinary output and avoid oliguria ($<$0.5–1.0 ml/kg per hour) for longer than twelve hours,
- ensure regulation of body temperature by providing enough fluid for transepidermal evaporation.

The range of fluid load neonates can deal with during phase I in healthy preterm infants (29–34 weeks gestational age), range from 96 to 200 ml/kg per day from the third day of life ((23) (LOE 2+)) but rarely exceed 130 ml/kg per day. The needs for fluid intake are dependent on birth weight and increase daily (see Table 6.1). Electrolyte administration during the first 3–5 days also depends on maturity and birth weight.

Sodium intake should be restricted in VLBW infants during the period of ECF contraction until a weight loss of approximately 6–10% has occurred. A restricted sodium intake has positive effects on oxygen requirements and the risk of later bronchopulmonary dysplasia ((24) (LOE 2++)). However, there is also evidence that sodium restriction induces higher risk to develop hyponatraemia ((25) (LOE 2−)), which has been associated with brain pathology (pontine myelinolyosis) ((26) (LOE 3)).

TABLE 6.1. *Parenteral fluid and electrolyte intake during the first postnatal week*

Days after birth	Recommended fluid intake (ml/kg body weight per day)					
	1st day	2nd day	3rd day	4th day	5th day	6th day
Term neonate	60–120	80–120	100–130	120–150	140–160	140–180
Preterm neonate >1500 g	60–80	80–100	100–120	120–150	140–160	140–160
Preterm neonate <1500 g	80–90	100–110	120 –130	130–150	140–160	160–180
Recommended Na^+, K^+, Cl^- supply (mmol/kg body weight per day)						
*Na^+	0–3 (5)					
**K^+	0–2					
Cl^-	0–5					

The expected weight loss is depends on treatment conditions (fluid intake) and environmental factors (humidity etc.).
*Careful adjustment of water and electrolyte administration is needed in ELBW infants at onset of diuresis and in polyuric patients.
**K^+ supplementation should usually start after onset of diuresis.

A review of four randomized clinical studies with different levels of fluid intake during the first week of life concluded that fluid restriction reduces the risk of patent ductus arteriosus, necrotising enterocolitis, and death, and tended to reduce the risk of bronchopulmonary dysplasia (n.s.) and to increase the risk of dehydration (n.s.) ((27) (LOE 1+)).

Phase II: The Intermediate Phase

The goals for fluid and electrolyte administration during phase II are to:

- replete the body for electrolyte losses, replace actual water and electrolytes.
- augment oral feedings.

Phase III: Stable Growth

The goals for fluid and electrolyte administration during phase III are to:

- replace losses of water and electrolytes (maintain water and electrolyte homeostasis).
- provide enough extra water and electrolytes to build up new tissue at intrauterine growth rates.

The recommended fluid intakes in phase II (Table 6.2) are based on studies suggesting that a daily fluid intake equal to or higher than 170 ml/kg body weight per day is accompanied by high urinary sodium excretion with negative sodium balance, even if Na^+ intake is as high as 10 mmol/kg body weight per day ((28) (LOE 3)). Fluid therapy in ELBW in excess of 200 ml/kg/d does not maintain Na^+ balance, regardless of the amount of NaCl provided. It is important to note that ELBW infants require more fluids than recommended during the first week of life for term infants, because of high insensible water loses ((29) (LOE 3)). Evaporation of water from upper respiratory passages accounts for approximately one third of net insensible water loss (30) and reaches the level of 0.8–0.9 ml/kg body weight per hour in premature infants, 0.5 ml/kg body weight per hour in term neonates ((31) (LOE 3)), 0.4 ml/kg body weight per day in older children and 0.3 ml/kg body weight per day in adolescents ((32) (LOE 3)).

Urinary output may be as high as 6.0 ml/kg per hour of free water in the presence of a total urine production of 9.8 ml/kg per hour in preterm infants with birth weight 2000 g (33). Fluid requirements during the phase III (Table 6.3) are related to the expected weight gain.

Water loss from stool is negligible in early life prior to establishing enteral feeding in premature infants. When full enteral feeding is achieved, faecal losses of 5–10 ml/kg per day are usually assumed to balance metabolic water production (34). Plasma Na^+ concentrations are normal in infants with sodium intakes of 1.1–3.0 mmol/kg body weight per day and fluid intakes of 140–170 ml/kg body weight per day with no relation of growth rates to sodium intake within these ranges ((35–38) (LOE 2–3)).

TABLE 6.2. *Parenteral fluid and electrolyte intake for newborn infants during the intermediate phase prior to the establishment of stable growth*

Birth weight	Fluid intake (ml/kg body weight per day)	Na^+ intake (mmol/kg body weight per day)	K^+ intake (mmol/kg body weight per day)	Cl^- intake (mmol/kg body weight per day)
Term neonate	140–170	2.0–5.0	1.0–3.0	2.0–3.0
>1500 g	140–160	3.0–5.0	1.0–3.0	3.0–5.0
<1500 g	140–180	2.0–3.0 (5)	1.0–2.0	2.0–3.0

TABLE 6.3. *Parenteral fluid and electrolyte intake for infants during the first month of life with stable growth*

	Fluid intake (ml/kg body weight per day)	Na^+ intake (mmol/kg body weight per day)	K^+ intake (mmol/kg body weight per day)
Term neonate	140–160	2.0–3.0	1.5–3.0
Preterm neonate	140–160	3.0–5.0 (7.0)	2.0–5.0

There is evidence that fluid intake lower than 140 ml/kg body weight day, together with Na^+ intake of about 1 mmol/kg body weight per day, is adequate to maintain sodium balance in ELBW neonates ((39–44) (LOE 2–3)). There is no increase in morbidity among infants given less Na^+ and less fluid. There was a non significant trend to higher incidences of patent ductus arteriosus and bronchopulmonary dysplasia in infants given more Na^+ and a higher fluid intake ((45,46) (LOE 2–3)).

Breast-fed term infants need as little as 0.35 to 0.7 mmol/kg body weight per day of Na^+ during the first 4 months of life to achieve adequate growth ((47) (LOE 3)). A recommendation to provide 1.0 to 2.0 mmol/kg per day of NaCl should counter-balance incidental losses from skin or gastrointestinal tract. In preterm infants, a higher growth rate explains a higher sodium requirement.

Preterm infants retain about 1.0 to 1.5 mmol/kg body weight per day K^+, which is about the same as foetal accretion ((48) (LOE 3)). The amount of potassium usually recommended is similar to the amount provided in human milk, about 2 to 3 mmol/kg per day (49).

Environmental factors influence insensible fluid loss:

- Double wall incubators reduce insensible water loss in VLBW neonates by about 30% when a humidity of 90% is used at thermo-neutral temperature. With maturation of the epidermal barrier it is possible to reduce ambient humidity step by step commonly after the first 5 days of life (50).
- The use of waterproof coverings (such as plastic films, plastic blankets, and bubble blankets) in addition to treatment in a double wall incubator leads to further reduction of insensible water loss by 30–60% (51).
- The use of radiant warmers or single wall incubators for VLBW care may increase water loss and impair thermoregulation (52).
- The use of emollient ointments decreases insensible water loss of up to 50% in open care conditions (53,54).
- Endotracheal intubation and mechanical ventilation using warmed and humidified air significantly reduce insensible respiratory water (55) and the needs for fluids are reduced by 20 ml/kg body weight per day.

In summary the treatment strategy during the adaptation of neonates to extrauterine life is:

- to expect decrease of body weight during the first 3–5 (max. 7) days after birth.
- to maintain normal serum electrolyte concentrations.
- to avoid oliguria $<$0,5 ml/kg body weight per hour for 8–12 h.

INFANTS BEYOND NEONATAL PERIOD AND CHILDREN

Recommendations for sodium intake range from 1 to 4 mmol/kg body weight per day ((56–58) (LOE 3)).

Requirements on electrolytes for infants and children are based on empirical evidences and are set on the level of 1–3 mmol for sodium and 1–3 mmol of potassium required per intake of 100 kcal ((59) (LOE 3)). The lower limit of intravenous sodium and potassium intake is in agreement with the Codex Standard for Infant Formula (60). The empirical recommendations for sodium and potassium intake in children do not exceed 3 mmol/kg body weight per day (LOE 4) (Table 6.4).

Electrolytes, urea and other substances constitute urine osmotic load. High nitrogen and energy supply with parenteral nutrition require sufficient water supply as the vehicle for nutrient delivery. Recommended fluid volume for paediatric patients beyond the neonatal period is provided in Table 6.5.

Water requirements in infants and young children depend on the rate of exchange of total body water which is more rapid than later in life and influence maintenance water requirements. Daily maintenance fluid requirement is a function of total caloric expenditure at rest; for infants below 10 kg of body weight it equals about 100 ml/kg body weight per day. Children with a body weight of 11–20 kg should receive 1000 ml + 50 ml/kg for each kg body weight above 10 kg, and children with a body weight above 20 kg 1500 ml + 20 ml/kg for each kg above 20 kg ((59) (LOE 3)).

Total water requirements consist of the maintenance needs, replacement of ongoing losses (insensible water loss, urinary losses, and stool losses) and, in particular situations, replacement of deficits. Insensible water loss from the skin and lungs is an energy costly procedure and

TABLE 6.4. *Parenteral electrolyte intake for infants after the first month of life and for children*

Electrolyte	Infants	Children $>$1 year
Na^+ (mmol/kg body weight per day)	2.0–3.0	1.0–3.0
*K^+ (mmol/kg body weight per day)	1.0–3.0	1.0–3.0

*K^+ supplementation should usually start after onset of diuresis.

TABLE 6.5. *Parental fluid intake for term infants after the first month of life and for children*

Age	Fluid intake (ml/kg body weight per day) (maximal volumes in brackets)
Term infants from the second month of life	120–150 (180)
1–2 years	80–120 (150)
3–5 years	80–100
6–12 years	60–80
13–18 years	50–70

consumes one fourth of the overall caloric expenditure, with loss of 1 ml of water related to energy needs of 0.5 kcal.

Urine osmotic load results from protein catabolism and electrolyte excretion, but is little affected by carbohydrate and fat metabolism which produce metabolic water and CO2. Water requirements increase with fever, hyperventilation, hypermetabolism and gastrointestinal losses and decrease in renal failure and congestive heart failure.

MONITORING OF PARENTERAL FLUID AND ELECTROLYTE TREATMENT

A monitoring protocol should be adapted to the individual patient's needs. Monitoring intervals depend on clinical status, underlying pathophysiology, medications and treatment modalities. Indications of changes of hydration and electrolyte status may include:

- clinical status of the patient
- body weight and body composition
- fluid balance
- blood electrolyte concentrations and acid base status
- haematocrit and blood urea nitrogen
- urine specific gravity, urine electrolytes
- water intake and excretion

In parenterally fed infants and children, serum electrolyte concentrations and weight are usually monitored daily for the first days of treatment; then the monitoring intervals are adapted depending on the clinical status and the stability of the patient's condition.

Recommendations

It is emphasized here that needs of individual patients may deviate markedly from the ranges of intakes recommended here, depending on clinical circumstances such as fluid retention, dehydration or excessive water losses.

Preterm and Term Infants During the Transition Phase

A gradual increase of fluid volume in preterm and term neonates is recommended. Sodium, chloride and potassium should be supplemented in the first 3–6 days after birth, i.e. in phase I (transition) when contraction of extracellular fluid compartment occurs. Na^+ supplementation may start after the first 2 days under monitoring of serum electrolytes levels has shown in Table 1. **GOR D**

Preterm and Term Infants During the Stabilisation Phase

Phase II (stabilisation) when extracellular fluid compartment contraction is completed may vary in duration from about 5–15 days and is completed when birth weight is regained and the kidneys produce more concentrated urine. Expected weight gain is 10–20 g/kg body weight per day (Table 2). **GOR D**

Preterm and Term Infants During the Phase of Established Growth

During phase III (established stable growth) the aim is to match physiological growth rates. Chloride supplementation follows sodium and potassium. Expected weight gain is 10–20 g/kg body weight per day (Table 3). **GOR D**

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Journal of Pediatric Gastroenterology and Nutrition
41:S39–S46 © November 2005 ESPGHAN. Reprinted with permission.

7. Iron, Minerals and Trace Elements

METHODS

Literature Search

Timeframe: 1990–2004, in addition relevant earlier publications were considered.

Type of publications: randomised controlled studies; case-control or cohort studies; case reports; case series; expert opinion.

Key Words: calcium, chromium, copper, iodine, iron, manganese, magnesium, molybdenum, newborn, parenteral nutrition, phosphorus, selenium, trace elements, zinc.

Language: English.

IRON

Introduction

Iron is not routinely provided in parenteral nutrition mixtures and is often not a component of commercially available trace element preparations. Currently there are no well-defined recommendations regarding the optimum content of iron in parenteral feeds, and intravenous administration of iron remains problematic. One major concern is that of iron overload. Parenteral administration of iron bypasses the homeostatic control of gastrointestinal iron absorption, causing loss of protection from iron overload if excessive quantities are provided. An accumulation of excess iron has been reported in children receiving prolonged parenteral nutrition. In a study of 30 children aged 1–18 years receiving ferrous sulphate 100 μg/kg per day for an average period of 43 months, 12 children showed evidence of plasma and hepatic iron overload. Ferritin concentrations were >800 ng/ml in eight children (>1100 ng/ml in five) and correlated with duration of PN. The degree of iron deposition in either hepatocytes or Kupffer cells was most pronounced in children with the higher ferritin concentrations ((1) (LOE 2+)). Thus, iron status of children receiving long-term PN should be monitored by regular measurement of serum ferritin, and supplementation decreased if ferritin concentration is raised. Although Ben-Hariz et al suggested halving iron intake at ferritin concentrations of 500 ng/ml and stopping completely at 1000 ng/ml, these concentrations probably leave only a small margin of safety. There is, therefore, an argument for curtailing iron supplementation at lower plasma ferritin concentration.

A further concern over parenteral iron administration is that it may impair immune function and stimulate bacterial growth thus increasing the risk of infection by iron-requiring pathogens (2). Iron availability correlates with bacterial growth and virulence, facilitates viral replication and reverses the bactericidal effect of lactoferrin and lysozyme (3,4). Furthermore, the antibacterial effect of cytokines is mediated by intracellular iron depletion. Interferon, IL-1, and tumour necrosis factor enhance ferritin synthesis resulting in a shift of cellular iron into a storage compartment and downregulate transferrin receptor production decreasing cellular iron uptake and, thereby, iron availability for intracellular pathogens (5). Iron therapy has also been implicated in decreased phagocytosis and inhibition of CD4 and CD8 helper T cell proliferation while enhancing the function of suppressor T cells (6). Yet, several components of the immune response are depressed in iron deficiency. An impaired capacity for the generation of the oxidative burst has been observed in phagocytes from iron deficient children (7). McFarlane et al studied 40 children with kwashiorkor and low serum transferrin given nutritional support including iron supplements. Many of the children who received iron therapy died shortly after supplements were begun suggesting that provision of iron in a setting of low transferrin may have resulted in higher circulating free iron that could have contributed to the development of overwhelming infection and death (8). Septicaemia with Yersinia enterocolitica has been reported in healthy children overdosed with oral iron (9). Nevertheless, there is little clinical evidence that iron supplementation in parenterally fed children increases the risk of sepsis (10).

Adverse drug reactions associated with parenteral iron therapy are common, although side effects are mild and self limiting ((11,12) (LOE 2+)). In various series 2–5% of patients experience significant side effects. The processes leading to iron dextran induced symptoms are unclear, but include a type I (IgE-mediated) anaphylactic reaction which is caused by preformed dextran antibodies. Additional mechanisms include a type I anaphylactoid reaction that may be caused by transient overload of the transferrin molecule resulting in small amounts of free iron in the circulation (which appears to be dose related) and immune complex activation by specific IgG antibody. Symptoms include dyspnoea, wheezing, hypotension, nausea, vomiting, abdominal pain, arthralgia and myalgia. Most side-effects are mild and self-limiting with severe reactions occurring in a minority of patients and in conjunction with infusion of larger iron doses. An increased incidence of adverse effects has been reported in patients with collagen diseases. Despite previous

episodes of allergic reactions safe administration of iron dextran is possible following a pre-treatment protocol of methylprednisolone, diphenydramine and ephedrine. While total dose infusions of iron dextran may be associated with allergic manifestations the administration of the standard maintenance doses (estimated at 1–2 mg/day up to 10–15 mg/day) may be well tolerated (11,13).

There is a paucity of studies on the effects and complications of intravenous iron in children. No adverse effects were reported in 14 children who received 15 mg/kg of iron dextran during a two hour period (13), in 2 children who received IV iron at a dose of 250–500 mg at an infusion rate of a 100 mg/min (14), or in 5 premature infants given iron dextran at a dose of 10–450 μg/kg per day (15). Similarly, no complications were observed in a study of 14 very low birth weight infants receiving IV iron supplementation at a dose of 200–250 μg/kg per day ((16) (LOE 1+)).

The ability of iron both as Fe^{3+} (bound form) or Fe^{2+} (free iron) to generate free oxygen radicals has also raised concerns regarding safety. In addition, parenteral lipid emulsion also generates peroxides (17). The rich content of double bonds of the lipid emulsion makes it a good substrate for iron-induced peroxidation. Light induced generation of peroxides in PN solutions and the interaction of iron complexes (iron dextran) with photons or substrates of photo-oxidation, such as vitamins or polysorbate, could explain the unexpected observation that bound iron is protective against spontaneous peroxide generation in PN solutions (18).

The compatibility of iron with PN solutions has not been clearly established. Iron dextran cannot be added to lipid emulsions or all-in-one mixes as it results in destabilisation of the emulsion. Compatibility of iron dextran has been shown in amino acid-glucose solutions for up to 18 hours (19). Ferrous citrate is also compatible with PN solutions, with no observed precipitation during infusion periods of 18–24 hours (20).

Whether or not there is a need for routine iron supplementation of PN remains controversial. A special concern is the low birth weight infant because of possible increased risk of infection observed following intramuscular iron (21). Arguments in favour of iron supplementation in VLBW infants include their low iron stores, rapid growth rate, increased requirements for iron when erythropoesis resumes at approximately 2 months of age, and caution required in relation to repeated blood transfusion. It has been estimated that these newborns need 700 to 1000 μg/kg per day to reach iron balance (15,16) although considerably lower doses may suffice ((22) (LOE 4)); possibly erythropoeitin is needed to use the iron administered. In term infants receiving PN it is estimated that the daily parenteral iron requirement is 100 μg/kg per day (22). Although iron reserves should be adequate to supply red cell production for 3–5 months, iron deficiency has been shown to develop much sooner. How early parenteral iron supplements should be commenced in infants and children receiving PN will depend on the underlying pathology and degree of blood loss. In short term PN of a few weeks no adverse effects resulting from lack of iron supplementation have been observed (10). During long-term PN the child's iron status should be monitored closely and supplementation begun as soon as impending deficiency is identified.

In summary, iron supplementation with iron dextran added to amino acid-glucose solutions can be safely administered at maintenance doses. Preterm infants require parenteral iron but may also require erythropoietin for utilisation. Term infants and older children probably do not need iron supplementation when receiving short-term PN. Timing the initiation of iron supplementation in the diverse population of children requiring PN should be based on their underlying morbidity, previous surgical interventions and potential blood losses. In children receiving parenteral iron supplementation close monitoring of iron status is mandatory to avoid iron overload.

Recommendations

- Patients receiving long-term PN (>3 weeks) should receive iron supplementation. **GOR C**
- In children who receive long-term iron supplementation in PN, the risk of iron overload requires regular monitoring of iron status using serum ferritin. **GOR B**
- Iron supplementation should be provided to very low birth weight infants receiving PN. **GOR B**
- The dose of iron for infants and children of 50–100 μg/kg per day is based on calculations extrapolated from studies showing that lower doses may not be sufficient to maintain iron balance and represents ''expert opinion''. The dose in premature infants may need to be 200 μg/kg per day. During short term PN (i.e. <3 weeks) iron supplementation is usually unnecessary. **GOR D**
- The preferred modality of iron administration is as regular daily doses. The ideal formulation (dextran, citrate etc) has not been adequately delineated but data in adults regarding iron dextran shows it to be safe and efficacious. **GOR D**

TRACE ELEMENTS

Introduction

Chromium, copper, iodine, manganese, molybdenum, selenium and zinc are essential micronutrients involved in many metabolic processes. Parenteral nutrition aims to meet nutritional needs while avoiding complications; precise requirements for individual nutrients remain a matter of debate ((23) (LOE 2+)). Trace elements are involved in enzymatic activities and immunologic

reactions. Although toxicity is infrequent, it is well described in patients receiving PN ((24) (LOE 2+)). Low-birth-weight infants (LBW) are at risk of trace element deficiency both because they are born before adequate stores can be acquired and because of the demands of their rapid growth ((25) (LOE 2++); (26)). Parenteral mineral and trace element delivery are calculated to prevent the development of deficiency syndromes ((27) (LOE 2+)) and to match in-utero accretion rates ((28) (LOE 2+)). Parenteral solutions are contaminated with metals such as aluminium and chromium; these require monitoring during long-term PN ((29)(LOE 2+)). A change from glass to plastic packaging for PN products may have implications for trace element supplementation through decreased contamination. Trace element status should be closely monitored in cholestatic patients and trace element preparations may need to be discontinued to avoid copper toxicity. Patients with renal impairment may not be able to excrete selenium, molybdenum, zinc and chromium ((29,22) (LOE 1+)). When taking blood samples for trace element analysis it is important to avoid contamination of the specimen.

