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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)

*Berthold Koletzko, †Olivier Goulet, *Joanne Hunt, *Kathrin Krohn, and ‡Raanan Shamir
for the Parenteral Nutrition Guidelines Working Group§

**Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University of Munich, Germany; †Hopital Necker-Enfants Malades, Paris, France, ‡Meyer Children's Hospital, Haifa, Israel*

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

[§]Parenteral Nutrition Guidelines Working Group: Carlo Agostoni, San Paolo Hospital, Milan, Italy; Patrick Ball, University of Auckland, New Zealand; Virgilio Carnielli, T.I.N., Az. Osp. G.Salesi, Ancona, Italy; Chris Chaloner, Booth Hall Children's Hospital, Manchester, UK; Jane Clayton, Booth Hall Children's Hospital, Manchester, UK; [5]Virginie Colomb, Hopital Necker-Enfants Malades, Paris, France; Monique Dijsselhof, Academical Medical Centre, Amsterdam, Netherlands; Christoph Fusch, University Children's Hospital Greifswald, Germany; Paolo Gandullia, G.Gaslini Institute, Genoa, Italy; [6]Orsolya Genzel-Boroviczeny, Dr. von Hauner Children's Hospital, University of Munich, Germany; Frédéric Gottrand, Hopital Jeanne de Flandre, Lille, France; *[7]Olivier Goulet, Hopital Necker-Enfants Malades, Paris, France; Esther Granot, Hadassah Medical Center, Jerusalem, Israel; James Gray, Birmingham Childrens Hospital, Birmingham, UK; Antonio Guerra, Antonio, Hospital S. Joao, Porto, Portugal; [8]Susan Hill, Great Ormond Street Hospital for Sick Children, London, UK; Chris Holden, Birmingham Childrens Hospital, Birmingham, UK; Venetia Horn, Great Ormond Street Hospital for Sick Children, London, UK; Loveday Jago, Booth Hall Children's Hospital, Manchester, UK; Frank Jochum, Dept of Paediatrics, Evangelisches Waldkrankenkaus Spandau, Berlin, Germany; [9]Sanja Kolacek, Children's Hospital Zagreb, Croatia, *Berthold Koletzko, Dr. von Hauner Children's Hospital, University of Munich, Germany; Sibylle Koletzko, Dr. von Hauner Children's Hospital, University of Munich, Germany, [10]*Kathrin Krohn, Dr. von Hauner Children's Hospital, University of Munich, Germany; [11]Janusz Ksiazyk, Children's Memorial Health Institute, Warsaw, Poland; Alexandre Lapillonne, Saint-Vincent de Paul Hospital, Paris, France; Päivi Luukkainen, Helsinki University Central Hospital, Helsinki, Finland; Malgorzata Lyszkowska, Children's Memorial Health Institute, Warsaw, Poland; Sarah MacDonald, Great Ormond Street Hospital for Sick Children, London, UK; Julije Meštroviæ, University Hospital Split, Split, Croatia; Walter Mihatsch, Dept. Paediatrics, Diakonie Krankenhaus Schwäbisch Hall, Germany; [8]Peter Milla, Institute of Child Health, London, UK; Francis Mimouni, Sourasky Medical Centre, Tel Aviv, Israel; Zrinjka Mišak, Children's Hospital Zagreb, Croatia; Irena Mršic, Children's Hospital Zagreb, Croatia; Liz Newby, Alder Hey Childrens Hospital, Liverpool, UK; Frank Pohlandt, Dept. of Paediatrics, University of Ulm, Germany; [7]Sue Protheroe, Birmingham Childrens Hospital, Birmingham, UK; [12,13]John Puntis, The General Infirmary, Leeds, UK; Jacques Rigo, Dept. Paediatrics, University of Liege, France; [10]Arieh Riskin, Bnai Zion Medical Center, Haifa, Israel; Jane Roberts, Booth Hall Children's Hospital, Manchester, UK; *Raanan Shamir, Meyer Children's Hospital, Haifa, Israel; Peter Szitanyi, University Hospital MOTOL, Prague, Czech Republic; [14]Adrian Thomas, Booth Hall Children's Hospital, Manchester, UK; [15]Nachum Vaisman, Sourasky Medical Centre, Tel Aviv, Israel; [16]Hans van Goudoever, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands; Ayala Yaron, Sourasky Medical Centre, Tel Aviv, Israel.

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.

*Project steering committee.

Correspondence: Berthold Koletzko, M.D., Professor of Paediatrics Div. Metabolic Diseases and Nutritional Medicine, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University of Munich, Lindwurmstr, 4, D-80337 München, Germany Tel: +49-5160-3967; Fax: +49-5160-3336 (e-mail: claudia.wellbrock@med.uni-muenchen.de).

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.

REFERENCES

1. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery* 1968;64:134–42.
2. Goulet O, Ruemmele F, Lacaille F, Colomb V. Irreversible intestinal failure. *J Pediatr Gastroenterol Nutr* 2004;38:250–69.
3. Heird WC, Driscoll JM, Jr. Schullinger JN, et al. Intravenous alimentation in pediatric patients. *J Pediatr.* 1972;80:351–72.
4. Koletzko B, Akerblom H, Dodds P, Ashwell M. (eds.) *Early Nutrition and Its Later Consequences: New Opportunities*. Perinatal Programming of Adult Health - EC Supported Research Series: Advances in Experimental Medicine and Biology, Vol. 569. New York: Springer, 2005:1–237.
5. Tsang R, Koletzko B, Uauy R, Zlotkin S. Nutrition of the preterm infant. Scientific basis and practical application. Cincinnati: Digital Educational Publishing; 2005.
6. Royal College of Paediatrics and Child Health. Withholding or withdrawing life saving treatment in children. A framework for practice. *Londeon: RCPCH* 1997.