Recommendations

- Trace elements should be supplied with long-term parenteral nutrition. **GOR D**
- Trace elements should be periodically monitored in patients on long-term parenteral nutrition. **GOR D**

Chromium

Chromium (Cr) is an essential micronutrient required for carbohydrate and lipid metabolism. Cr deficiency has been described in patients receiving long-term PN, but patients receiving PN also have been reported to show increased serum Cr level ((30) (LOE 2+)). Efforts are required to find PN components with low or, if possible, no Cr contamination (30). High serum Cr competes with iron for binding to transferrin and, hence negatively interferes with iron metabolism and storage ((31) (LOE 3)). A daily intake of 0.2 μg/kg per day has been recommended for infants and children (maximum of 5 μg/day) receiving PN ((22) (LOE 2++)), although there is some evidence that lower intakes would be adequate ((32) (LOE 2+)). Supplementation is unnecessary since Cr contaminates PN solutions to a degree that satisfies requirements ((33) (LOE 2+)).

Recommendation

- Cr contaminates PN solutions to a degree that satisfies requirements, therefore, additional supplementation of Cr is considered unnecessary. **GOR C**

Copper

Copper (Cu) is a component of several enzymes, including cytochrome oxidase, superoxide dismutase (Cu/Zn SOD), monoamine oxidase and lysyl oxidase. Copper concentrations in plasma and cells as well as copper metalloenzymes are indicative of copper status ((34,35) (LOE 2++)). Monitoring plasma concentration of both Cu and caeruloplasmin, the major Cu transport protein, should be considered during PN ((36) (LOE 2+)). However, superoxide dismutase (SOD) activity in erythrocytes seems to be a more sensitive indicator of Cu deficiency than plasma concentration of Cu or caeruloplasmin ((37) (LOE 2++)). Other indicators of Cu status include neutrophil counts (low in deficiency), SOD activity, platelet cytochrome-c oxidase activity and platelet copper concentration ((35) (LOE 2++)). Cu should be carefully monitored in patients with cholestatic liver disease ((22,38) (LOE 2++)).

Plasma total Cu and caeruloplasmin are invariably reduced in children with burns ((36) (LOE 2+)). PN in these patients must be supplemented with more than 20 μg/kg Cu to avoid deficiency ((39) (LOE 2+)). The high Cu content in gastrointestinal fluid means that losses should be balanced by a higher Cu intake (increased by 10 – 15 μg/kg) in PN (22). A routine intravenous supply of 20 μg/kg per day copper for infants (preterm and term) and children is recommended ((22) (LOE 2++)).

Recommendations

- Parenterally fed infants and children should receive an intravenous supply of 20 μg/kg per day copper. **GOR D**
- Plasma copper and caeruloplasmin concentrations should be monitored in patients receiving long term PN and in parenterally fed patients with burns or with cholestasis, and adjustment of copper supply be considered accordingly. **GOR D**

Iodine

Iodine is an essential part of the thyroid hormones, thyroxin (T4) and tri-iodothyronine (T3), which are necessary for cellular metabolism and maintenance of metabolic rate. Thyroid function remained normal and serum iodine levels were not reduced in children receiving long-term PN without iodide supplementation, probably due to iodine contamination of the solutions and skin absorption of topical iodinated disinfectant ((40) (LOE 2+)). It is also possible in these patients that there was some absorption of iodine present in the ingested food. However, a daily dosage of 1 μg/d is recommended for infants and children receiving PN ((22) (LOE 2++)). Now

that use of iodine for skin cleaning is relatively uncommon, there may need to be a reassessment of iodine requirements.

Recommendation

- Parenterally fed infants and children should receive a daily iodine supply of 1 μg/d. **GOR D**

Manganese

Manganese (Mn) is a component of several enzymes including mitochondrial superoxide dismutase and also activates other enzymes such as hydrolases, kinases and transferases. High Mn intake during PN is probably one of several factors contributing to the pathogenesis of PN associated cholestasis or other hepatic dysfunction ((41) (LOE 3); (38) (LOE 2++); (42) (LOE 2++); (43) (LOE 1)). Mn should, therefore, be carefully administered, particularly in patients receiving long-term PN ((38) (LOE 2++); (44) (LOE 3); (45) (LOE 2+)). Studies using magnetic resonance images (MRI) have reported high-intensity areas in basal ganglia, thalamus, brainstem and cerebellum due to Mn intoxication with disappearance of symptoms and MRI abnormalities after withdrawal of manganese administration ((46) (LOE 2+); (47) (LOE 3); (48) (LOE 3); (44) (LOE 3)). As central nervous system deposition of Mn can occur without symptoms, regular monitoring of manganese blood concentration should be performed in children on long-term PN. Taking into account the hazards of high Mn levels in children receiving long-term PN, a low dose regimen of no more than 1.0 μg (0.018 μmol)/kg per day (maximum of 50 μg/d for children) is recommended ((22,38) (LOE 2++)) together with regular examination of the nervous system (38).

Recommendation

- In children receiving long-term PN, a low dose supply of no more than 1.0 μg (0.018 μmol)/kg per day (maximum of 50 μg/d for children) is recommended. **GOR D**

Molybdenum

Molybdenum (Mo) is essential for several enzymes involved in the metabolism of DNA. To our knowledge there are no reports of Mo deficiency in infants. However, low-birth-weight infants (LBW) might be at particular risk for Mo deficiency ((49) (LOE 2+)). Excess of Mo interferes with Cu metabolism. According to some authors an intravenous intake of 1 μg/kg per day (0.01 μmol/kg per day) seems to be adequate for the LBW infant ((49) (LOE 2+)). 0.25 μg/kg per day is recommended for infants and children (to a maximum of 5.0 μg/day) ((22) (LOE 2++)). Intravenous Mo supplements are recommended only with long-term PN.

Recommendations

- An intravenous molybdenum supply of 1 μg/kg per day (0.01 μmol/kg per day) seems adequate and is recommended for the LBW infant. **GOR D**
- For infants and children an intravenous molybdenum supply of 0.25 μg/kg per day (up to a maximum of 5.0 μg/day) is recommended. **GOR D**

Selenium

Selenium (Se) acts as an antioxidant by being an essential component of active glutathione peroxidase (GSHPx), an enzyme that may protect against oxidative tissue damage. Oxidative injury, particularly in the first days of life, is associated with long-term complications of prematurity ((50) (LOE 2++)). Low Se status has been documented in pre-term infants and has been implicated in oxidative diseases such as bronchopulmonary dysplasia and retinopathy of prematurity ((51) (LOE 3); (50) (LOE 2++)). Tissue concentrations of Se and activities of selenium-dependent glutathione peroxidase (Se-GSHPx) are useful indicators of Se status ((52) (LOE 2+)). In order to identify Se deficiency in children receiving PN, it has been recommended that plasma and red cell selenium concentration and Se-GSHPx are monitored ((53) (LOE 3)). Erythrocyte and platelet GSHPx activity are sensitive indexes of Se status in PN patients ((54) (LOE 2+); (55) (LOE 2++)).

Several authors have cautioned against high doses of selenium supplementation because of the risk of toxicity. However there have been no reports of selenium toxicity in infants. Se is also known to be important in thyroid metabolism but selenium deficiency does not seem to play a major role in neonatal hypothyroidism ((56) (LOE 2++)). A non-specific myopathy has also been associated with Se deficiency on long-term home PN ((57) (LOE 3)). A dose of 2–3 μg/kg per day has been recommended for LBW infants, although the optimal form and dose remain unclear ((22) (LOE 2++); (58) (LOE 2++); (56) (LOE 2++)). It should be kept in mind that Se supplementation may also affect copper metabolism ((59) (LOE 1)).

Se content in mature breast milk ranges from 6–28 μg/L in the USA and Europe (52) representing an average intake of around 2.5 μg/kg per day with perhaps an 80% absorption. Serum Se concentration is lower in

PN fed infants than those who are enterally fed with either formula or mother's milk using current recommended intakes ((60) (LOE 2++)). Premature infants (particularly the very low birth weight) might require double the currently recommended Se intake of 1–3 μg/kg per day. Selenite is retained better than selenate, although it has a more variable absorption. The organic compound selenomethionine is chemically stable and well retained by the body and can be used in parenteral nutrition.

Recommendation

- An intravenous selenium supply of 2 to 3 μg/kg per day is recommended for parenterally fed LBW infants. **GOR D**

Zinc

Zinc (Zn) is involved in the metabolism of energy, proteins, carbohydrates, lipids and nucleic acids and is an essential element for tissue accretion. Urinary Zn excretion occurs in the parenterally fed infant. Some amino-acids like histidine, threonine, and lysine have been shown to bind Zn increasing its renal ultrafilterability ((61) (LOE 2+)). Increased urinary losses of Zn and decreased plasma concentrations occur following thermal injury in children ((39) (LOE 2+)). Premature infants need a higher zinc intake than term infants because of their rapid growth: 450–500 μg/kg per day to match in-utero accretion rate ((62) (LOE 2+)). Standard trace element preparations do not supply this amount, and additional zinc (zinc sulphate) may need to be added to PN fluid in the preterm infant, or those patients with high zinc losses e.g. from diarrhoea, stomal losses or severe skin disease ((63) (LOE 2+)). Recommendations are for an intravenous intake of 250 μg/kg per day and 100 μg/kg per day respectively for infants less or more than 3 months of age, and 50 μg/kg per day for children (maximum of 5.0 mg/day) ((22) (LOE 2++)). Zn is the only trace element that should be added to solutions of patients on short-term PN (22).

Recommendations

- Parenteral zinc supply is recommended in daily dosages of 450–500 μg/kg per day for premature infants, 250 μg/kg per day for infants less than 3 months, 100 μg/kg per day for infants aged 3 months or older, and 50 μg/kg per day (up to a maximum of 5.0 mg/day) for children. **GOR D**
- Excessive cutaneous or digestive losses of zinc require additional supplementation. **GOR D**

CALCIUM, PHOSPHORUS AND MAGNESIUM

Introduction

The requirements of calcium (Ca) and phosphorus (P) are considered together because the majority of both elements are found together as components of the bone mineral apatite [$Ca_5(PO_4)_3OH$]. 97% of whole body Ca is stored in apatite together with 80% of whole body P (64,65). The molar Ca: P ratio is 1.3 in the whole body and 1.67 in apatite. Serum calcium exists in three fractions: ionised calcium (approximately 50%), protein-bound calcium (approximately 40%), and a small amount of calcium that is complexed, primarily to citrate and phosphate ions. Serum calcium is maintained at a constant level by the actions of several hormones, most notably parathyroid hormone and calcitonin. Calcium absorption is by the passive vitamin D-independent route or by the active vitamin D-dependent route.

Calcium

Calcium is the most abundant mineral in the body. Approximately 99% of total body calcium is found in the skeleton, with only small amounts in the plasma and extra-vascular fluid. Precise calcium requirements are uncertain. In the newborn infant the total body Ca content is around 28 g with 98% in bone. Based on body composition measurements, approximately 1kg of calcium is deposited in the skeleton between birth and adulthood. Daily accretion rates for boys and girls must average around 150 and 200 mg calcium/d, however, since growth is not uniform, accretion rates may be as high as 400 mg calcium/d during infancy and puberty. A recent study using dual energy x-ray absorptiometry found an average bone calcium accretion rate of 220 mg/d and 317 mg/d in girls and boys respectively during stage III puberty (66). The amount of dietary calcium needed to satisfy the demand for skeletal growth and mineralization is greater than the theoretical accretion rate because of incomplete calcium absorption and losses from skin, urine and gastrointestinal tract. The limited information available regarding calcium needs in children is reflected in wide variation in recommended intakes (22,67,68), and is generally based on recommended oral intake of calcium. Administration of intravenous calcium during parenteral nutrition is limited by solubility.

Phosphorus

Phosphorus (P) is a major intracellular mineral and also crucial for bone mineralisation. In newborn infants total body phosphorus is around 16 g (rising to 600–900 g in an adult) with 80% in bone and 9% in skeletal muscle. In the kidney 85–90% of the filtered phosphate is reabsorbed. In the presence of a low phosphate intake the kidney retains phosphate and it disappears from the

urine. Hypercalcaemia and hypercalciuria may result from phosphate deficiency. Excess phosphate intake may lead to hyperphosphataemia, hypocalcaemia and secondary hyperparathyroidism. Deficiency of phosphate results in bone demineralisation and rickets. Extreme hypophosphataemia can be precipitated by nutritional restitution ('refeeding syndrome') and can result in muscle paralysis, cardiac dysfunction and respiratory failure.

Magnesium

Magnesium is the fourth most abundant metal in the body and the second most abundant intracellular electrolyte. In the newborn infant the total body Mg is around 0.8 g (rising to 25 g in an adult) with 60% in bone. The physiological importance of magnesium lies in its role in skeletal development and in the maintenance of electrical potential in nerves and muscle membranes. Calcium homoeostasis is controlled in part by a Mg requiring mechanism which releases parathyroid hormone. Plasma Mg represents only 0.3 to 11% of total body stores and total plasma Mg concentration does not estimate the biologically active fraction-ionised Mg (69). Inadequate intakes of Mg, Ca and P may induce rickets, fractures, impaired bone mineralization and reduced linear growth (70,71).

Parenteral Supply of Ca and P

In selecting compounds suitable for parenteral nutrition it must be considered that Ca cations may precipitate with inorganic phosphate anions. To some degree this can be avoided by mixing Ca and phosphate with amino-acids and glucose (72–75) but even more so by using organic phosphorus compounds (76–85). Glycerophosphate is available as di-sodium salt in Europe. Parenteral solutions containing Ca may cause damage to peripheral veins, and extravasation may induce severe tissue necrosis. The adequacy of Ca and P intakes in young infants should be adjusted until both are excreted simultaneously with low urine concentrations (1–2 mmol/L) indicative of a slight surplus (86).

Calcium, Phosphate and Magnesium in Children

Taking into account percentage absorption from the diet, parenteral intakes of Ca, P and Mg can be estimated from Recommended Nutrient Intakes (RNI), the amount of nutrient that is enough, or more than enough, for about 97% of people in the group (87). Around 66% of calcium is absorbed from breast milk, but net dietary absorption in older children is around half this level. Absorption of phosphorus is about 60% with the RNI for phosphorus being set equal to that for calcium in mmol (87). Between 20-50% of dietary magnesium is absorbed, but much more can be absorbed when dietary intakes are low. Recommendations for parenteral intake of Ca, P and Mg are given in the tables below. Blood concentrations require periodic monitoring; phosphate concentration may drop suddenly in malnourished patients starting PN.

TABLE 7.1. *Recommended parenteral Ca, P, and Mg intake*

Age	Suggested parenteral intake Ca mg (mmol)/kg	Suggested parenteral intake P mg (mmol)/kg	Parenteral intake Mg mg (mmol)/kg
0–6 m	32 (0.8)	14 (0.5)	5 (0.2)
7–12 m	20 (0.5)	15 (0.5)	4.2 (0.2)
1–13 y	11 (0.2)	6 (0.2)	2.4 (0.1)
14–18 y	7 (0.2)	6 (0.2)	2.4 (0.1)

Recommended parenteral calcium, phosphorus and magnesium intakes for infants and children are shown in Table 7.1. **GOR D**

Calcium and Phosphorus in the Premature Newborn

The total amounts of Ca and P accreted in foetal life are strongly correlated with body weight (88–91). This was confirmed for the bone mineral content in newborn infants including those with intrauterine growth retardation (92). In preterm infants the retention of Ca and P is proportional to growth (93). Foetal bone mineral accretion rate can be achieved in preterm infants given sufficient supplementation with Ca and P (86).

Requirements

The foetal mineral accretion rate corresponds to 2.0 mmol Ca/10 g newly grown body weight and 1.52 mmol P respectively. This has been proposed as a reference mark for parenteral nutrition of infants born preterm and at term. The dosage should be adjusted to the individual growth per body weight. Preterm infants growing at a rate of 20 g/d need 4.0 mmol Ca and 3.0 P per infant and day to meet the foetal requirements. If the baby weighs 1.0 kg this dose would correspond to 4 and 3 mmol/kg per day. If the baby weighs 2 kg then this dose would correspond to 2 and 1.5 mmol/kg per day. If the baby is growing at a slower rate (10 g per day) the dose would correspond to only 1 mmol Ca and 0.75 mmol P/kg per day. Therefore, a wide range covers the spectrum of requirements: Ca 1.0–4.0 mmol/kg per day, P 0.75–3.0 mmol/kg per day which provides a molar Ca:P ratio of 1.3. (64,65).

Recommendations

- Growing newborn infants should usually receive 1.3–3 mmol calcium/kg per day and 1–2.3 mmol phosphorus/kg per day, with a Ca:P ratio (mol/mol) in the range of 1.3–1.7. **GOR D**

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Journal of Pediatric Gastroenterology and Nutrition
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8. Vitamins

METHODS

Literature Search

Time frame of publication search: 1992–2004; relevant publications from 1984–1992 were considered.

Key Words: parenteral nutrition [MESH] AND vitamins [MESH] with limits (English language, infant, children <18 years).

VITAMINS

Introduction

Parenteral vitamins are usually applied as a mixture of different vitamins. Vitamins pose particular pharmacological problems, when given intravenously, since some may adhere to the tubing and/or be degraded by light. Also stability in regard to admixture and ''ingredients'' may have an effect. Therefore the actual amount of vitamins delivered to the patient may be much lower than the intended dose, particularly in the case of retinol (vitamin A) and in premature infants who receive solutions with slow infusion rates. The optimal parenteral vitamin requirements for children and neonates have never been determined. While there are several parenteral vitamin preparations for adults and older children, there are just a few multivitamin preparations available for preterm infants and neonates. The available products for infants contain the same relative amount of lipid soluble vitamins despite different pharmacological properties in different preparations (combined water and fat soluble vitamin solution versus only fat soluble vitamin preparation). Adult formulations containing propylene glycol and the polysorbate additives are not recommended for use in infants because of concerns on potential toxicity. There is little data on vitamin needs of children with acute and chronic diseases whose requirements might differ.

Vitamin concentrations in the effluents of the application sets are the result of a complex interaction of several factors, including flow rates, tubing materials and sizes, intensity of light exposition, environmental humidity and temperature as well as the relative content of each vitamin.

Little new data has been published in this area during the last 20 years. Therefore, this chapter cannot provide a fully evidence based recommendation but tries to provide a reasonable framework for the pediatrician who prescribes parenteral vitamins and to point out particular areas of problems. All studies determining vitamin levels during intravenous supply have been undertaken with commercially available mixtures, either given in the glucose–amino acid solution or in the lipid emulsion. Therefore, current recommendations are based on the composition of specific products.

Given the lack of adequate evidence, it is recommended to maintain, for the time being, parenteral vitamin dosages that have been previously recommended ((1–3) (LOE 4)) and have been used without apparent harmful effects in clinical practice for a number of years, with the exception of thiamine where needs may be higher than previously assumed. (**GOR D**)

Recommendations

- Infants and children receiving PN should receive parenteral vitamins. **GOR D**
- When possible water and lipid soluble vitamins should be added to the lipid emulsion or a mixture containing lipids to increase vitamin stability. **GOR D**
- Intermittent substitution twice or three times a week has not been studied. There is a hypothetical risk of adverse effects by transient high levels. Present recommendations are based on daily infusion. An exception is Vitamin K, which can be given weekly. **GOR D**
- Optimal doses and conditions of infusion for vitamins in infants and children have not been established, therefore, recommendations in Tables 8.1 and 8.2 are based on expert opinion. **GOR D**
- Measurement of vitamin concentrations in individual parenterally fed children may be needed based on clinical indications and in patients on long term parenteral nutrition, but in other patients routine monitoring is not recommended because of lack of evidence on adequate benefits. **GOR D**

Fat Soluble Vitamins

A sufficient supply of vitamins is essential for growth and development. Infants and particularly low birth weight infants have low body stores of vitamins at birth due to a limited transfer of lipid-soluble substrates across the maternal placenta. Therefore, a sufficient supply of vitamins to preterm infants from the first days of life is recommended. The parenteral vitamin supply to premature infants is extensively exposed to light and oxygen and to the lipophilic surfaces of tubing materials due to the small infusion rates.

TABLE 8.1. *Recommended intakes for parenteral supply of lipid soluble vitamins for infants and children (2,24,27,29,43–45)*

	Infants (Dose/kg body weight per day)	Children (Dose per day)
Vitamin A (μg)*	150–300	150
Vitamin D (μg)	0.8 (32 IU)	10 (400 IU)
Vitamin E (mg)	2.8–3.5	7
Vitamin K (μg)	10 (recommended, but currently not possible)**	200

*1 μg RE (retinol equivalent) = 1 μg all-trans retinol = 3.33 IU vitamin A.

**Current multivitamin preparations supply higher vitamin K amounts without apparent adverse clinical effects.

Vitamin A is most vulnerable to degradation by light emitted near its absorption maximum at wavelengths of 330 to 350 nm, vitamin E at 285 to 305 nm. Red plastic bags offered for protecting the syringes are impervious for wavelengths from 190 to 590 nm and amber light protecting tubing material absorb wavelengths from 290 to 450 nm. The most detrimental factor for vitamins A and E is intensive sunlight, consisting of the whole light-spectrum including the ultraviolet range. In contrast, neon light illuminating the intensive care unit at night is mainly emitting wavelengths in the visible part of the light spectrum, and the phototherapy lamp used emits mainly wavelengths of 400 and 450 to 460 nm, respectively. Both light sources have little degrading effect on vitamin A.

Losses to tubing and light degradation depend on whether vitamins are given with a lipid emulsion or in the glucose amino acid mixture and vary for different lipid soluble vitamins.

Vitamin A

Vitamin A plays an essential role in normal differentiation and maintenance of epithelial cells and adequate immune function. Prophylactic supplementation of vitamin A was reported to protect against bronchopulmonary dysplasia and to reduce the requirement for oxygen support ((4) (LOE 3); (5) (LOE 2)).

The adequate supply of vitamin A for premature neonates remains controversial. The ''adequate'' concentration of plasma vitamin A in very low birth weight infants is not known. Serum concentrations below 200 μg/L (0.7μmol/L) have been considered to indicate deficiency in premature infants and concentrations below 100 μg/L (0.35 μmol/L) indicate severe deficiency and depleted liver stores. The range of normal values for children older than 6 months of age (including adults) is 300–800 μg/L. Both the plasma retinol binding protein (RBP) response ((6) (LOE 3); (7) (LOE 3)) and the relative rise in serum retinol concentration (8) following intramuscular (I.M.) vitamin A administration have been described as useful tests to assess functional vitamin A status.

TABLE 8.2. *Recommended intakes for parenteral supply of water soluble vitamins for infants and children (2,30,33,38)*

	Infants (Dose/kg body weight per day)	Children (Dose per day)
Ascorbic acid (mg)	15–25	80
Thiamine (mg)	0.35–0.50	1.2
Riboflavin (mg)	0.15–0.2	1.4
Pyridoxine (mg)	0.15–0.2	1.0
Niacin (mg)	4.0–6.8	17
B12 (μg)	0.3	1
Pantothenic acid (mg)	1.0–2.0	5
Biotin (μg)	5.0–8.0	20
Folic acid (μg)	56	140

Delivery of vitamin A is complicated by substantial photo-degradation and adsorptive loss when given in combination with the water soluble vitamins as part of the glucose-amino acid infusion. Loss to tubing also depends on the tubing material. Alternative methods of delivery have been proposed to ensure the application of reproducible amounts of vitamin A to premature neonates by using shorter IV tubing and a shorter infusion time with reduced duration of exposure to light and tubing material or by supplying the more stable vitamin A ester retinyl palmitate or the multivitamin solution with the lipid emulsion ((9–11) (LOE 2)).

The total delivery of retinol from parenteral infusions has been consistently reported to be below 40% of the intended dose (9,12,13). Contradictory results have been reported by different authors on the effects of light protection on vitamin A release under ''ambient light conditions'' that were usually not specified or quantified in the published studies. Thus, light protection should only be considered for protection of retinol exposed to strong direct day light. Under artificial lighting conditions, the use of light protecting tubing materials will have only a marginal influence on retinol delivery compared to the amounts lost by extensive adsorption onto the tubing.

Retinyl palmitate in the lipid emulsion provides reproducible amounts delivered during the infusion period, indicating that it is a stable ester of vitamin A and that it is further protected by the lipid emulsion, presumably because lipid droplets disperse the light and thus protect the vitamin. The major proportion of retinol losses is due to adsorption onto the tubing materials within the first hour of infusion, whereas retinyl palmitate tends to adsorb to tubing material to a lesser extent. A smaller surface of tubing and less passage time of the infusion through the tubing provide improved delivery. However, the available ''micro tubing'' made of polyurethane are more prone to adsorb lipophilic substances than standard PE tubing (14). PE and PVC tubing materials seem to have comparable adsorption behaviors. Supplying vitamin A in a lipid emulsion is the most feasible way to reduce losses.

In infants an intravenous vitamin A supply of about 920 IU/kg per day together with the water soluble

mixture or 230–500 IU/kg per day with the lipid emulsion are often used. Since losses are quite variable and losses are higher in the water soluble mixture, the amount delivered to the patient may be estimated to be approx. 300 to 400 IU/kg per day for both options. Supplementing vitamin A as retinyl palmitate (1000 IU/d Vitamin A) in premature infants for 28 days in addition to parenteral nutrition (400 IU/day) and enteral supply (1500 IU/day) led to significantly higher serum levels than at birth but with a wide range of variation. 32% still had levels below 20 μg/dL ((15) (LOE 3)).

Vitamin A supplementation for preventing morbidity and mortality in very low birth weight infants. Level 1 evidence exists only for VLBW infant with gestational age <32 weeks or birth weight <1500 g. A Cochrane review (16) found an association of vitamin A supply and a reduction in death or oxygen requirement at one month of age and of oxygen requirement of survivors at 36 weeks post-menstrual age, with this latter outcome being confined to infants with a birth weight <1000 g.

Five eligible trials supplemented vitamin A intramuscularly soon after birth over the next 28 days in various doses of 4000–5000 IU three times a week to 2000 IU every other day. One study supplemented vitamin A as retinyl palmitate in lipid emulsion at approx. 700 RE/kg per day for the first two weeks and 600–700 RE/kg per day for the next two weeks. Control and study infants also received ''Standard'' vitamin A. The conclusion of the review was that whether clinicians decide to use repeat intramuscular doses of vitamin A to prevent chronic lung disease may depend upon local incidence of this outcome and the value attached to achieving a modest reduction in this outcome balanced against the lack of other proven benefits and the acceptability of the treatment. The benefits, in terms of vitamin A status, safety and acceptability of delivering vitamin in an intravenous emulsion compared with repeated intramuscular injection should be assessed in a further trial.

The NICHD trial necessitates 12 intramuscular injections with 5000 IU (17). Compared with this regimen, once-per week (15 000 IU) worsened, and a higher dose (10,000 IU 3x per week) did not reduce vitamin A deficiency (serum retinol <20 μg/dL, RBP <2.5 mg/dL, and/or RDR >10%) (18).

Conclusion: Vitamin A delivery is improved by the infusion of retinyl palmitate with lipids, but light protecting tubing provides only a marginal benefit.

Dosage recommendations for parenteral vitamin supplementations for premature infants are based on clinical studies measuring vitamin levels during supplementation. Most of these studies were done with the water soluble solution containing water and lipid soluble vitamins. The true needs of the infants are not known. The LOE in I.M. high dosages imply that higher levels of substitution may be warranted in this patient population.

Vitamin E

Vitamin E is a lipid-soluble antioxidant, protecting cell membrane polyunsaturated fatty acids from free radical oxidative damage. Appreciable prenatal vitamin E accretion occurs only in the third trimester of pregnancy with increasing fetal lipid stores. The dietary requirements of a-tocopherol are dependent on the amount of PUFA in the diet. Early vitamin E administration to preterm infants was reported to reduce the severity of retinopathy of prematurity ((19) (LOE 2); (20) (LOE 2)) and incidence and severity of intracranial hemorrhage ((21) (LOE 2); (22)). a-tocopherol tends to adsorb to some extent onto tubing materials, which can be prevented by application with the fat emulsion or by use of a vitamin E ester ((9, 11) (LOE 2); (23) (LOE 2)). Vitamin E is little affected by exposition to light. Light protection of the infusion devices is therefore not necessary to protect vitamin E. Since vitamin E stores are very low at birth in premature infants and these infants are at increased risk for oxidative stress, supplying 2.8–3.5 IU/kg per day of vitamin E is probably advisable ((2) (LOE 4); (24) (LOE 4)).

Vitamin E supplementation in preterm infants leading to serum levels >3.5 mg/dl reduced the risk of intracranial haemorrhage but increased the risk of sepsis (25). In very low birth weight infants it increased the risk of sepsis, and reduced the risk of severe retinopathy and blindness among those examined. Evidence does not support the routine use of vitamin E supplementation by intravenous route at high doses, or aiming at serum tocopherol levels greater than 3.5 mg/dl (25). In premature infants, safe blood levels of vitamin E are 1–2 mg/dL (2). For infants and children, recommended blood levels are 0.5–1.5 mg/dL (2). However, since vitamin E is carried in blood by lipoproteins, the ratio between serum vitamin E/total serum lipids should be used to assess vitamin E status (deficiency: serum vitamin E to total lipid ratio <0.8) ((25) (LOE 1–4)).

Vitamin D

In general, Vitamin D maintains calcium and phosphorus homeostasis together with PTH by increasing intestinal absorption of Ca and P, by affecting the renal re-absorption of P, and to a lesser extent Ca, and by modulating turnover of these minerals in bone. However, it is not known whether preterm infants on parenteral nutrition require vitamin D. The parenteral vitamin D requirements might be lower than enteral requirements, since no enteral intake of minerals needs to be facilitated. It has been suggested that as little as 30 IU/kg per day i.v. might be sufficient ((27) (LOE 3)).

Vitamin K

Vitamin K's most important physiologic role is the regulation of the coagulation factors (factors II, VII, IX, X)

via carboxilation of these factors which is vitamin K dependent. Two proteins, involved in coagulation, namely protein C and protein S, are also vitamin K dependent. In addition, vitamin K plays a role in the synthesis of osteocalcin, a marker of bone formation.

It was recommended that for preterm infants the daily dose should be 100 μg phylloquinone/kg per day. Premature infants supplemented with vitamin K (1 mg) intramuscularly, followed by parenteral nutrition with 60 μg/d (<1000 g) and 130 μg/d (>1000 g) had high plasma vitamin K levels compared with those at 40 weeks postconceptual age ((28) (LOE 2)). A parenteral vitamin K supply of 80 μg/kg per day (29) in premature infants might be excessive if combined with an i.m. dosage of 1 mg on day 1, and lower supplies may suffice during the first weeks of life. Current multivitamin preparations contain high amounts of vitamin K which tend to supply 100 μg/kg (10 times higher than recommended enteral intakes), but adverse clinical effects have not been reported.

The suggested daily intake for children is 200 μg per day.

Statement and Recommendations

- Ranges of reasonable parenteral vitamin supply for infants and children are given in table 1. **GOR D**
- There are substantial losses of vitamin A when given with a water soluble solution; therefore parenteral lipid soluble vitamins should be given with the lipid emulsion whenever possible. **GOR D**
- For preterm infants, serum tocopherol levels should be between 1–2 mg/dL, but not exceed 3.5 mg/d. **GOR A**. To properly assess vitamin E status, the ratio between serum vitamin E/total serum lipids should be used.
- A vitamin K supply of 80 μg/kg per day parenterally in premature infants might be excessive if combined with an i.m. dosage of 1 mg on day 1. **LOE 2**
- In exclusively parenterally fed infants Vitamin D supply of 30 IU/kg/d might be sufficient. **GOR D**

Water Soluble Vitamins

Introduction

Current recommendations are expert opinions based on observed biochemical responses to variations in parenteral intake and on comparison with enteral recommendations. Controlled randomized trials investigating the effect of different parenteral vitamin substitution regimens on clinically relevant long term outcome parameters are lacking.

Given the lack of adequate evidence, it is recommended to maintain, for the time being, dosages that have been recommended previously ((1–3) (LOE 4)) and have been used without apparent harmful effects in clinical practice for a number of years. However, in the case of thiamine (vitamin B1), the needs of preterm infants might be higher than previously recommended ((30) (LOE 2)), therefore a higher dosage is recommended (Table 8.2).

Water-soluble vitamins must be administered on a regular basis as they are not stored in significant amounts, except for B_{12}. Excess is excreted by the kidneys and there is little toxicity. Term infants and children appear to adapt to large variations in vitamin intakes because similar blood levels have been measured despite several-fold differences in intake on a body weight basis. By contrast, the finding of marked elevation of some vitamins and low levels of others seen in infants less than 1500 g suggests that this group has less adaptive capacity to high- or low-dose intakes ((31) (LOE 4); (32) (LOE 2)). Therefore, there may be a need to develop specific vitamin preparations for low birthweight infants ((1) (LOE 4); (2) (LOE 4); (33) (LOE 4)).

Vitamin preparations can protect intravenous lipid emulsions from peroxidation. The administration of multivitamins with the intravenous lipid emulsions provides a practical way to reduce peroxidation of the lipid while limiting vitamin loss (34,35).

Vitamin C (ascorbic acid)

L-ascorbic acid is the biologically more active form of the vitamin and it is a cofactor in hydroxylation reactions in many biosynthetic processes, as well as an antioxidant. The classic clinical manifestation of vitamin C deficiency is scurvy. Vitamin C is particularly important in premature infants as it is involved in the catabolism of tyrosine and its deficiency can result in transient tyrosinemia. Due to its rapid renal clearance, toxicity of vitamin C is rare even when doses exceeding the RDA are used. However, very large doses have been associated with uricosuria, hypoglycaemia and hyperoxaluria ((36) (LOE 4)).

The infusion of an average of 48 mg/kg per day of ascorbic acid for 4 weeks to premature infants resulted in plasma concentration that were substantially higher than those detected in term infants or children ((37) (LOE 2)). Therefore, substantially lower doses (15–25 mg/kg per day) have been recommended for parenteral nutrition (33). In premature infants the parenteral administration of 100 mg/kg per day vitamin C for 7 days led to plasma levels twice as high as the level of the umbilical artery ((38) (LOE 2)). However, Friel et al., demonstrated that for most premature infants the recommended daily dosage of 25 mg/kg per day would be adequate ((30) (LOE 2)).

Thiamine (Vitamin B_1)

Thiamine pyrophosphate is involved in carbohydrate metabolism as well as in lipid synthesis. Its requirements depend on carbohydrate intake. Deficiency of thiamine may lead to beriberi with neurologic and cardiovascular symptoms. Thiamine is excreted by the kidneys and toxicity is rarely detected. In parenterally fed infants and children a deficient thiamine supply may lead to severe lactic acidosis and even death within a period of days to weeks (39). In preterm infants a parenteral thiamine intake of 780 μg/kg per day led to 10-fold higher serum levels than in cord blood ((37) (LOE 2)). Consequently, a considerable lower parenteral intake (200–350 μg/kg per day) has been recommended and repeatedly reiterated until Friel et al. challenged this recommendation ((30) (LOE 2)). In their study a mean parenteral and enteral intake of thiamine of 510 μg/kg per day maintained a normal functional thiamine status and levels slightly below cord blood concentrations (30). Therefore, the current parenteral recommendation for preterm infants (200–350 μg/kg per day) might be too low and dosages up to 500 μg/kg per day seem more appropriate, but further information is required.

Riboflavin (Vitamin B_2)

Riboflavin forms flavin adenine dinucleotides and thus participates in energy metabolism. The requirement for riboflavin is associated with protein intake. The adequacy of the riboflavin status can be assessed by measuring plasma concentrations and by the erythrocyte glutathione reductase test (EGRAC). Clinical manifestations of deficiency include hyperemia of mucous membranes, stomatitis, dermatitis and anaemia. Riboflavin is very light sensitive and is rapidly photodegraded in PN solutions.

A recent trial showed tolerance of a combined enteral and parenteral riboflavin intake up to 624 μg/kg per day in preterm infants (30), however, parenteral riboflavin dosages above 281–500 μg/kg per day were repeatedly shown to exceed requirements ((11) (LOE 2); (40) (LOE 2); (41) (LOE 2); (42) (LOE 4)). Therefore, the recommended dosage of 0.15–0.2 mg/kg per day to preterm infants remains unchanged. As suggested by Greene et al (2), the recommended dosage of 1.4 mg riboflavin per day for term infants and children is more than necessary, but due to the lack of toxicity and studies of actual requirements, this suggested dosage remains unchanged.

Loss of riboflavin through photo-degradation can be very high (65%) and can be halved by adding the water soluble vitamin solution to the lipid solution, and further reduced by using dark tubing (34). Data on the signs and symptoms of riboflavin toxicity in infants and children is insufficient. The precise requirement of riboflavin in parenterally fed infants and children has not yet been defined. In very low birth weight infants, the current practice of riboflavine supply leads to elevated plasma levels after birth.

Pyridoxine (Vitamin B6)

Pyridoxine, pyridoxal and pyridoxamine are the three natural pyridines and their phosphorylated forms are involved in metabolism of amino acids, prostaglandins and carbohydrates as well as the development of the immune system and neurologic function. Pyridoxine deficiency presents with hypochromic anemia and neurologic symptoms.

The optimal parenteral pyridoxine intake in infants and children has not been defined. In a recent trial, a considerably higher intake ((30) (LOE 2)) than the previously recommended intake ((33) (LOE 4)) was tolerated in preterm infants. However, this recent data does not justify altering current recommendations.

Cobalamin (Vitamin B12)

Vitamin B_{12} is an organometallic complex. It participates in metabolic reactions involving the synthesis of DNA nucleotides. A supply of 0.6 μg/kg per day has led to elevated serum levels ((37) (LOE 2)). The adequacy of current recommendations remains to be confirmed.

Niacin

Niacin is essential for the synthesis of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate which serve as cofactors for electron transport and energy metabolism. Niacin deficiency results in pellagra characterized as cutaneous, gastrointestinal and neurologic symptoms. No new studies are available. Adequacy of current recommendations needs to be confirmed in ELBW infants.

Pantothenic Acid

Pantothenic acid is a precursor of coenzyme A and thus involved in many reactions of energy metabolism. No new studies are available. Adequacy of current recommendations needs to be confirmed in ELBW infants.

Biotin

Long term parenteral nutrition free of biotin together with long-term use of broad spectrum antibiotics leads to a clinical syndrome of lethargy, hypotonia, irritability, alopecia and dermatitis. Adequacy of current recommendations needs to be confirmed.

Folic Acid

Folic acid is needed in the biosynthesis of purines and pyrimidines, in the metabolism of some amino acids, and

Recommendations

- Ranges of reasonable parenteral vitamin supply for infants and children are given in table 2. **GOR D**
- Water-soluble vitamins should be administered regularly to parenterally fed patients, preferably on a daily basis. When feasible, vitamin preparations should be added to the lipid emulsion. **GOR D**

in the catabolism of histidine. The adequacy of current recommendations needs to be confirmed.

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Journal of Pediatric Gastroenterology and Nutrition
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9. Venous Access

METHODS

Literature Search

Timeframe: Publications from 1992 until 2004, single publications from 1981 were considered.

Type of publications: original articles, case-control and cohort studies, randomised trials, meta-analyses, systematic reviews, case studies.

Key Words: catheterisation, catheter, Broviac, Hickman, ultrasound, replacement, complications, bacteraemia, parenteral nutrition, central venous catheter, central line, venous access, heparin, catheter handling, skin hygiene, dressing type, frequency of dressing change, intravenous infusions, catheter infections.

Language: English, French.

VENOUS ACCESS

Introduction

The use of central venous catheters (CVCs) to provide venous access has become increasingly common for the purpose of administration of different treatment regimens, intravenous nutrition and blood products, preventing at the same time trauma associated with repeated punctures. However, their insertion and usage may be associated with complications. Therefore, educated personnel should insert and look after the catheter, provide aseptic conditions in handling the catheter and maintain appropriate skin hygiene around the catheter.

The terminology used to identify various types of catheters differs and may be confusing. However, for the purpose of providing parenteral nutrition (PN), it is necessary to differentiate peripheral from central venous access, and among the central venous catheters (CVC) those non-tunnelled i.e. inserted either peripherally (PICC) or directly percutaneously, from tunnelled central catheters.

Intravascular Catheters for Parenteral Nutrition

Types of Catheters

Establishing a peripheral venous access is defined as placement of a needle or short catheter in a subcutaneous vein. As phlebitis of peripheral veins can be expected when the osmolality of i.v. solution exceeds 600 mOsm (1 (LOE 2+)), peripheral veins are only used for short-term venous access and for providing partial nutritional supplementation. Initiation of full PN requires the placement of a CVC. Central venous access is obtained by advancing a catheter into the superior or inferior vena cava or outside of the right atrium. A percutaneously placed CVC can be inserted directly through one of the deep veins e.g. subclavian, internal jugular, or femoral. Another option is a peripherally inserted central catheter (PICC), which uses a subcutaneous vein as the entry site to reach the central vein (2,3, LOE 3). For long-term continuous or frequent use, tunnelled catheters, such as Broviac or Hickman CVC's, are usually placed ((4) (LOE 2+), (5) (LOE 2+)). The extra vascular portion of these devices is tunnelled subcutaneously. A Dacron cuff is implanted subcutaneously, allowing for better fixation and, because of the distance between the insertion site and the entry into the vein, inhibits migration of micro organisms ((6) (LOE 1+); (7) (LOE 2+)). Totally implantable devices i.e. subcutaneous ports, are ideal for long-term but intermittent vascular access. Each port access requires needle sticking and, therefore, their value for PN is limited ((8) (LOE 2+)).

Recommendation

- Peripherally inserted central catheters (PICC's) and tunnelled central venous catheters (CVCs) should be used preferentially to provide central venous access in neonates and children receiving prolonged PN. **GOR C**

Catheter Material

Catheters made of stiffer material (polyvinylchloride, polypropylene, polyethylene) are easier to insert, but have been associated with more infectious and mechanical complications ((9) (LOE 2+)). Softer catheters (silicone and polyurethane) are less thrombogenic and less traumatic, and are, therefore, preferable for long-term use ((10) (LOE 2+); (11) (LOE 3)).

In adults, catheters coated with chlorhexidine/silver sulfadiazine and minocyline/rifampin, on both the external and internal surfaces, reduce the rate of catheter-related bloodstream infections ((12) (LOE 1+), (13) (LOE 1+)). In adults, in settings associated with high risk for infections (e.g. ICU patients), the use of these expensive devices might be cost-effective, and may justify the possible emergence of resistant bacterial strains ((14) (LOE 1+)).

Recommendation

- Silicone and polyurethane coated with hydromers are preferable materials for catheters used for long-term PN. **GOR C**

Insertion Sites

When a CVC is inserted into a deep vein, the choice of insertion site depends on the expected risk for thrombophlebitis, for mechanical complications and/or for catheter infection, which may all be specific for each insertion site.

The subclavian site is widely accepted as the preferred site of insertion, as it causes less patient discomfort, and in adult patients, carries the lowest risk of infection risk ((15) (LOE 2+), (16) (LOE 1−)).

In children, the subclavian site is also the most common site for insertion of tunnelled CVC's, although it has not been proven to carry less infection risk ((17) (LOE 1+); (18) (LOE 3)); (5) (LOE 2+)). Cannulation of the subclavian vein might be associated with dangerous complications such as pneumothorax and haemothorax. However, with adequate experience of the physician performing the procedure and sufficient sedation or general anaesthesia, the risk of mechanical complications in children at subclavian sites does not exceed the rate of complications at other insertion sites ((19) (LOE 3); (20) (LOE 3)). In contrast to adults, femoral catheters in children have not been shown to have a higher incidence of mechanical and infectious complications compared to jugular and subclavian sites ((21) (LOE 2+); (22) (LOE 3); (17) (LOE 1+); (23) (LOE 3); (24) (LOE 3)). However, femoral access is uncomfortable for the child while the consequences of potential inferior vena cava thrombosis may be severe. The insertion of a CVC is customarily followed by chest radiography for verification of the catheter's course and the position of its tip. In addition, ECG-monitoring may be helpful.

Statements and Recommendations

- In infants and children, in contrast to adults, femoral catheters do not show a higher incidence of mechanical and infectious complications in comparison with jugular and subclavian sites. **LOE 2**
- In children the risk of mechanical complications of subclavian venous access does not exceed the rate of complications with other insertion sites under appropriate conditions of insertion. **GOR C**

Positioning of the Catheter Tip

Cardiac tamponade is a rare but life threatening complication of CVC's ((25) (LOE 3), (26) (LOE 3)). There may be an increased risk of pericardial tamponade when the tip is placed within the heart outline as seen on chest x-ray ((27) (LOE 3), (28) (LOE 4)). It is, therefore, advisable that the CVC tip lies outside the pericardial sac and should be repositioned whenever possible ((27) (LOE 3); (29) (LOE 3)). The preferable position for the catheter tip on the chest x-ray is at least 0.5 cm outside the cardiac outline for the small infant, and 1.0 cm in larger infants ((28) (LOE 4)). For older children and adults, positioning above the carina, which can be used as an anatomic landmark, suggests that the catheter tip of the CVC placed in the superior vena cava is likely to be outside the pericardial sack ((30) (LOE 4)). The risk of perforation depends on the angle of the catheter and the vessel wall; therefore, the catheter should be parallel with the long axis of the vein ((31) (LOE 4)).

Statement and Recommendations

- The CVC tip should lie outside the pericardial sac to avoid the risk of pericardial tamponade. **GOR D**
- In small infants the catheter tip of a jugular or subclavian CVC should lie at least 0.5 cm outside the cardiac outline on a chest x-ray, while in older/larger infants that distance should be at least 1.0 cm. The catheter tip of a femoral catheter should lie above the renal veins. **GOR D**
- In older children, as in adults, positioning above the carina suggests that the catheter tip lying in the superior vena cava is likely to be outside the pericardial sack. **LOE 4**
- The risk of perforation increases with the acute angle of the catheter and the vessel wall. Therefore, the catheter should be parallel with the long axis of the vein. **GOR D**

Ultrasonic Guidance

The ultrasound-guided technique can significantly increase the precision and safety of CVC placement in children and newborns when the internal jugular vein is cannulated ((32) (LOE 3); (33) (LOE 3)).

Statement

- Ultrasound guidance may help reducing complications during internal jugular venous catheterization in children and in newborns. **LOE 3**

Methods of Insertion

Methods of insertion of CVCs, including tunnelled CVC's, are percutaneous placement and the surgical cut-down technique. The chance of permanent damage to the vein is increased when the cut-down method is used ((34) (LOE 2+)). The percutaneous insertion method is as effective as the surgical cut-down ((34) (LOE 2+), (35) (LOE 2+)).

Also, the diameter of the inserted catheter should be as small as possible to minimize the risk of scaring,

stricture, occlusion and distortion of the cannulated vein ((36) (LOE 3)).

In adults, administration of antibiotics before CVC insertion or the CVC flush with a combination of an antibiotic and heparin has been justified ((37) (LOE 1++)). In children, the use of vancomycin concurrent with catheter insertion was associated with decreased incidence of CVC blood stream infections ((38) (LOE 2+), (39) (LOE 2+)).

Statement and Recommendation

- Percutaneous, radiologically controlled, insertion method is equally effective as surgical cut-down, and carries less risk of damaging the vein. **LOE 2+**
- CVC placement should be done under strict aseptic environment, and preferably under general anesthesia and by an experienced team. **GOR D**

Umbilical Catheters

In neonates, umbilical vessels may be directly accessed in the first few days of life and, therefore, this route of central venous approach can regularly be used for PN. However, the risk of expected thrombotic complications limits the use of umbilical catheters to being a bridge procedure while awaiting placement of a long-term device ((40) (LOE 2+); (41) (LOE 2+); (42) (LOE 2+); (43) (LOE 2+)). Umbilical artery catheters placed above the diaphragm are associated with a lower incidence of vascular complications ((44) (LOE 1+)).

Statements

- In neonates, umbilical vessels can be used for PN.
- The risk of complications increases if umbilical artery catheters are being left in place for more than 5 days. **LOE 2++**
- The risk of complications increases if umbilical venous catheters are being left in place for more than 14 days. **LOE 1+**
- Umbilical artery catheters placed above the diaphragm are associated with a lower incidence of vascular complications. **LOE 1+**

Replacement Schedule

Routine replacement of CVC's and PICC's does not prevent catheter-related bloodstream infections ((45) (LOE 2+); (46) (LOE 1+); (47) (LOE 1+)). Functioning CVC's without evident complications should, therefore, be left in place as long as needed. A malfunctioning CVC can be replaced using a guide-wire insertion technique ((47) (LOE 1+)). This technique lowers the risk of mechanical complications associated with CVC replacement and may make chest radiography unnecessary in adult patients ((48) (LOE 2+)). Replacement over the guide-wire should, however, not be performed in the presence of bacteraemia or in patients suspected to have catheter related infection ((47) (LOE 1+)).

Recommendations

- CVC's and PICC's should not be replaced routinely. **GOR B**
- Malfunctioning non-tunelled CVCs can be replaced by using a guide-wire exchange technique, if there is no evidence of bacteraemia or catheter related infection. **GOR B**

Alternative Sites for CVC Placement

CVC complications following multiple catheterisations can lead to thrombosis and depletion of commonly used venous access sites. Alternative approaches in these children should be regarded as rescue accesses and include the transhepatic, translumbar, intercostal ((49) (LOE 3); (50) (LOE 3) (51) (LOE 3)), and the arteriovenous fistula (52). Preferences among the alternative sites depend on the experience of the physician performing the procedure and the condition of each individual patient.

Lines Designated Only to PN

In order to prevent catheter related infections, several recommendations have been suggested, including dedicating the CVC to PN only, i.e. not using it for blood sampling or for delivering other fluids or drugs ((53) (LOE 2++)). However, many of the patients who require PN are critically ill and have poor venous access, so the use of multiple lumen catheters allows additional access ports for the provision of compatible medications. Double and triple lumen catheters seem to be associated with an increased risk of bacteraemia compared to single lumen devices ((54) (LOE 2+); (55) (LOE 2++); (56) (LOE 2++)). They also seem to be more prone to the development of catheter-related sepsis, possibly because of more frequent catheter manipulations ((53) (LOE 2++); (57) (LOE 2+); (58) (LOE 1+)). The rate of catheter related sepsis has been reported to be as high as 10–20% compared to 0–5% associated with single lumen catheters ((53) (LOE 2++); (59) (LOE 1+); (58) (LOE 1+)).

In contrast, some adult studies showed that the use of multi lumen catheters for PN is safe and that they did not result in an increased incidence of catheter related sepsis ((60) (LOE 2+); (61) (LOE 2+); (62) (LOE 2++); (63) (LOE 1+); (64) (LOE 2++); (65) (LOE 1+)). It is

important to emphasize that in most of these studies either one port of the multiple lumen catheter was reserved only for PN, or the catheter was limited to administration of compatible medications and solutions while administration of blood products, withdrawal of blood and measurement of central venous pressure were prohibited. The authors concluded that PN can safely be given through multiple lumen catheters provided that these measures are strictly followed ((63) (LOE 1+), (64) (LOE 2++), (65) (LOE 1+)).

Statements and Recommendations

- Where possible a central venous line should be dedicated for the administration of PN. **GOR B**
- If a CVC is used to administer PN, use a catheter with the minimal number of ports or lumens essential for the management of the patient. **GOR B**
- If a multi lumen catheter is used to administer PN, designate one port exclusively for PN. Blood administration and central intravenous pressure monitoring from the designated line should be avoided. **GOR B** (from adult studies)
- If single lumen catheters are used, the risk of complications increases with blood sampling from the catheter. **GOR B** (from adult studies). However, to improve the quality of life of patients on long-term or home PN, blood sampling could be done from single lumen catheters, provided that the procedure is aseptic. **LOE 4**

Catheter Heparinisation

In children, central venous lines are the most frequent cause of venous thromboembolism and are responsible for over 80% of venous thromboembolism in newborns and 40% in other children ((66) (LOE 2++); (67) (LOE 2+)). Furthermore, CVC related thrombosis is, alongside sepsis, the most common clinically significant complication of PN ((68) (LOE 2+), (69) (LOE 2+)). Factors that have been associated with initiation and propagation of thrombosis include endothelial damage during catheter placement, blood vessel occlusion, low flow states, blood stasis, turbulent flow, blood hyperviscosity or hypercoagulability, patients' and infusates' characteristics and catheter composition ((70) (LOE 2++), (71) (LOE 1+)).

In an attempt to prolong the duration of catheter patency and to prevent venous thromboembolism as well as its potentially fatal complications, the use of heparin has been suggested ((72) (LOE 2+), (73) (LOE 2+)). Heparin is a glycosaminoglycan with anticoagulant effects mediated largely through its interaction with antithrombin III that markedly accelerates its ability to inactivate coagulation enzymes (thrombin, factor Xa and factor IXa) ((74) (LOE 2++)).

In providing PN, heparin could have the following potential benefits:

1. *anticoagulant action* – besides reducing fibronectin deposition, heparin makes the line hydrophobic, giving it a negative charge, both of which may influence the catheter thrombogenicity ((70) (LOE 2++); (75) (LOE 1+); (76) (LOE 1++));
2. *prevention of infection* – a thrombus might serve as a nidus for microbial colonization of intravascular catheters ((77) (LOE 1+); (78) (LOE 2++)). Heparin bonded catheters were reported to diminish bacterial adherence ((79) (LOE 2++)), as well as to lower the incidence of positive blood cultures, presumably related to the lower incidence of thrombosis ((70) (LOE 2++)) or to a reduced number of microorganisms attached to the surface of the catheter ((75) (LOE 1+));
3. *activation of lipoprotein lipase* - given in infusion, heparin also activates lipoprotein lipase and increases lipolysis and reesterification of infused triglycerides, but has no effect on lipid oxidation and net energy gain ((80) (LOE 1+); (81) (LOE 1+); (82) (LOE 2++); (83) (LOE 2++)).

There are certain possible complications related to the use of heparin in PN, notably bleeding, heparin induced thrombocytopenia, allergic reactions, osteoporosis, which all may result in serious long-term sequelae ((84) (LOE 2+); (85) (LOE 1++); (74) (LOE 2++); (86) (LOE 3)). In addition, neonates are unique in their sensitivity and resistance to heparin and in their higher propensity to develop intracranial haemorrhage ((87) (LOE 2−); (88) (LOE 2+)). Both low molecular weight heparin and heparin used as a catheter coating agent are associated with these complications, although the risk associated with low molecular weight heparin is reduced compared to unfractionated heparin ((85) (1++), (89) (2++), (90) (3)).

Another risk of adding heparin to PN solutions is the possibility of inducing incompatibility. Calcium and heparin can destabilize lipid emulsions leading to flocculation and separation of the lipid from the aqueous phase (91). However, this is unlikely if low heparin concentrations are used (0.5 to 1 U/ml) ((92) (LOE 2+)). Together with minimizing their contact time (having the delivery tube between the point of mixing lipid and amino acid solutions as short as possible), co-administration of vitamin preparations will further decrease this effect ((92) (LOE 2+)).

The current attitude towards prescribing heparin, therefore, differs with regard to whether to use it at all or not, and if yes, in what way (as a flush or in PN infusion), how often and how much. In practice, wide variations are observed in volumes of provided heparin ranging from 5 to 10 ml ((93) (LOE 2+), (94) (LOE 1+), (95) (LOE 1−)), concentration of heparin ranging from 10 U/ml to 200 U/ml ((93) (LOE 2+), (94) (LOE 1+), (69) (LOE 2+)) as well as in the frequency of

heparinisation that ranges from daily infusions ((96) (LOE 2++)) to flushes once or twice daily ((94) (LOE 1+); (97) (LOE 2+)) to once a week ((98) (LOE 2−)) or even once in three weeks ((99) (2++)). Boluses in children frequently contain 200 to 300 U of heparin, and for infants weighing less than 10 kg, a dose of 10 U/kg is frequently used ((89) (2++)). In a meta-analysis evaluating the benefit of heparin prophylaxis (3 U/ml in PN solution; 5000 U every 6 to 12 hours flush or 2500 U of low molecular weight heparin subcutaneously) in patients with CVC's, the risk of central venous thrombosis was significantly reduced. Although bacterial colonization was also decreased, no substantial difference in the rate of catheter related infection was observed ((100) (LOE 1+)). Of the 11 studies included in this meta-analysis only one was performed in the paediatric population. This randomised cross-over study showed that there was no significant difference in the incidence of blocked catheters or other complications between the group of paediatric patients whose CVC's were flushed twice daily with a heparin solution and the group with isotonic saline flushes applied once a week ((94) (LOE 1+)).

Another randomized double blind trial on paediatric patients demonstrated that the use of normal saline compared to heparinised infusion (saline + 1U of heparin/ml) did not significantly adversely affect patency of CVC's ((101) (LOE 1+)). The proportion of non patent catheters was smaller in the heparinised group but the difference was not statistically significant. However, both studies had a small sample size and thus not enough statistical power to draw definitive conclusions.

Shah et al performed a systematic review on the prophylactic use of heparin for prevention of complications related to peripherally placed percutaneous central venous catheters in neonates but not even one well designed randomized controlled trial was found. Therefore, the routine use of heparin for this purpose could not be recommended ((102) (LOE 1++)).

Later, Kamala et al performed a randomized, double-blind controlled study of heparin infusion (1 U/ml) for prevention of blockage of peripherally inserted central catheter in neonates and found no significant difference in the incidence of blocked catheters, catheter sepsis, hypertrigliceridaemia, hyperbilirubinaemia, coagulopathy or intraventricular haemorrhage between treated and untreated group ((103) (LOE 1−)). However, the study sample was again too small and with a high risk of bias.

Statements and Recommendation

- There is no proven benefit of heparin for the prevention of thrombotic occlusion of CVC's under regular use in children. Therefore its routine use is not recommended. **LOE 1−**
- With respect to CVC's not in regular use, in adults, flushing with 5 to 10 U/ml of heparinised saline once to twice weekly was useful in maintaining CVCs patency and is recommended. **GOR D**
- Routine use of heparin has not been shown to be useful in prevention of complications related to peripherally placed percutaneous CVCs in neonates. **LOE 1−**

Skin hygiene, Dressing Methods and Frequency of Dressing Changes

Skin Antisepsis and Hygiene

Extensive studies have been done to determine which antiseptic solution is the most effective way of removing micro organisms from the skin surface before catheter insertion and during catheter care. The best option appears to be 2% chlorhexidine, which was found to significantly reduce catheter related infections (CRI) ((104) (LOE 1+); (105) (LOE 2++)). In a comparison of 2% chlorhexidine to povidone-iodine and 70% alcohol, it was shown that the two latter solutions were associated with a fourfold higher incidence of CRI ((106) (LOE 1+)). However, when 0.5% chlorhexidine was applied and compared to 10% povidone-iodine no difference in prevention of catheter related bacteriemia could be demonstrated ((107) (LOE 1+)).

Recommendations

- Before insertion of an intravascular device and for post-insertion site care, a clean skin should be disinfected. Application of 2% chlorhexidine is preferred, rather then 10% povidone-iodine or 70% alcohol. **GOR A**
- Antiseptic solution should remain on the insertion site and air dry before catheter insertion or dressing application. **GOR D**
- Organic solvents (acetone, ether, etc.) should not to be applied on the skin before insertion of a catheter or during dressing changes. **GOR D**

Dressing Methods and Frequency of Dressing Changes

Apart from providing protection from external contamination, the purpose of the dressing is to secure the CVC and to prevent dislodgement and trauma. Traditionally it was common to dress the CVC site with dry gauze and tape. This method gave way to transparent polyurethane film dressings, defined as dressing composed of a thin

polyurethane membrane coated with a layer of acrylic adhesive. Potential advantages of these dressings include improved security of the catheter, visibility of the wound site, provision of an effective barrier to micro organisms and, therefore, less frequent need for dressing changing. However, there is a concern that the polyurethane dressings may increase the skin surface humidity, resulting in increased colonization of the micro organisms at the catheter insertion site ((108) (LOE 1+); (109) (LOE 1+); (110) (LOE 1+)), thereby increasing the risk of catheter related infections ((108) (LOE 1+), (111) (LOE 2+)).

Numerous studies have investigated the differences between dressing regimens (incidence of CVC-related infection, catheter security, dressing condition and ease of application, tolerance to dressing materials) ((112) (LOE 4)). The first meta-analysis that compared the effect of two different dressing types concluded that the risk of catheter tip infection, but not sepsis, was significantly increased with transparent CVC dressings compared to gauze and tape ((113) (LOE 1−)). However, according to the recent Cochrane Systematic Review by Gillies, et al., several factors could have biased the results of the above mentioned meta-analysis (114). This review failed to demonstrate any difference in the incidence of infectious complications between any dressing types compared (gauze and tape vs Opsite IV300, Opsite vs Opsite IV300, Tegaderm vs Opsite IV300, Tegaderm vs Opsite). As most of the included studies were performed on a small patient sample, they probably did not have a sufficient power to detect any differences between the groups. The authors, therefore, concluded that at this stage the choice of dressing for CVC can be based on patient preference, while the answer on ''What is the appropriate dressing to use for CVC'' requires further research ((114) (LOE 1++)).

Most of the studies mentioned have been done in adult populations, as there are very few studies involving children. A trial looking at the prevention of CVC infections in neonates concluded that the use of alcohol for cutaneous antiseptics with a subsequent placement of a chlorhexidine-impregnated dressing (Biopatch) over the insertion site of CVC (which should be left on for up to 7 days between dressing changes), provides protection against catheter tip colonisation. The rates of catheter related blood stream infections and blood stream infections without a source were, however, similar among treatment groups. A substantial risk of contact dermatitis at the dressing site may limit its use in low birth weight infants in the first 2 weeks of life ((115) (LOE 1+)).

Taylor et al, conducted a study on paediatric population with the aim of determining whether ''microbial growth increased significantly over time when occlusive dressings were used to cover CVC insertion sites''. They concluded that occlusive dressings, changed every 3 to 4 days using an aseptic technique, are safe and efficient and provide a barrier that prevents CVC exit site contamination with children's body fluids, food, and surgical wound drainage, and helps to anchor and stabilise the tubing ((116) (LOE 2−)). Although tunnelled central venous catheters with well-healed exit sites do not require any dressing to prevent dislodgement, it is useful to have them covered.

Concerning catheter submerging, according to Robbins et al, swimming does not increase the risk of catheter-related infections in children with tunnelled catheters ((117) (LOE 2−)).

The use of topical antibiotic ointments to clean the insertion sites at dressing changes is not recommended, as such ointments are associated with an increased frequency of fungal infections ((118) (LOE 1−)), antibiotic resistance ((119) (LOE 3)), and might adversely affect the integrity of polyurethane catheters ((120) (LOE 3), (120) (LOE 3)).

Recommendations

- Both, sterile gauze + tape and various transparent polyurethane film dressings can be used for the catheter site. **GOR A**
- If the catheter site is bleeding or oozing, a gauze dressing is preferable to a transparent, semi-permeable dressing. **LOE 4**
- The catheter-site dressing should be replaced when it becomes damp, loosened, or when inspection of the site is necessary. **GOR D**
- On short term CVC sites dressings should be replaced every 2 days for gauze dressings and at least every 7 days for transparent dressings, except in those paediatric patients in which the risk for dislodging the catheter outweighs the benefit of changing the dressing. **GOR B**
- Topical antimicrobial ointments should not be used routinely at the insertion site as they may promote fungal infection, antimicrobial resistance and damage the surface of the catheters. **GOR D**
- With tunneled catheters swimming is possible if the catheter is secured with water resistant dressing. **LOE 4**

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Journal of Pediatric Gastroenterology and Nutrition
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10. Organisational Aspects of Hospital PN

METHODS

Literature Search

Timeframe: publications from 1992–2003, in addition relevant publications from 1980–1992 and 2005 were considered.

Type of publications: randomised control trials, case control or cohort studies, case series, case reports, reviews (expert opinion).

Key Words: parenteral nutrition, computer assisted prescribing, nutritional care teams, nutrition support teams, monitoring, nutritional assessment, nutritional support, anthropometry, growth monitoring, intravenous therapy, infusion pumps, filters, nutrition team.

Language: English.

ORDERING AND MONITORING PARENTERAL NUTRITION IN HOSPITAL

Introduction

The process of providing parenteral nutrition (PN) is far from being evidence based (1,2). The ordering process, in particular, has not been investigated systematically, and much more attention has been focused on defining the requirements for various nutrients. The aim of the following summary is to provide a framework for the nutrition team member responsible for ordering PN.

The purpose of PN is to correct or prevent nutritional deficiencies when adequate enteral feeding is precluded by impairment or immaturity of gastrointestinal function. The PN order should be part of an overall nutritional care plan. Mandatory steps before the initiation of PN include a thorough nutritional assessment (medical and dietary history, physical examination, laboratory data, etc). Probable duration of PN administration should be estimated, and nutritional goals set. The process is dynamic, and the order should take into account changes in nutritional and clinical status.

PN Ordering

There is little evidence of efficacy from randomised control trials of PN improving outcome (3). Accepted goals for PN are prevention of weight loss, maintenance of normal growth, and promotion of catch-up growth. Essential pre-requisites to the ordering process include secure venous access, and the availability of medical, nursing, dietetic and pharmacy staff skilled in the management of PN and its complications. Clinical pathways have been designed to facilitate the management of PN in children. These pathways include developing a nutrition support team, and structuring a comprehensive set of clinical, laboratory, and management parameters to ensure adequate PN administration (4,5). Bowman et al have demonstrated that monitoring compliance with such a nutrition support algorithm can improve quality of care.

Delivery of Parenteral Nutrition

PN may be given via a peripheral or central venous catheter (PVC/CVC) depending upon the availability of venous access and the osmolality of the solution (for further discussion on this topic see chapter on venous access). Weight gain is more commonly achieved with central versus peripheral infusion (6). In certain circumstances PN may be given in dialysis solutions (7) or via ECMO (8).

Individualised Versus Standard Parenteral Nutrition

Time pressures on the pharmacy, limitations of resources and cost considerations make the use of standard solutions an attractive option. These standard formula do not meet all the requirements of newborns, infants and children (9,10), although even in those units relying on individualised prescribing, there is some scope for their use in stable patients (11). A study comparing short term standard solution (fixed amino acid/glucose ratio) with a computer generated individualized prescription, taking enteral intake and additional fluids into account, did not find any differences in the weight gain of premature infants (12). In contrast, a randomized control study comparing individualised versus standard PN formulation in premature infants demonstrated higher intakes of amino acids, lipids and energy, with greater weight gain, in the group receiving individualised PN (13). However, the difference in caloric intake and weight gain might not be attributable to the administration of standard solutions per se, but to the more intensive monitoring assisted by pharmacists in the group receiving individualized PN. Uncritical use of standard formulations, particularly over longer periods of time, may be detrimental to growth and development (LOE 4).

Computer Assisted Prescribing

The ordering process is time consuming, necessitates knowledge and experience, and involves the risk of fatal

errors (14). Computer programs for ordering PN are widely used (14–19). One such program reduced the time needed to calculate a nutrition plan from a mean of 7.1 minutes to 2.4 minutes, with errors in calculation being corrected interactively and reduced from 56% to 22% (14). In another study, the time required to write and deliver PN orders was significantly lower using computer rather than manual methods (1.4 ± 0.2 vs 4.5 ± 0.5 minutes; $P = 0.0001$), and the use of computer ordering lead to significant improvements in the nutrient composition of the PN for energy, protein, calcium, and phosphate (20). In addition, alkaline phosphatase concentrations improved, and caloric and protein goals were achieved sooner, compared with the manual method of ordering (20). Available programs can provide rapid definition of the nutrition plan with reduced likelihood of providing excessive glucose and energy (21).

Initial Prescription

Fluid requirements, nitrogen and energy needs should be established and the total fluid volume available for PN solutions determined. Details of water and nutrient requirements at different ages are given elsewhere in this publication.

Monitoring

Suggested assessment before PN initiation is given in Table 1. Selection and frequency of biochemical monitoring parameters will reflect clinical and nutritional status in addition to duration of feeding. For example, patients with abnormal fluid losses or organ failure require more frequent monitoring, as do those who are under weight and at risk of re-feeding syndrome. Sudden, unexpected and serious biochemical abnormality in stable patients without severe malnutrition when receiving PN is uncommon (22). Nursing observations will include catheter inspection together with temperature and heart rate; periodically the nutrition team should review nutritional status and goals of nutritional intervention. Quality indicators of a PN service include regular audit of PN utilization/wastage, complications (particularly CVC sepsis), and communication with pharmacy (23).

TABLE 10.1. *Suggested assessment before ordering PN for infants and children* depending on clinical status (LOE 4)*

- complete diet history
- anthropometry (weight, height/length, head circumference)
- full blood count (including platelets and differential white count)
- electrolytes
- urea/creatinine
- glucose
- calcium/phosphate
- albumin (or pre-albumin)
- liver function tests
- cholesterol/triglycerides
- urinary glucose and ketones

*These parameters are examined 2–3 per week initially, and the frequency is ''tapered'' based on the patients' clinical status and long term goals. When PN extends beyond three months, trace elements, ferritin, folate, vitamin B_{12}, thyroid function, clotting, and fat soluble vitamins are often measured.

TABLE 10.2. *Review of nutritional status undertaken during parenteral nutrition*

Weight for height (% expected): 100 × weight, divided by 50th centile weight for observed height when plotted on 50th centile.
Triceps skin folds thickness (27)
Mid arm circumference (28)
Arm fat area
Mid arm circumference: head circumference ratio (29)

Recommendations for Ordering and Monitoring Parenteral Nutrition in Hospital

- Nutritional support algorithms should be followed for the ordering and monitoring of parenteral nutrition. **GOR D**
- Compliance with the algorithm should be monitored to improve quality of care. **GOR D**
- Although individualized PN is preferred, with adequate monitoring and the scope for addition of deficient electrolytes and nutrients, standard PN solutions can be used for short periods of up to two weeks (LOE 4). This is potentially more useful in newborn infants when providing PN soon after birth, and when a range of standard regimenns to suit different clinical conditions might be available. **GOR D**
- Computer assisted prescribing of PN should be encouraged, as this can save time and improve the quality of nutritional care. **GOR B**

NUTRITIONAL ASSESSMENT

Introduction

A multidisciplinary nutrition support team should monitor the process of parenteral nutrition. Nutritional status can be assessed using simple and non-invasive measurements of body dimensions (anthropometry). Appropriate equipment and trained staff ensure consistency. Early nutritional assessment identifies children at nutritional risk. Nutritional intervention minimizes wasting and restores body cell mass, optimises nutritional status, improves quality of life and prolongs survival. The aim of a nutritional assessment is to establish baseline subjective and objective nutritional parameters (24) by which to judge the effects of parenteral nutrition, and is divided into clinical examination, anthropometry, laboratory indices, and assessment of dietary intake. It should also identify specific nutritional deficits, determine nutritional risk factors for individual patients,

establish nutritional needs, and identify medical and psychosocial factors influencing the prescription and administration of parenteral nutrition (25,26).

Clinical Examination

Clinical examination provides an important overall impression of health. Severe nutritional deprivation is easily detectable in most instances. Through medical, dental history and physical examination, signs suggestive of nutrient deficiency or excess should be documented and supported with biochemical, anthropometric and dietary evaluation.

Anthropometry

Anthropometric data includes height, length, head circumference (under 3 years old), current weight, ideal weight and weight/height ratio.

Standardised nutritional assessments should be accurately recorded and form the basis for PN audit. Serial data show changes and rates of changes, giving a dynamic picture of progress. Regular measurements of height, weight and head circumference with comparison to normal values for chronological age using percentile charts remain the most useful assessment tools for nutritional interventions ((30) (LOE 4)). Accurate chronological ages are essential when using growth charts (31,32). Expression of measurements in terms of standard deviation scores allows changes in rates of growth with time to be detected more easily than from observation of percentile charts. Measurements of skin fold thickness and mid arm circumference, along with calculation of mid arm fat area and mid arm muscle area, reflect body fat and protein. Skin fold thickness provide an index of body energy stores and is used in conjunction with 'weight for height' to assess body composition (33).

Laboratory Assessment

Laboratory investigations provide an objective assessment of nutritional status and are useful in the detection of early physiological adaptation to malnutrition and the recognition of specific mineral and vitamin deficiencies (34). Laboratory data should be reviewed and documented. A number of biochemical measurements, usually of serum proteins, are used. None is ideal, as they have differing half lives and are all affected by other non-nutritional physiological and pathologic states.

Dietary Intake

Subjective assessment must include a dietary record that focuses on nutritional history. Recent changes in dietary intake, review of enteral feeds and parenteral nutrition, gastrointestinal symptoms, cultural and religious dietary prescriptions, as well as concurrent medical and surgical problems that may affect nutritional assessment should be documented.

Recommendation

- Accurate measurements and clinical evaluation of patients receiving PN should be undertaken 2–3 times weekly by a skilled practitioner (e.g. Dietitian or Nutrition Support Nurse). **GOR D**

WEANING FROM PN

Children with an acute episode of severe intestinal failure e.g. post surgery or during a course of chemotherapy may tolerate rapid reintroduction of a normal diet. Children with primary gut disease need the method of feed introduction tailored according to the underlying disease.

The following factors should be considered when introducing enteral nutrition:

- Appropriate minimal enteral feeds should be given wherever possible to prevent gut atrophy ((35) (LOE 3)), encourage adaptation ((36,37) (LOE 3), (38) (LOE 4)), ((39) (LOE 4)) and reduce the risk of PN-associated liver disease ((40) (LOE 3)). In newborn infants with short gut expressed breast milk is the preferred nutrition to optimise adaptation. The mother's milk should be given either fresh (in case of small bolus feeding) or pasteurised (in case of continuous feeding).
- Always make one change in treatment at a time to assess tolerance e.g., when the volume of enteral nutrition is increased, the concentration of the nutrition solution should remain constant.
- In severe intestinal failure feed volumes should be increased slowly, according to digestive tolerance.
- An experienced dietitian/nutrition support team should be involved.
- Central venous access should be maintained until the child can be fully fed enterally.

The initial over-riding priority is to wean the child off PN since there are life-threatening risks to continuing it. Enteral nutrition can be introduced as liquid enteral feed infused as continuous enteral nutrition over 4 to 24 hour-periods, using a volumetric pump via an artificial feeding device. The main advantage of a continuous feed is that full use of the intestinal tract is made, particularly if given over 24 hours. The feeding should be prepared under strict hygiene condition and should not be kept at room temperature longer than 8 hours. To reduce the risk for *Enterobacter sakazakii* infetion a ready made liquid formula is preferred over a powdered formula. Although continuous feeding is not practical in the long-term, it is often necessary as an initial manoeuvre.

Some children can be weaned straight on to bolus feeds. Liquid enteral nutrition can be given as bolus or sip feeds

either orally or via an artificial feeding device. This is most likely to be the case when the intestinal tract has significantly improved since the need for PN arose. It may be necessary to give the bolus feeds as frequently as 2-hourly while the child is awake and as an option continuously at night. If they are needed more frequently, a continuous feed should be commenced. Bolus feeds should be offered by mouth whenever possible. Smaller infants should not be woken up to give oral feeds to avoid fatigue. If gastric feeds are poorly tolerated (vomiting/large amounts of feed aspirated) feeding into the jejunum should be considered. The decision should be taken only by an expert gastroenterology team, as this is a high risk technique.

Children who rapidly recover intestinal function may be weaned straight on to normal food. However, if there is any possibility of persistent intestinal inflammation, diet may need to be adjusted. For example, the prognosis of neonates with short gut syndrome is improved with breast milk ((40) (LOE 3)) or an amino acid based formula feed ((41) (LOE 3)) as there appears to be a high incidence of cow's milk or soya protein intolerance.

Every possible attempt is made to encourage children to eat normally. Spoon feeding should be introduced at normal age, that means around 6 months of age, even if only small amounts can be offered. Some children may develop severe oral disability which may be associated with gastro-oesophageal reflux (42) that worsens with an increase in feed. Some mothers will find it difficult to accept that their child ceases to eat voluntarily when an adequate amount of enteral feed is infused via an artificial feeding device.

Recommendations

- Rather than enteral starvation, minimal enteral feeds should be given whenever possible. **GOR D**
- An experienced dietitian/nutrition support team should be involved. **GOR D**
- When introducing enteral feeding only one change in treatment at a time should be made to assess tolerance. **GOR D**
- In severe intestinal failure feed volumes should be increased slowly, according to digestive tolerance. **GOR D**
- Enteral feeding can be introduced as liquid enteral feed infused as continuous enteral nutrition over 4 to 24 hour-periods, using a volumetric pump via an artificial feeding device. **GOR D**
- Liquid enteral nutrition can be given as bolus or sip feeds either orally or via artificial feeding device, if tolerated. **GOR D**
- Children who rapidly recover intestinal function may be weaned straight on to normal food. **GOR D**

Types of Feed

Children with a primary gastrointestinal disease causing intestinal failure usually require a specially formulated paediatric enteral feed when weaning. If at all possible a commercially available complete feed that provides the child's entire nutritional requirements should be used. This reduces the risk of providing an unbalanced diet and the risk of infectious complications.

Elemental, hydrolysed protein or whole protein feeds are selected according to the child's ability to tolerate the feed constituents or availability in the case of expressed breast milk. Short bowel syndrome is an indication for hydrolysed diet, at least in children <1 year, during the first months of the adaptive period. There is evidence that an amino acid based feed might be even better tolerated ((41) (LOE 3), (43) (LOE 3)). A high osmolarity may be of disadvantage.

Modular feeds should only be used when feeds appropriate for the individual have not been tolerated. The advantage of a modular feed is that protein, carbohydrate and fat (MCT vs LCT) can each be gradually introduced as tolerated. Electrolytes, vitamins and minerals must all be added according to requirements. A tailor made feed can be produced for the individual child. Modular feeds are generally not recommended due to the risk of bacterial contamination; the possibility of accidentally omitting essential nutrients, preparation at home can be complicated, and there may be settling out of the feed constituents when the feed is administered continuously. However, in children with ultra short bowel syndrome modulare feeds enable to improve and increase the enteral energy intake and tolerance.

Recommendation

- Children with a primary gastrointestinal disease causing intestinal failure usually require a specially formulated paediatric enteral feed when weaning. **GOR D**

When to Wean

Reduction in the amount of PN may be attempted as soon as the child is stabilised i.e. intestinal losses from vomiting and diarrhoea have been minimised and an optimal nutritional state reached. The underlying intestinal failure should be investigated and treated in a specialist unit with specialist expertise in paediatric gastroenterology.

All children on parenteral nutrition should continue to have a minimal amount of enteral feed to maintain enterohepatic circulation and possibly gut integrity ((44) (LOE 3), (40) (LOE 3), (45) (LOE 3)) whenever possible. As soon as a small volume of the desired feed is tolerated at low rate, the volume should be increased. The feed

should be given at normal concentrations and not diluted, otherwise the child will achieve normal fluid intake without adequate nutrition. The aim should be to maintain a good nutritional intake by decreasing the parenteral feed and increasing the enteral feed by similar amounts. This is best achieved by reducing the parenteral feed slightly faster than the rate the enteral feed is increased. Enteral tolerance is more likely to be achieved by avoiding excessive fluid intake. In children with more severe intestinal failure, enteral feeds may need to be introduced and increased as slowly as 1 ml/kg per 24 hours. Parenteral nutrition might be reduced by 5 ml/kg per 24 hours every few days. If a chosen weaning strategy fails it is worth trying again, but at a slower pace e.g. with smaller rate increments.

In children who are stable and thriving on PN at home, many experts try to remove one PN infusion per week to improve the quality of life for the family. If tolerated, further reductions are made by reducing one night at a time over several weeks or months. Weaning can be facilitated by reducing/halving the PN given one night a week and seeing how well the child is the following day. If fluid and electrolyte loss is the main issue noctural application of a rehydration solution via a gastric tube may be a solution. In older children it may be possible to reduce the PN by a night per week even when they are still having virtually all their nutrition intravenously. In infancy a night off would, usually, only be tried when at least 50% of nutrients are tolerated enterally. The ability to tolerate a night off PN varies according to the underlying disease. A night off is usually well tolerated by children with short bowel syndrome who are stable with improving intestinal function. In children with short bowel, weaning is prolonged in the presence of bacterial overgrowth and associated enteritis (42). In children with chronic intestinal pseudo-obstruction, especially with ileostomy and major faecal losses, removing one night of PN often leads to a rapid increase in water/feed intake leading to aggravation of symptoms.

The child's ability to tolerate the reduction is assessed by checking weight gain, growth, and blood indices (see Complications chapter).

Problems that can arise when weaning is not tolerated include D-lactic acidosis due to lactate production from fermentation of non absorbed nutrients by the bacterial flora in the colon and distal ileum due to the increased intake of enteral nutrition. Although some studies have indicated that bacterial fermentation is more of a problem in the absence of the ileocaecal valve ((46) (LOE3)), this does not always seem to be the case ((42) (LOE3)). Such complication may be prevented/treated by a low fibre diet, bicarbonates and, sometimes, anti anaerobic antibiotics (Metronidazole) plus probiotics ((42) (LOE 3)). Sometimes it is necessary to reduce intestinal load and increase PN again whilst waiting for intestinal adaptation to improve allowing for recommencement or continuation of the weaning process.

Recommendations

- Enteral nutrition should be given at normal concentrations and not diluted. **GOR D**
- PN should be reduced by similar amounts or slightly more than the increase in EN. **GOR D**
- If a chosen weaning strategy fails, trying again more slowly is an option. **GOR D**

Psycho-Social and Developmental Aspects of Feeding

Whenever possible it is important to maintain small volumes of oral feeds and monitor the adequacy of feeding skills, even if the infant or child is established on continuous feeds.

Solids should be started at the usual recommended age for healthy infants when possible. It is best to limit these initially to a few foods that are least likely to have an allergenic effect (especially in intestinal inflammation) e.g. rice, chicken, carrot, and which will be suitable for the underlying gastrointestinal disease e.g. low sucrose/low in LCT fat or low fibre in short bowel and/or extensive colon resection.

When food is introduced, the aim is to encourage normal textures for age ((47) (LOE 4)). Even if the amount and range of foods are limited, introducing normal food will promote normal feeding behaviour. Encouraging oral feeding will help to prevent feeding problems which can continue for many months or even years.

Even in younger infants, bolus feeds may have beneficial psychologic and social effects. For example, the mother will feel that she is doing something to help her sick child. Maternal bonding may be improved by the close contact between mother and child. Feeding by mouth should be a pleasurable event for mother and child.

Recommendation

- Whenever possible small volumes of oral feeds should be maintained. **GOR D**

INFUSION EQUIPMENT AND INLINE FILTERS

As with most parenteral therapy, one of the greatest hazards to patients during administration of nutrient solutions arises from the risk of free flow or poor rate control of the infusion. To the potential risks of fluid overload and heart failure are added complications such as hyperglycaemia, aminoaciduria and biochemical imbalance. A modern infusion pump is preferred with its capability to accurately deliver at low flow rates (48,49). Alarm functions are necessary, but sensitivity is

often limited at low rates of flow. The ability of children to learn to manipulate devices should not be underestimated. If pumps are not available, the use of portable, battery powered drop counting devices can provide effective warning of free flow conditions.

PN solutions contain particulate matter (50) and biochemical interactions can lead to chemical precipitates and emulsion instability. PN solutions are also media for microbiologic contamination. Localised tissue damage at the infusion site is related both to osmolarity of the solution and particulate contamination (51). The routine use of inline filtration has been advocated. Some endotoxin retaining 0.22 μm filters allow cost savings through extended use of the administration set. With appropriate filters, sets can be used for 72–96 hours. Many solutions are stable for extended hang-times but explicit stability advice should be sought from the manufacturer or a competent independent laboratory. Filter blockages indicate a problem with the solution, not the filter, and must be thoroughly investigated.

Recommendations

- All PN solutions should be administered with accurate flow control. The infusion system should undergo regular visual inspection. Peripheral infusions should be checked frequently for signs of extravasation. The pump should have free flow prevention if opened during use, and have lockable settings. **GOR D**
- All PN solutions should be administered through a terminal filter. Lipid emulsion (or all-in-one mixes) should be passed through a membrane of pore size around 1.2–1.5 μm. Aqueous only solutions should be passed through a filter of 0.22 μm. **GOR D**

NUTRITION SUPPORT TEAMS

A multidisciplinary nutrition support team (e.g. doctor, nurse, dietitian/nutritionist, pharmacist, possibly others) has an important role in coordinating optimum nutritional care, educating staff, developing guidelines, promoting research (52) and reducing inappropriate PN use ((53) (LOE 3)). A specialist clinical nurse has been shown to reduce catheter related blood stream infection rates in a number of different studies involving adult patients (54–60). Staff training by a nutrition nurse has also been shown to reduce the prevalence of catheter sepsis on a busy neonatal surgical ward ((61) (LOE 2)). Insertion of central venous catheters by an experienced physician is associated with a reduced risk of complications (60,62). The implementation of nutrition support teams has been recommended by the ESPGHAN Committee on Nutrition (63).

Recommendation

- Supervision of parenteral nutrition patients necessitates a multidisciplinary nutritional support team as this is associated with decreased use of inappropriate PN, and decreased metabolic and catheter related complications. **GOR D**

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Journal of Pediatric Gastroenterology and Nutrition
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11. Home Parenteral Nutrition in Children

METHODS

Literature Search

Timeframe: publications from 1990, but single publications from 1980 onward were also considered.

Type of publications: case-control or cohort studies.

Key Words: Children, parenteral nutrition (PN), home, long-term, cost, quality of life, complications, liver disease, metabolic bone disease, catheter-related sepsis, prevention.

Language: English.

INDICATIONS

Why Start an HPN Programme?

In children, as in adult patients, long-term total or complementary PN is required to preserve nutritional status when oral or enteral nutrition cannot provide protein-energy needs, especially in diseases which impair digestive function. When a child does not need hospitalization but depends on long-term PN, home PN (HPN) is an alternative to prolonged hospitalisation and is recognized as the best option for improving the quality of life of these children and their families within the constraints of the disease.

Underlying Disease

The main indications for prolonged PN and thus HPN in children are primary digestive diseases causing intestinal failure 1. Short bowel syndrome ((2) (LOE 4); (3) (LOE 4); (4) (LOE 4)), mainly congenital, is the largest group, accounting for at least 30% of cases in the major published surveys ((5) (LOE 3); (6) (LOE 3); (7) (LOE 3)). The main other digestive indications are intractable diarrhoea of infancy ((8) (LOE 3)), chronic intestinal pseudo-obstruction ((9) (LOE 3)) and inflammatory bowel diseases, especially Crohn's disease. Primary non-digestive indications such as immune deficiency including AIDS, tumours, metabolic diseases, and end stage liver diseases before transplantation account for about 20% of patients. The need for HPN in these diseases is usually shorter than for primary digestive diseases.

Age

Age for safely commencing PN at home depends on each individual condition. Most paediatric HPN programmes cater for children under one year old and include babies under the age of 6 months ((5) (LOE 3); (7) (LOE 3)).

Condition

Patients eligible for HPN should be in a stable condition. This includes stability of the underlying disease, fluid and electrolyte requirements, and reliable central venous access.

Social and Familial Requirements for HPN

Whatever the medical indication, some social and familial criteria have to be fulfilled before a child's HPN programme is organized. Parents have to be informed, motivated and should be able to cope with all medical, emotional and technical problems related to HPN. Family suitability for HPN must be carefully assessed by a health care team member ((10) (LOE 4)). This may include visiting the home, to examine practical details such as space for dedicated refrigerator, electricity, and connected telephone ((11) (LOE 4); (12) (LOE 4)).The assistance of a social worker, before discharge, is needed, especially the home environment is inadequate (e.g. bathroom facilities on the same level as the child's bedroom). In other cases, the professional status of both parents needs to be carefully examined, for occasionally one of them has to stop working. In one-parent households, the mother is usually the parent responsible for administering HPN. A single-parent family is not always a contraindication for HPN, but social help and home nursing assistance may become necessary ((5) (LOE 3); (6) (LOE 3)). Separated parents who share the child's care should be trained providing they each connect/disconnect the PN at least once a week to maintain their skills.

Cost Savings

HPN is an expensive technique. The annual cost of HPN per patient, including nutrients, pump and disposable equipment, was evaluated to amount to about 60,000 to 80,000 £ ((11) (LOE 4)) in England ((13) (LOE 2+)), but as much as 100,000 to 150,000 US dollar in the USA ((14) (LOE 4); (15) (LOE 4)). However, cost-benefit studies have demonstrated that HPN is about 65% more cost-effective than hospital treatment for children as for

adults ((16) (LOE 2++); (14) (LOE 4); (13) (LOE 2+)). The longer a patient survives on HPN, the more cost-effective home-treatment becomes. A paediatric study showed that HPN in the UK led to cost savings of about 2 millions euros in a single year by the decrease in the incidence of septic episodes from 1/142 days in hospital to 1/567 days at home ((17) (LOE 2+)).

Statement and Recommendation

- HPN is less costly than hospital care. **LOE 2+**
- All children who depend on long-term PN should be discharged on HPN, if familial criteria are fulfilled. **GOR D**

PREPARATION OF AN HPN PAEDIATRIC PROGRAMME

Prior to discharge, parents must undergo structured training in all aspects of care and complications ((18) (LOE 3); (6) (LOE 3); (11) (LOE 4); (12) (LOE 4), (19) (LOE 4)). The teaching programme should begin as soon as the decision to proceed to HPN has been taken. It is best undertaken during the period when at least one parent, or preferably both, is resident in the hospital, especially if the family lives far from the HPN centre. The mean duration of the teaching programme is about 2 weeks ((6) (LOE 3); (11) (LOE 4)), but the duration needs to be tailored to each family's needs. The structured teaching programme must have a written plan, step by step instructions and a method to record competence comprising theoretical and practical aspects. Written and audiovisual tools may be used. Each session is limited to learning one particular skill, and a new subject should only be introduced when parents are competent and confident in the previous one. A written record of progress should be kept (Table 11.1). Some teams recommend that the parents spend 1 to 2 nights with their child in a special ''isolation'' room, close to the medical unit but without any help from hospital nurses, to simulate home conditions and to assess their autonomy, just before the family returns home ((6) (LOE 3)). When parents cannot be autonomous, especially in case of a single parent family, the help of a community nurse is required ((6) (LOE 3); (12) (LOE 4)). In some countries, candidates for HPN can be referred to outside service organizations, which use nurses who sometimes meet the family in the hospital for the first encounter and then visit the patient at home to complete the training given at the hospital. Community health professionals should be involved in all aspects of discharge planning and subsequent shared care ((11) (LOE 4); (20) (LOE 4); (21) (LOE 4)). The physician and the teaching nurse from the HPN centre should inform staff from the patient's local hospital about guidelines for emergencies such as fever, pump or line failure ((11) (LOE 4)). This may be done by holding a discharge planning meeting attended by parents and all professionals involved in the child's care. It is best held at the patient's local hospital. Those attending may include the child (if old enough), parents, members of the specialist nutrition team, local paediatrician and a nurse from the local hospital, community nurse and the patient's general practitioner.

Recommendations

- Parents should undergo a structured teaching and training programme, conducted by a nurse from the HPN centre's nutrition support team. **GOR D**
- Parents' skills and knowledge should be checked before home discharge. **GOR D**
- Community health professionals and staff from the local hospital should be involved in all aspects of discharge planning and subsequent shared care. **GOR D**

TECHNIQUES

Vascular Access

Children on HPN require a reliable central venous access (see chapter on venous access). No data is available to compare implanted ports with Broviac-type catheters for paediatric HPN use in terms of quality of life and complications. Extensive thromboses are a possible problem in patients who receive HPN over long periods of

TABLE 11.1. *Parents' knowledge required before home discharge on HPN*

Parents' knowledge	Handling	Catheter and line	Pump	Child
Current care	Hand washing technique Preparation of sterile field Drawing up solutions into syringe	Flushing or heparinisation Initiation and termination of infusion	Operation Maintenance	Catheter exit site Temperature
Emergency What to do? Who to contact?	Materials missing	Blockage of line Breakage/split catheter Air in the line	Alarms	Exit site Infection Fever Digestive problem

time. In these circumstances, alternative sites for venous access may need to be used. Rarely, arterio-venous fistulae can be used for long-term HPN programs, especially in the case of repeated catheter complications ((6) (LOE 3)).

The Infusion Cycle

HPN is based on cyclical (10 to 18 hours per day) parenteral infusion of nutrient formula ((6) (LOE 3); (11) (LOE 4)). Children, like adults, almost always tolerate a nocturnal infusion over a period of 10 to 12 hours, especially when oral or enteral feeding is possible. Cyclic infusion has metabolic, physical and psychologic advantages. In infants, especially when enteral feeding is not tolerated, or in children with major digestive fluid and electrolyte losses, a longer period of infusion is required (14 to 18 hours). When PN is initially started in hospital all children are infused continuously 24 hours per day. They then undergo a period of adaptation, during which time the rate of infusion is gradually increased and the infusion period decreased, usually from 24 to 12h per day, and in exceptional circumstances to a maximum of 18 hours. A progressive increase and decrease of infusion rate during the initial and final hours of infusion should be considered to avoid hypoglycemia and hyperglycemia in some patients ((6) (LOE 3)).

Pumps, Equipment and Ancillaries

A pump is essential for parenteral infusion in children. Pumps for PN at home should reach a good compromise between safety and comfort. The main requirements for safety are: volumetric accuracy in wide range of flow rates, no risk of sudden discontinuation of infusion (reliable battery), no risk of free flow, ''keep vein open'' status, audible and written alarms (e.g. for air bubbles in line, empty container, occlusion, change in pressure, dose limit or low battery) and child proof ((20) (LOE 4)). Other requirements are also important for the quality of life: simplicity to prime the set and clear air, preselection of infusion rates and of programmed stepwise increased and decreased flow rates at the onset and end of the infusion times, minimum false alarms, minimum motor noise, minimum weight and volume with carrying handle and binding on IV poles. Portable pumps are now more widely available and can have a major impact on improving quality of life. Any faulty pump should be replaced within a reasonable time span (e.g. 4 hours), or a second pump should be available at home. Pumps should be annually serviced.

The supply of equipment and ancillaries should be delivered to the home. Families should not have to collect equipment from different sources ((20) (LOE 4)).

Filters

The importance of filtration to reduce the risk of precipitates reaching the patient has been emphasized ((22) (LOE 3); (23) (LOE 2++)). Filters should be 1.2 μm air-eliminating filters when an all-in-one, lipid-containing formula is delivered, in contrast to 0.22 μm air-eliminating filters usable for non-lipid-containing PN.

Recommendations

- Single lumen catheters should not routinely be used for blood sampling. However, to reduce stress and trauma to the child blood sampling from single lumen catheters may be considered when connecting or disconnecting PN on an individual basis. **GOR D**
- Flow control should be provided by a pump with free flow prevention, air alarm, occlusion alarm and lockable settings. **GOR D**
- HPN delivery should be cyclic. A progressive increase and decrease of infusion rate should be considered to avoid hypo-/hyperglycaemia. **GOR D**
- Filters should be used to avoid the risk of precipitates/particulates. **GOR C**

FLUIDS AND NUTRIENTS

Requirements vary depending on age, weight, underlying disease, hydration status and environmental conditions. When PN is not the sole source of protein-calorie intake, intestinal absorptive function should be estimated. Digestive tract losses due to diarrhoea or from stomas should be measured (volume and sodium concentration), replaced and the patient should be on a stable regimen before starting a HPN programme.

Vitamins and Trace Elements

Each PN infusion should provide vitamins and trace elements, according to patient's age, weight and specific needs. In certain circumstances, e.g. patient weaning from PN, vitamins and minerals may be given enterally (will also reduce the cost of the bags). Vitamins will need to be given separately if it is not possible to obtain stability in the PN, e.g. if PN bags can only be delivered on a monthly basis.

Nutrition Mixtures for Paediatric HPN

Binary mixtures including glucose, amino acids, electrolytes, trace elements and vitamins (lipids being administered separately on a Y-line) or all-in-one mixtures are provided to children on HPN. Mixtures may be

manufactured and delivered to patients with ancillary equipment weekly, fortnightly or monthly. Vitamins or drugs added to nutrient mixtures might impair their stability and, on the other hand, availability of drugs and vitamins might be reduced when introduced into PN mixtures ((24) (LOE 3)). Thus, depending on these limiting factors, the "safe" duration of PN bag storage varies from about 8 to up to 30 days. Bags should be stored at 4 C from their production to their delivery to patients. Home care companies should provide the families with dedicated refrigerators for PN bag storage. Special mixtures should be prepared according to individual requirements ((6) (LOE 3)). The so-called standard PN mixtures compounded by pharmaceuticals companies, usable only for adult patients on short-term and/or complementary PN, cannot meet children's nutritional requirements and are free of vitamins and trace elements. The use of non paediatric-standard PN formulas in children at home can lead to severe metabolic complications. Currently, no standard formulas are suitable for children on HPN.

Recommendations

- The patient should be on a stable regimen before starting PN. **GOR D**
- Standard PN mixtures are usually not suitable for long-term PN in infants and young children. Therefore, PN solutions providing macro- and micronutrients for paediatric HPN should be compounded according to individual patients needs. **GOR D**

ORGANISATION - MONITORING AND FOLLOW UP

Management of children on PN at home should be undertaken by specialist multidisciplinary hospital nutrition support teams that include physician(s), pharmacist(s), nurse(s), dietitian(s), social worker(s) and psychologist(s). HPN centres should have adequate expertise and resources to ensure a good standard of care. Physicians should be trained and qualified to be responsible for the appropriate use, prescription and follow-up of patients on HPN programmes. Nurses who are responsible for parents' teaching and training should evaluate their capacities to deal with all medical and technical issues related to the child's treatment. Pharmacists should ensure safety of compounding and storage of the PN mixtures.

Once discharged from hospital, a regular out-patient follow up is planned to check clinical and biologic parameters (Table 2). Visits are planned according to each individual situation, initially at monthly intervals, more frequently if necessary, especially in infants. A 24 hours hot-phone contact should be provided by the hospital nutrition support team ((18) (LOE 3); (6) (LOE 3); (20) (LOE 4); (21) (LOE 4)). A close connection with general practitioners and local non specialized hospital units is indispensable in an emergency.

Recommendations

- Centres caring for infants and children on HPN must have adequate expertise and resources, including multidisciplinary nutrition support teams, trained and qualified to be responsible for use and prescription of HPN in children and a 24 hour telephone hotline. **GOR D**
- Paediatric HPN patients must be followed-up by an experienced team on a regular basis. **GOR D**

COMPLICATIONS

Catheter-Related Sepsis

Although the incidence of catheter related sepsis (CRS) in HPN patients is lower than in hospitalized patients ((17) (LOE 2+)), CRS is the most frequent complication of HPN in children. Its incidence varies from 1 to 4 per 1000 days HPN among published studies

TABLE 2. *Clinical and biologic monitoring in children on long-term home PN*

Intervals	Clinical assessment	Other investigations
1 to 3 months	• Weight • Height • Clinical examination • Dietetic assessment	ALT, bilirubin, GGT, alkaline phosphatase, Blood chemistry, including Ca, P, Mg, urea, creatinine Blood count Clotting tests Urinary electrolytes (Ca, Na, K) Ferritin Zinc Thyroid function parameters
6 months to 1 year		Plasma vitamins A, E and D Liver and biliary tract ultrasonography Bone densitometry

((6) (LOE 3); (25) (LOE 3); (26) (LOE 3); (27) (LOE 3); (17) (LOE 2+); (28) (LOE 3)). The risk of CRS is higher at young ages ((25) (LOE 3); (26) (LOE 3) which may partly explain the higher incidence of sepsis during the first two years of HPN as compared to later years ((26) (LOE 3); (17) (LOE 2+)). All studies have shown that some children have more than one infection over the period of study whilst others remain infection free. Risk factors, except for young age are uncertain. Underlying disease, ostomy, and the socio-economic level of the family have not appeared to be discriminant. A recent study showed that the increase in HPN duration was associated with a lower incidence of CRS and suggested that early occurrence of the first episode of CRS after starting HPN was a predictive factor for later infections ((28) (LOE 3)).

Coagulase-negative Staphylococci accounted for at least 60% of sepsis in several large studies ((6) (LOE 3); (25) (LOE 3); (28) (LOE 3)). However, the incidence of *Staphylococcus aureus*, gram-negative bacilli and fungal catheter infections was higher in other paediatric surveys ((26) (LOE 3); (27); (17) (LOE 2+)). The cost of infectious complications is about 10,000 € per episode, corresponding to 10 to 15 days in hospital, more in case of catheter replacement ((13) (LOE 2+); (17) (LOE 2+)). Parents should be taught about the signs of CRS. They have to contact their general practitioner and the hospital (referring local hospital and/or HPN centre) in case of fever or any signs of infection (See chapter on Complications).

Other Complications

Children on long term PN are at risk of pulmonary emboli (29,30). Catheter displacements or obstruction are discussed in the venous access chapter. Parenteral nutrition associated liver disease and metabolic bone disease are discussed in the chapter on complications.

Quality of Life

Although one of the aims of HPN is to give recipients and families the ''best possible'' quality of life, the burden of care on the parents is enormous. Assessments of quality of life using validated techniques have been rarely performed. Several surveys have mentioned that most children on HPN have normal physical activity ((31) (LOE 3)), are able to attend a regular school, to practice sports and that families can take holidays with their child on HPN ((6) (LOE 3); (32) (LOE 3); (11) (LOE 3); (33) (LOE 3)). However, sleeping is frequently impaired by nocturia and pump alarms. In a survey of children on HPN in Sweden, children and adolescents with HPN were found to be quite distressed psychologically ((34) (LOE 3)). A recent survey in parents of children with chronic intestinal failure requiring HPN showed that child's illness was associated with significant deterioration, compared to controls, in the social life, family life, sex life and work in these parents, who were also more likely to be physically tired ((35) (LOE 3)). Therefore, nursing assistance and psychologic assistance should be provided to children on HPN and to their families when possible and acceptable to the family.

Recommendation

- The nutrition support team should provide nursing assistance and psychologic assistance for children on HPN and their families. **GOR D**

LONG-TERM OUTCOME: THE ROLE OF CENTRALISED HPN EXPERT CENTRES

The largest paediatric surveys ((5) (LOE 3); (6) (LOE 3); (7) (LOE 3)) reported a mean HPN duration of about 2 years with an upper duration longer than 15 years. Children on HPN have better survival rates and greater likelihood of resuming full enteral nutrition after 1 year than older patients ((15) (LOE 3)). About 50% of paediatric patients can be weaned from HPN, the functional prognosis being better for congenital short bowel syndrome and inflammatory bowel diseases than for other indications ((6) (LOE 3); (7) (LOE 3)).

In children with chronic intestinal failure who cannot be weaned from PN, small bowel transplantation might be an alternative to lifelong HPN, according to each individual situation (complications of long-term PN, tolerance of the family). Since the first isolated small bowel transplantations using cyclosporine A, major advances have result from use of new immunosuppressive treatments ((36) (LOE 4)). When liver structure and function are impaired by long-term PN, a combined small bowel and liver transplantation should be considered. However, the timing of referral and criteria for isolated intestinal or combined transplantation is still a matter of debate ((36) (LOE 4); (37) (LOE 4); (38) (LOE 4); (39) (LOE 4)). The role of expert centralised HPN centres is to improve the quality of HPN and thus to decrease the number of transplantations which are due to, or precipitated by PN-associated complications. Therefore, early referral of patients on long-term PN to specialized HPN centres, and especially before irreversible liver failure occurs, might increase their quality of life and survival and reduce the cost of care.

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Journal of Pediatric Gastroenterology and Nutrition
41:S76–S84 © November 2005 ESPGHAN. Reprinted with permission.

12. Complications

METHODS

Literature Search

Timeframe: 1990–2003 plus publications referred to in studies identified by search.

Type of publications: randomised controlled trials, cohort studies, case control studies and case series. Most studies were in adults.

Key Words: central venous thrombosis, child, compatibility, complication, drug interaction, growth retardation, infection, liver disease, metabolic disease, occlusion, parenteral nutrition, pulmonary embolism.

Language: English.

COMPLICATIONS OF PARENTERAL NUTRITION

Introduction

Complications may be considered in four groups: central venous catheter (CVC) related stability of the PN solutions and interactions with added drugs, metabolic or nutritional and other organ systems. CVC related complications include infection, occlusion, central venous thrombosis, pulmonary embolism and accidental removal or damage. Metabolic or nutritional complications include deficiency or excess of individual PN components including electrolytes, minerals, glucose, essential fatty acids, vitamins, trace elements and the presence of contaminants. Some of these are considered in the relevant chapters. Other organ systems may be affected by the PN solutions, the underlying disease process or both. Complications include hepatobiliary disease, metabolic bone disease and growth impairment, some of which may be life threatening and raise the need for other therapeutic interventions such as non-transplant surgery or small bowel and liver transplantation.

Complications of Central Venous Catheters

Infection

Infection is one of the commonest complications of CVC's and is potentially fatal. The emphasis should be on prevention by using an aseptic technique as detailed in the Venous Access chapter. PN fluids should be prepared in a suitable environment for aseptic compounding according to Good Pharmaceutical Manufacturing Practice. Amino acid/glucose infusion giving sets and extensions can be left for 72 hours in-between changing ((1) (LOE 1); (2) (LOE 2); (3) (LOE 1)) but lipid sets should be changed every 24 hours ((4) (LOE 4)). Carers should be taught about the signs of catheter related sepsis (CRS) and monitor the child's temperature daily. Infection should be suspected if the child develops clinical sign such as fever (temperature $>38.5°C$ or rise in temperature of $>1°C$) metabolic acidosis, thrombocytopenia or glucose instability. Blood cultures should be taken from the CVC ((5) (LOE 4); (6) (LOE 3); (7) (LOE 3)). Simultaneous peripheral blood cultures are generally only useful if a semi-quantitative or quantitative culture technique is used (e.g. pour plate blood cultures; time to positive on continuous monitoring blood culture systems). Commence broad spectrum intravenous antibiotics promptly. The choice of antibiotic must be based on local resistance patterns and changed to a narrower-spectrum therapy once the infecting microorganism(s) has/have been identified. The duration of therapy should be guided by the organism identified. Fungal CVC infection is an indication to remove the CVC. Persistent pyrexia with positive blood cultures after 48 hours of appropriate antibiotics may be an indication to remove the CVC. CVC infection rates should be regularly audited and prompt action taken if any increase is detected ((8) (LOE 4); (6) (LOE 3)).

Recommendations

- PN fluids should be prepared in a suitable environment for aseptic compounding according to Good Pharmaceutical Manufacturing Practice. **GOR D**
- Amino acid/glucose infusion sets & extensions should be changed after no more than 72 hours or as recommended by manufacturer. **GOR A**
- Lipid sets should be changed after no more than 24 hours or as recommended by manufacturer. **GOR B**
- Carers should be taught about the signs of catheter related sepsis (CRS). **GOR D**
- CVC blood cultures should be taken for any unexplained fever or other signs of CRS. **GOR D**

- Simultaneous peripheral blood cultures are generally only useful if a semi-quantitative or quantitative culture technique is used. **GOR D**
- For suspected CRS broad-spectrum IV antibiotics should be commenced promptly after taking CVC blood cultures, the choice of agents being based on local resistance patterns. Change to narrower-spectrum therapy should be practiced once the infecting microorganism(s) has/have been identified. The duration of therapy should be guided by the organism identified. **GOR D**
- CVC complication rates should be audited continually, any change should be investigated & appropriate action taken. **GOR D**

Occlusion

Occlusion of the CVC can originate within the CVC lumen (blood, drug or PN fluid precipitate), in the vein (clot or fibrin sheath), external to the CVC due to the tip resting against a vein wall or due to external compression e.g. clavicle, or patient positioning. Sodium chloride 0.9% should be used to flush the CVC between all therapies and blood sampling to help prevent precipitation ((9) (LOE 4)). When not in use, the CVC should be flushed at least once a week with heparin (see venous access chapter). The use of terminal in-line filters reduces the risk of debris entering the CVC and should be used for all PN fluids ((10) (LOE 4); (11) (LOE 4)). Occlusion of in-line filters should be investigated and the problem addressed, rather than just replacing the line and filter. Blood sampling increases the risk of occlusion due to fibrin deposition; it should be avoided if possible or at least kept to a minimum with careful planning. Any signs of leakage from the CVC, stiffness or increase in infusion pressures should be assessed and dealt with immediately by an experienced practitioner. If malposition or occlusion is suspected (e.g. inability to aspirate from catheter, increased infusion pressures) a chest X-ray should be performed to verify the catheter tip position ((12) (LOE 3); (13) (LOE 4)). CVC occlusion can be treated with: urokinase or alteplase for suspected blood deposits and ethyl alcohol or hydrochloric acid for suspected lipid or drug deposits ((14) (LOE 3); (15) (LOE 3); (16) (LOE 3); (17) (LOE 3); (12) (LOE 3); (18) (LOE 3); (13) (LOE 4); (19) (LOE 3); (9) (LOE 3); (20) (LOE 3)). A combination of more than one treatment may be required. Some manufacturers recommend that syringes smaller than 10 ml should not be routinely used to clear an obstruction as they can generate very high internal pressures (21). Unblocking the CVC with a guide-wire is not recommended. Catheter venography should be performed for persistent or recurrent occlusion ((12) (LOE 4); (13) (LOE 4); (22) (LOE 4)).

Recommendations

- Sodium chloride 0.9% should be used to flush the CVC between all therapies and heparin should be instilled at least weekly when the CVC is not in use. **GOR D**
- Terminal in-line filters should be used for all PN fluids. **GOR D**
- Occlusion of in-line filters should be investigated. **GOR D**
- Using the CVC for blood sampling should be avoided if possible. **GOR D**
- Leakage from the exit site, stiffness of the CVC or increased infusion pressures should be reported immediately to an experienced practitioner and appropriate investigations performed. **GOR D**
- CVC occlusion can be treated with: urokinase or alteplase for suspected blood deposits and ethyl alcohol or hydrochloric acid for suspected lipid or drug deposits. **GOR D**
- Syringes less than 10 ml should not be routinely used on CVC's. **GOR D**
- Unblocking the CVC with a guide-wire is not recommended. **GOR D**

Central Venous Thrombosis & Pulmonary Embolism

Central venous thrombosis (CVT) and pulmonary embolism (PE) are potentially fatal complications in children receiving prolonged PN. CVT tends to develop after several weeks of PN. It may result in facial swelling, prominent superficial veins or pain on commencing PN. CVT is confirmed by echocardiography, Doppler ultrasound, CT scan and/or venography ((23) (LOE 3); (24) (LOE 3), (25) (LOE 3); (26) (LOE 3); (27) (LOE 4); (28) (LOE 4)). PE may present with chest pain, dyspnoea, haemoptysis, syncope, tachypnoea, tachycardia, sweating and fever. Small thrombi may be asymptomatic or have vague symptoms such as tiredness.

CVT and PE are associated with recurrent CVC infection, repeated CVC changes, proximal location of the CVC tip in the superior vena cava, frequent blood sampling, concentrated glucose solutions, chemotherapeutic agents or may be idiopathic. Carers should look for any distress of the child, breathlessness, redness or swelling in the neck or limbs, leakage from the exit site or stiffness of the CVC on flushing and for any increase in pressure of the infusion pumps. These should be reported immediately to an experienced practitioner for assessment and action.

Acute symptomatic thrombosis may be best treated with thrombolytic agents but anticoagulation remains the most common therapeutic approach ((27) (LOE 4); (28) (LOE 4)). Consideration should be given to removing the

catheter, especially if infected ((29) (LOE 3); (5) (LOE 4); (28) (LOE 4)). Vitamin K antagonists ((30) (LOE 1/2); (31) (LOE 3)) or low molecular weight heparins ((32) (LOE 1/2)) may reduce the risk of thrombo-embolism and may be given to patients on long-term PN with previous or at increased risk of thrombo-embolism.

Recommendations

- Symptoms or signs of thrombo-embolism should be reported immediately to an experienced practitioner and appropriate investigations performed. **GOR D**
- Acute symptomatic thrombosis can be treated with thrombolytic agents or anticoagulation. **GOR D**
- Vitamin K antagonists or low molecular weight heparins may be given prophylactically to patients on long-term PN at risk of or with previous thrombo-embolism. **GOR B**

Accidental Removal or Damage

This can occur accidentally or deliberately by traction to the CVC. CVC's should be kept securely taped to the body to prevent excessive trauma to them, especially when not in use. Postoperative dressings should be secure, but allow observation of the exit site and be easily removable ((10) (LOE 4)). Dressings should stay in situ as per surgeons' instructions unless they become damp, soiled, loosened or there is swelling, bleeding and/or leakage from the CVC exit site and the dressing prevents observation. Tight vests, tape (trouser leg) splints or looping of the CVC can be used as extra security ((33) (LOE 4); (10) (LOE 4)).

Over time the integrity of long-term CVC's can be adversely affected and they may develop holes, tears or weakened connections. Some CVC manufacturers make repair kits and these can often be used to replace the damaged portion. Any damage to the CVC should be reported immediately to an experienced practitioner and appropriate repairs performed as soon as possible. Bleeding can occur from damaged CVC's or loose connections and is a potentially fatal complication. Luer lock connectors should be used to reduce the risk of disconnection and clamps should be available at all times to stop any bleeding. Children (as soon as they are aware) and all carers should be educated about the safety of the CVC ((33) (LOE 4); (10) (LOE 4)).

Recommendations

- CVC's should be securely taped to the body to prevent accidental removal, traction or damage. **GOR D**
- Postoperative dressings should be secure but allow observation of the exit site and easy dressing removal. **GOR D**
- Any damage to the CVC should be reported immediately to an experienced practitioner and appropriate repairs performed promptly. **GOR D**
- Luer lock connectors should be used to reduce the risk of accidental leakage and haemorrhage. **GOR D**
- Clamps should be available at all times to prevent bleeding from a damaged CVC. **GOR D**
- Children (as soon as they are aware) and all carers should be educated about the safety of the CVC. **GOR D**

Compatibility

The major issues affecting admixture stability were clearly set out by Barnett et al ((34) (LOE 4)). The use of organic-bound phosphates reduces the risk of precipitation. Addition of heparin to admixtures, even where validated, carries a small risk of emulsion instability occurring with individual batches of heparin ((35) (LOE 4)).

Parenteral nutrition in paediatrics can be admixed into '2 in 1' or '3 in 1' admixtures. A '2 in 1' admixture is one that contains amino acids, carbohydrates and electrolytes in a single container with lipid emulsion kept in a separate container. A '3 in 1' admixture has all the components including lipid in a single container. With up to 100 chemical species present in an admixture, enormous potential for interaction exists. It is recommended that a formulation is used that has been thoroughly studied in the laboratory and is backed by a clear statement from an authoritative body such as a licensed manufacturer or an academic institution, but there may still be variability through factors such as the variation in pH between different batches of glucose due to decomposition during autoclaving ((34) (LOE 4)) and changes in trace element profiles due to adsorption onto, or leaching from, admixture containers and tubing ((36) (LOE 3); (37) (LOE 3); (38) (LOE 3)). A '3 in 1' admixture is administered through a single line and the emulsion stability has been confirmed within the overall package. A '2 in 1' admixture validation generally excludes the lipid emulsion from any consideration during stability testing. The lipid emulsion is infused 'separately' but in practice this usually means into the same infusion line, through a 'Y' connector. This approach does not ensure stability (39,40 (LOE 3)). As there are risks associated with instability of regimens, it

has been recommended that PN admixtures be administered through a terminal filter ((41) (LOE 4)).

Recommendations

- PN should be administered wherever possible using an admixture formulation validated by a licensed manufacturer or suitably qualified institution. **GOR D**
- A matrix table should be sought from the supplier of the formulation detailing permissible limits for additions of electrolytes and other additives. **GOR D**
- Alternative ingredients should not be substituted without expert advice or repeat validation. **GOR D**
- Phosphate should be added in an organic-bound form to prevent the risk of calcium-phosphate precipitation. **GOR D**
- If inorganic phosphate is used, stability matrices and order of mixing must be strictly adhered to and occasional precipitates may still occur. **GOR D**
- Use of '2 in 1' admixtures with Y-site addition of lipids should be fully validated by the manufacturer or accredited laboratory or the lipid infused through an alternative line. **GOR D**
- PN admixtures should be administered through a terminal filter. **GOR D**

Drug Interactions

Interactions between PN and medications occur in three main ways; physiological interactions that occur at all times, altered behaviour of medications owing to the complications of the presenting condition or sub-optimal nutritional support and direct chemical interaction in the tubing during administration ((42) (LOE 4)).

Examples of the first type would be steroid-related hyperglycaemia or hypoglycaemia seen with concurrent insulin. These are predictable from the mode of action of the drug. In the second case, altered acid-base balance can lead to altered drug/receptor interactions or altered levels of protein binding, as can abnormal plasma albumin levels. It is difficult, for example, to reverse acidosis with bicarbonate if the patient is being overloaded with a non-metabolisable base such as chloride ((43) (LOE 4)). Similarly, if the patient is sodium depleted, diuretics will be ineffective. In neonatal jaundice bilirubin may be displaced from binding sites of plasma proteins by a number of medications, particularly sulphonamides, antimalarials and drugs containing benzoyl alcohol as a preservative ((44) (LOE 4)).

There are many short reports in the literature looking at the physical and/or chemical stability of certain medications in specific PN admixtures. Extrapolation of these is difficult without expert advice. Medications are given in the form of a formulated product which frequently contains excipients (substances required for formulation of a drug which should be inactive) in addition to the active medication ((45) (LOE 4)). Studies must therefore be regarded as specific to the particular branded product(s) investigated. The pH of a PN admixture will generally be close to the pH of the amino acid mixture from which it was prepared ((34) (LOE 4)) but marketed products range from around pH 5.0 to pH 7.0. Drugs that ionise in aqueous solution are those most likely to cause precipitation. A drug that is largely unionised at pH 5.0 may be fully dissociated at pH 7.0 and *vice versa* so it is not possible to extrapolate findings between different admixtures.

The problem is further complicated because of the behaviour of fluids within infusion tubing, particularly at low flow rates. Sharp corners and hanging loops within the tubing can lead to 'non-circulating fluid spaces' where medications can pool, and not necessarily be cleared by flushing ((46) (LOE 4)). Adding medication into infusion sets can force a bolus of an equivalent volume of PN solution ahead of the medication. Also, depending upon where the drug is added to the set, it may delay delivery of all or part of the dose to the circulation if the dose volume is less than the residual volume of the tubing ((46) (LOE 4)). This means that any study of drug compatibility with PN can only be reliably applied to the particular products, concentrations, flow rates tested and the precise equipment, tubing, connectors and adaptors used. Extrapolation should only be attempted by those with relevant expertise. Problems will frequently manifest as in-line precipitation or lipid droplet enlargement (or both). In-line filtration can prevent these reaching the patient.

Recommendations

- Mixing of medications with PN in administration lines should be avoided unless validated by the manufacturer or accredited laboratory. **GOR D**
- Medications known to affect plasma protein binding of bilirubin should be avoided in parenterally fed newborn patients with severe hyperbilirubinaemia. **GOR D**

Refeeding Syndrome

The hormonal and metabolic changes of starvation aim to facilitate survival by a reduction in basal metabolic rate, conservation of protein, and prolongation of organ function, despite the preferential catabolism of skeletal muscle tissue and loss of visceral cell mass.

Refeeding the malnourished child disrupts the adaptative state of semi-starvation. Thus, refeeding syndrome may be observed in severely malnourished patients receiving concentrated calories via PN ((47) (LOE 4); (48) (LOE 4)). These rapid changes in metabolic status can

create life-threatening complications, so the nutritional regimen must be chosen wisely and monitored closely. To reduce the risk of refeeding complications, several conditions are required at the initial phase of re-nutrition of severely malnourished infants and children.

Prevention of Water and Sodium Overload

This can be achieved by:

- reducing water and sodium intake (some times up to 60% of the theoretical requirements), depending on the hydration state.
- monitoring to detect early fluid retention related excessive weight gain. It is preferable to maintain weight stable or even to achieve weight loss during the first 2–3 days of parenteral renutrition.
- preserving the oncotic pressure with the infusion of macromolecules such as albumin (1 g/kg at a slow infusion rate and if necessary twice a day).
- monitoring uncontrolled losses (skin and obligatory losses) as well as those from the gastrointestinal tract, intraperitoneal or intestinal fluid retention.

In clinical practice the early phase of renutrition requires monitoring at least once a day body weight changes, urine collection, assessment of blood and urinary electrolytes.

Carbohydrate Intake

Constant administration of carbohydrate is required to maintain blood glucose homeostasis as the reserves are very low; parenteral administration of glucose requires care because of the risk of hyperglycaemia with osmotic diuresis and hyperosmolar coma. According to age of the patient, continuous glucose infusion rate may be at least equal to the glucose production rate (see Carbohydrate chapter).

Potassium Repletion

Correction of potassium depletion should be achieved progressively with monitoring of renal and cardiac function. It can be dangerous to try to correct the deficiency too rapidly at a stage where the capacity for fixing potassium remains low because of low glucose intake and reduced protein mass and synthesis. At an early stage of re-nutrition; excessive potassium intake may cause hyperkalaemia and cardiac arrhythmias.

Phosphorus Repletion

Correction of phosphorus depletion should be achieved progressively with monitoring of neurological status and renal function. At least 0.5 mmol/kg per day should be administered and proportionally increased according to the total protein-energy intake up to 1.0 mmol/kg per day. Daily monitoring of phosphoraemia and phosphaturia is mandatory, aiming at a limited phosphaturia.

Protein and Energy Intake

It is difficult to suppress protein catabolism in the early phase of re-nutrition since energy intake should be increased very slowly. Excessive nitrogen intake may lead to hyperammonaemia and/or metabolic acidosis by exceeding the renal clearance capacity for H+ and phosphate ions. An intake of 0.5–1 g/kg of parenteral amino acids or oral peptide is sufficient to maintain the plasma amino acid pool. The protein energy deficiency and other related disorders must be corrected during the days following the initial period of stress. This type of correction should be made carefully and gradually since the deficits are profound and of long standing. It is essential to provide both nitrogen and calories simultaneously and in the correct ratio (see chapter on amino acids).

Adaptation of Intake

The provision of appropriate nutrient solutions requires an understanding of the nutritional relationships between macronutrients, electrolytes, vitamins and trace elements. It is during this initial phase that any deficit due to incorrect intake will become apparent through either clinical or laboratory signs. These deficits can usually be prevented by giving them in the following proportions: 200 to 250 kcal, nitrogen 1 g, calcium 1.8 mmol, phosphorus 2.9 mmol, magnesium 1.0 mmol, potassium 10 mmol, sodium and chloride 7 mmol, zinc 1.2 mg. Similarly, it is essential to adapt the intake of essential fatty acids, copper, manganese, chromium, iron, iodine, cobalt, fluoride, selenium, tocopherol and the group B vitamins especially.

Monitoring

After the initial phase of re-nutrition, most complications may be prevented by careful supervision and the provision of appropriate intakes. It is essential that the infusion rate, body temperature, cardiac and respiratory function, urinary volume, twice daily weight and digestive output are continuously monitored. During the first 5 days, and also when the osmotic load is increased, urine should be checked for osmolality, pH, glucose and protein. The plasma and urinary ion data, plus the calcium, phosphorus, magnesium, glucose and haematocrits should be obtained twice during the first week, and then once weekly. Plasma proteins, albumin, bilirubin, alkaline phosphatase and transaminase values should be assessed routinely. This data, and knowledge of the patient's state and age, should make it possible to progressively regulate and control the intake and avoid problems of overload or depletion.

Prevention of Infection

The infective, metabolic and GI problems must be borne in mind during treatment of paediatric patients with severe malnutrition. The risk of infection, an expression of both specific and non-specific immunity depression, may jeopardize the prognosis and aggravate nutritional problems at any time. Clinical and paraclinical investigations must be performed repeatedly, to look for widening foci of infection (respiratory, GI, skeletal and urinary) and for their systemic spread. When a localized or systemic infection is identified, specific treatment is urgently required. The routine use of antibiotics in the absence of bacteriological evidence in a malnourished child is inadvisable; antibiotics should only be given if sufficient indirect evidence points to the likelihood of infection. Active intestinal parasitosis should be vigorously treated.

Metabolic Bone Disease

PN-related metabolic bone disease (MBD) with a decrease in bone mineral density (BMD), osteoporosis, pain and fractures has been described in adults on long-term parenteral nutrition. Little data exists in children, although its occurrence has been reported in children weaned from long-term PN ((49) (LOE 3); (50) (LOE 3); (51) (LOE 3)). The cause of MBD is probably multifactorial including both underlying disease and PN-related mechanisms: excess vitamin D, phosphorus, nitrogen and energy imbalance, excess amino acids and aluminium contamination ((52) (LOE 3)). Measurements of urinary calcium, plasma calcium, plasma phosphorus, plasma parathyroid hormone, vitamin D concentrations and serum alkaline phosphatase activity aid in the evaluation of MBD in patients on PN. Use of aluminium contaminated products should be kept to a minimum (avoid glass vials and certain minerals and trace elements known to have high aluminium content), and products with measured and labelled aluminium content preferred. Diagnosis of bone disease relies primarily on the measure of bone mineralization by validated imaging methods (e.g. peripheral quantitative computer tomography, dual energy X-ray absorptiometry).

Recommendations

- In children on HPN, regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and vitamin D concentrations and serum alkaline phosphatase activity should be performed. **GOR D**
- Aluminium contamination of parenteral nutrition solutions provided to patients receiving long-term PN should be kept to a minimum. **GOR D**
- Regular assessment of bone mineralisation should be performed. **GOR D**

Hepatobiliary Complications of Parenteral Nutrition

The liver and biliary tree have many essential roles including metabolism of carbohydrate and lipid; detoxification and elimination of endogenous and exogenous lipophilic compounds and heavy metals; and synthesis and secretion of albumin, bile acids, coagulation factors, cytokines and hormones. Most hepatobiliary complications of PN are moderate and reversible. In a few patients there may be more severe outcomes ranging from biliary sludge and gallstones to cirrhosis, hepatic decompensation and death.

The pathogenesis of PN associated liver disease is not completely understood ((53) (LOE 3); (54) (LOE 4)). It probably results from the interaction of many factors related to the underlying disease, infectious episodes and components of the PN solution. Elaborate discussion on the various approaches to the avoidance or treatment of the rare case of PN related hepatobiliary disease is discussed elsewhere ((55,56) (LOE 4)).

Patient and/or Disease Related Factors

Children requiring long-term PN are at high risk of developing liver disease. Absence of oral feeding impairs choleresis and increases the risk of biliary sludge formation. Short bowel syndrome may be associated with disruption of bile acid enterohepatic circulation due to ileal resection, bacterial overgrowth due to bowel obstruction or severe motility disorders and ileocaecal valve resection, which are all factors thought to contribute to PN-associated cholestasis ((57) (LOE 3), (58) (LOE 4)). Recurrent septic episodes either catheter-related (gram positive bacteria) or digestive related (gram negative sepsis from intraluminal bacterial overgrowth) also contribute to liver injury. Prematurity is an associated factor especially when necrotizing enterocolitis or septic infections occur ((59) (LOE 4)).

PN Related Factors

PN may have additional deleterious effects on the liver:

- It was experimentally demonstrated that an excess of total energy delivered induces liver lesions, reversible when decreasing the energy supply.
- Excessive or inadequate amino acid supply (60,61).

- Continuous PN infusion and/or excessive glucose intake is associated with hyperinsulinism and subsequent steatosis ((62) (LOE 3)), although it is not clear whether this is also associated with cholestatic liver disease.
- The role of inadequate lipid supply with excessive delivery of fat and subsequent lipoperoxidation has been suggested ((54) (LOE 4)). Phytosterols contained in lipid emulsions may be a marker for liver dysfunction ((63) (LOE 3); (64) (LOE 3)).

Monitoring

Careful monitoring of hepatic function is extremely important during PN in order to minimize or correct factors responsible for liver disease. The earliest and most sensitive, but not specific laboratory markers are plasma alkaline phosphatase and gamma-glutamyl transferase activities, while hyperbilirubinemia is the latest marker of cholestasis to appear. Clinical liver enlargement, confirmed by ultrasonography, may appear within a few days after PN onset. Liver biopsy is not indicated at the early stage of liver dysfunction. However, it was shown that steatosis is the first non specific histological abnormality resulting from excessive glucose supply leading to lipogenesis, rather than from the deposition of exogenous IVFE. Cholestasis together with portal and periportal cell infiltration leads to fibrosis. This indicates severe liver disease, with possible progression to cirrhosis and liver failure, unless digestive factors are corrected and PN is performed correctly.

Early referral to an experienced paediatric liver and intestinal transplant centre for further assessment is recommended in infants and children with a poor prognosis (e.g. ultra short bowel <10 cm, congenital enteropathy, megacystis microcolon and disorders of uncertain natural history. Clinical criteria include: parenteral nutrition >3 months, serum bilirubin >50 μmol/l, platelet count <100, PT $>$ 15 sec, PTT $>$ 40 sec or hepatic fibrosis ((65) (LOE 3)).

Prevention and Treatment of Cholestasis

Some measures may limit or reverse liver disease including:

- The stimulation of the entero-biliary axis by promoting oral feeding with breast milk or long-chain triglycerides containing formulae, or by injection of cholecystokinin analogues ((66) (LOE 3)).
- The reduction of intraluminal bacterial overgrowth caused by intestinal stasis by giving metronidazole ((67) (LOE 3)) and/or by performing venting enterostomy or tapering enteroplasty ((68) (LOE 4)).
- The use of ursodeoxycholic acid (10 to 30 mg/kg per day) or tauroursodeoxycholic acid might contribute in decreasing liver injury ((69) (LOE 3)).

Persistant Cholestasis

If cholestasis occurs in spite of the above preventive management, the clinician has to rule out biliary obstruction, infection or drug toxicity by using appropriate investigations. A decrease in platelet count below 150,000/mm^3 associated with an increase in plasma transaminases, may be suggestive of lipid toxicity when all other explanations are ruled out. Bone marrow aspiration and/or liver biopsy and temporary suspension or decrease in lipid infusion should be considered. If lipid infusion is stopped, essential fatty acid status should be monitored.

Recommendations

- Liver disease should be prevented by reducing patient-related and PN-related risk factors. **GOR D**
- Provide maximal tolerated EN even if minimal residual gut function. **GOR A**
- Commence cyclical PN as soon as possible. **GOR C**
- Consider and treat intraluminal bacterial overgrowth. **GOR D**
- Consider reducing or stopping IV lipids temporarily if conjugated bilirubin steadily increases with no other explanation. **GOR D**
- If the transaminases, alkaline phosphatase or conjugated bilirubin continue to increase consider commencing ursodeoxycholic acid. **GOR D**
- Early referral to an experienced paediatric liver and intestinal transplant centre for further assessment is recommended in infants/children with poor prognosis or if on PN for >3 months and serum bilirubin >50 μmol/l, platelet count <100, PT $>$ 15 sec, PTT $>$ 40 sec or hepatic fibrosis. **GOR D**

Growth Retardation

A child dependent on PN must receive adequate nutrition to meet its basic metabolic requirements but also to allow for normal growth ((70) (LOE 1)). This is particularly important in preterm infants who inevitably accumulate a significant nutrient deficit in the early weeks of life ((71) (LOE 3)) and may require aggressive nutritional support ((70) (LOE 1)). It is important to assess longitudinal growth as excessive weight gain with growth retardation has been described ((72) (LOE 3)). It has been suggested that the addition of ornithine a-ketoglutarate to the PN solution given to growth retarded children receiving home PN has an advantageous affect on growth as it provides key factors in both the Kreb's and the urea cycles ((73) (LOE 3)), but the efficacy of this approach has not been tested by other authors.

As a child's gut adapts and tolerates increasing enteral feeds, there is a temptation to cut back on PN days as soon as possible to ease the lifestyle constraints imposed

by PN. If the growth velocity slows when this is done, there may be a tendency to add the additional calories onto the reduced number of PN days rather than increasing PN days. This may lead to excessive weight gain without longitudinal growth ((74) (LOE 3)). Care must be taken in adjusting PN composition and amount frequently in line with growth ((74) (LOE 3)).

Parenteral nutrition is widely used in neonatal units to support preterm babies until enteral feeding can be established. The generally accepted goal is to provide adequate nutrition to allow for growth and weight gain as expected of a foetus of that post conceptional age ((75) (LOE 4)). The metabolic requirements of a sick preterm may be high and optimal intake is not always possible. Retrospective studies looking at the actual energy intake of preterm babies, rather than that prescribed have shown a significant deficit in relation to their requirements ((76) (LOE 3)). This deficit can be directly related to postnatal growth retardation. The use of insulin to maintain normoglycaemia rather than reducing glucose concentrations may have a beneficial effect on growth but may also have side effects ((77) (LOE 3)).

Recommendation

- Paediatric patients on long term PN require regular monitoring of growth and body composition. **GOR D**

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Journal of Pediatric Gastroenterology and Nutrition
41:S85–S87 © November 2005 ESPGHAN. Reprinted with permission.

ESPGHAN and ESPEN Guidelines Paediatric Parenteral Nutrition – Annex: List of Products

Annex

To the Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research.

List of Products Commonly Used for Paediatric Parenteral Nutrition in Europe

This list is intended to provide an overview of commonly available products, but does not attempt to provide a complete list of all products that may be available in different European countries. While efforts have been made to provide accurate information, no responsibility can be taken for accuracy of the data presented.

Amino acid solutions

Brand name	Manufacturer	Total AA (g/l)	Ess AA in %[1]	Cysteine (g/l)[2]	Tyrosine (g/l)	Taurine (g/l)	Theoret. Osmolality/Osmolarity	pH
Aminopäd 10%	Fresenius Kabi/ in Germany: Baxter	100	42	0.5[3]	1.1[7]	0.3	790 mosmol/l	6.1
Aminoplasmal B. Braun 10%*	B. Braun	100	42	**	0.4	—	864 mosmol/l	5.7–6.3
Aminoven infant 10%	Fresenius Kabi	100	51	0.5[3]	4.2[5]	0.4	885 mosmol/l	5.5–6.0
Pädamin	Fresenius Kabi	74	38	1.1[4]	2.65[6]	0.75	590 mosmol/l	5.0–6.0
Primene 10%	Baxter	100	47.6	1.89	0.45	0.6	780 mosmol/l	5.5
Vamin 9 Glucose[8]	Fresenius Kabi	70	41	1.4[9]	0.5	—	1350 mosmol/kg H_2O	5.2
Vaminolact	Fresenius Kabi	65	44	1.0[2]	0.5	0.3	510 mosmol/kg H_2O	5.2

[1]Included: 8 ess. AA.
[2]As Cysteine/Cystine.
[3]Included as 0.7 g ac-cys.
[4]Included as 1.5 g ac-cys.
[5]Included as 5.2 g ac-tyr.
[6]Included as 3.26 g ac-tyr.
[7]Included as 1.3 g ac-tyr.
[8]Contains glucose: 100 g/L.
[9]As Cysteine/Cystine; included as cysteine-HCl.
*For children older than 2 years. Also available in 5% with electrolytes, 10% with electrolytes, 16%.
**200 mg acetyl-cysteine as excipient.
For dosage mode of administration recommendation, please refer to the package insert.

Lipid emulsions

	Composition	Manufacturer	TG (g/L)	Soybean oil (g/l)	Olive oil (g/l)	MCT (g/L)
20% emulsions						
ClinOleic 20%	80% Olive oil/20% soybean oil	Baxter	200	40	160	
Intralipid 20%	Soybean oil emulsion	Fresenius Kabi#	200	200	—	
Ivelip 20%	Soybean oil emulsion	Baxter	200	200	—	
Lipofundin MCT/LCT 20%	50% Soybean/50% coconut (MCT) oil	B. Braun	200	100	—	100
Lipofundin N 20%	Soybean oil emulsion	B. Braun	200	200	—	
Lipovenoes 20%	Soybean oil emulsion	Fresenius Kabi	200	200	—	
10% emulsions						
Intralipid 10%	Soybean oil emulsion	Fresenius Kabi#	100	100	—	
Lipofundin MCT/LCT 10%	50% Soybean/50% coconut (MCT) oil	B. Braun	100	50		50
Lipofundin N 10%	Soybean oil emulsion	B. Braun	100	100		
Lipovenoes 10% PLR*	Soybean oil emulsion	Fresenius Kabi	100	100	—	

	% of total fatty acids							
	C8:0	C10:0	C12:0	C16:0	C18:0	C18:1 (n-9)	C18:2 (n-6)	C18:3 (n-3)
20% emulsions								
ClinOleic 20%				13.5	2.9	59.5	18.5	2.0
Intralipid 20%				11.0	4.0	24.0	53.0	8.0
Ivelip 20%				11.0	4.0	20.0	52.0	8.5
Lipofundin MCT/LCT 20%	27.0	21.0	1.5	5.0	2.0	12.0	27.0	4.0
Lipofundin N 20%				12.0	4.5	24.0	50.0	7.0
Lipovenoes 20%				10.0	4.0	24.0	54.0	8.0
10% emulsions								
Intralipid 10%				11.0	4.0	24.0	53.0	8.0
Lipofundin MCT/LCT 10%	27.0	21.0	1.5	5.0	2.0	12.0	27.0	4.0
Lipofundin N 10%				12.0	4.5	24.0	50.0	7.0
Lipovenoes 10% PLR*				10.0	4.0	24.0	54.0	8.0

Contents of docosahexaenoic and arachidonic acids, respectively, each <0.5% of fat in all emulsions. The routine use of 10% emulsions with high phospholipid/triglyceride ratios is not recommended by these guidelines (cf. chapter lipids).

#Distributor for Germany: Baxter.

*PLR = Phospholipid reduced, similar phospholipid/triglyceride ratio as found in 20% emulsions.

For dosage and mode of administration recommendations of the manufacturers, please refer to the package insert.

Vitamin preparations

Brand name	Manufacturer	Concentration	Vit A	Vit D	Vit E	Vit K
Cernevit†	Baxter	per vial	3500 IU/1.06 mg	220 IU/5.5 μg	11.2 IU/10.2 mg	—
Soluvit N	Fresenius Kabi*	per vial				
Vitalipid adult†	Fresenius Kabi*	per 10 mL	3300 IU/990 μg	200 IU/5 μg	10 IU/9.1 mg	150 μg
Vitalipid infant	Fresenius Kabi*	per 10 mL	2300 IU/690 μg	400 IU/10 μg	7.0 IU/6.4 mg	200 μg

Brand Name	Vit B1	Vit B2 (Riboflavine)	Vit B6	Vit B12	Vit C	Niacin	Pantothenic acid	Biotin	Folic acid
Cernevit†	3.51 mg	4.14 mg	4.53 mg	6 μg	125 mg	46 mg	17.25 mg	69 μg	0.41 mg
Soluvit N	2.5 mg	3.6 mg	4 mg	5 μg	100 mg	40 mg	15 mg	60 μg	0.4 mg
Vitalipid adult†									
Vitalipid infant									

*Distributor for Germany: Baxter.

†for children >11 years.

For dosage and mode of administration recommendations of the manufacturers, please refer to the package insert.

Trace elements

Brand Name	Manufacturer	Concentration	Magnesium	Zinc	Copper	Manganese
Addel N/Addamel N[1]	Fresenius Kabi*	per 10 mL		6.5 mg/100 μmol	1.3 mg/20 μmol	270 μg/5 μmol
Inzolen-Infantibus sine NaK	Köhler	per 10 mL	2.5 mmol	0.97 mg/14.9 μmol	0.32 mg/5 μmol	0.27 mg/5 μmol
Oligo-éléments Aguettant pédiatrique	Aguettant	per 10 mL		1 mg	0,3 mg	0,1 mg
Peditrace	Fresenius Kabi*	per 10 mL		2.5 mg/38.2 μmol	0.2 mg/3.15 μmol	10 μg/0.182 μmol

Brand Name	Chromium	Selenium	Iodide	Iron	Cobalt	Fluoride	Molybdenum
Addel N/Addamel N[1]	10 μg/0.2 μmol	32 μg/0.4 μmol	130 μg/1 μmol	1.1 mg/20 μmol	—	0.95 mg/50 μmol	19 μg/0.2 μmol
Inzolen-Infantibus sine NaK	0.08 mg/1.6 μmol	—		0.91 mg/16.3 μmol	0.14 mg/2.4 μmol		
Oligo-éléments Aguettant pédiatrique	0.02 mg	0.05 mg	0.05 mg	0.5 mg	0.015 mg	0.5 mg	0.05 mg
Peditrace	—	20 μg/0.253 μmol	10 μg/0.078 μmol	—	—	0.57 mg/30 μmol	—

[1]For children weighing 15 kg or more.
For dosage mode of administration recommendation, please refer to the package insert.
*Distributor for Germany: Baxter.