



ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Guideline development process for the updated guidelines

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ARTICLE INFO

Article history:

Received 29 May 2018

Accepted 29 May 2018

1. Background

In 2005, 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) were published [1]. The current

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document is a revision of these guidelines produced by the same 3 organizations (ESPEN, ESPGHAN, ESPR) together with the Chinese Society of Parenteral and Enteral Nutrition (CSPEN). Its primary goal is to provide up-to-date evidence for health professionals working with infants, children and adolescents receiving parenteral nutrition (PN). It is based on literature collected in a systematic way and on expert opinion.

Experts participating in the guideline updating process were all professionals with extensive experience in managing PN. The guideline development process was coordinated by the guideline steering committee: Mihatsch WA (Department of Pediatrics, Ulm University, Ulm, Germany), Shamir R (Schneider Children's Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel), van Goudoever JB (VU University Medical Center, Amsterdam, The Netherlands), Fewtrell M (UCL Institute of Child Health, London, UK), and Lapillonne A (APHP Necker-Enfants Malades Hospital, Paris-Descartes University, Paris, France). Each chapter of the guideline was prepared by a separate author group. These author groups were responsible for screening titles and abstracts identified by a systematic search for inclusion, for conducting additional expert searches (including secondary sources such as other published valid guidelines), for evaluating the quality of studies included in the given chapter and assigning evidence levels to the literature. Based on the evidence level of included studies experts formulated and graded recommendations.

A consensus conference was held in February 2015 in Hersching, Germany, where all experts participating in the guideline updating process were invited to participate. At this conference delegates of each author team presented the existing scientific knowledge in the field of PN in the form of a short but focused presentation. Following the presentation, the suggested evidence levels were discussed and final decisions were made by voting. Only 'yes' or 'no' was allowed, to ensure clear majority decisions. Recommendations with more than 75% agreement were accepted, while recommendations with less than 75% agreement were modified according to the feedback of the consensus panel members in order to achieve a higher degree of agreement. Chapter manuscripts were revised accordingly and then reviewed and edited by the Project Steering Committee. There was no final consensus meeting, however, consensus on each individual guideline and its individual recommendations was achieved and assessed by online voting. This process lasted until January 2018.

The recommendations were ultimately developed from a combination of the available literature and the opinions of experts representing different disciplines and from a wide range of European countries, Israel and China.

Funding for the consensus conference (including travel expenses for participants) was provided by ESPGHAN, ESPEN, ESPR and CSPEN. No other funding was received for the guideline updating process and participants received no payment. Support was provided by the Hungarian Cochrane organization.

2. Criteria for considering studies for this guideline

Studies had to have direct relevance to the specific issue covered in the given chapter to be included in the guideline. Studies investigating children (aged 0–18 years) were eligible for inclusion (except for chapter 10 where no age limit was imposed). No restriction was made according to study type or the quality of information.

3. Search methods and selection of studies

A systematic literature search was conducted for each chapter. The Ovid Medline database was searched using a search strategy with both MESH terms and text words; the search was in the form [terms for parenteral nutrition] and [terms for the specific topic of the given chapter] limited to Children (aged 0–18 years) and to years "2004-Current". An exception was made in the case of Chapter 10 (terms for PN were not used) and Chapter 14 (a slightly different structure was used because of the broad topic of the chapter). The search strategy for each Chapter can be found at the start of each chapter. Most of the chapters attempted to identify all relevant trials regardless of language. However, in the case of chapters 7, 10 and 11 results were limited to studies written in English. Since this is an update of the PN guideline published in 2005, the electronic search was limited to studies published between 2004 and December 2014, the date when searches were conducted. Studies published before 2004 were included from the previous guideline. In parallel, experts conducted searches independently from the main search, using other, more specific search terms specific to the given chapter. For each individual guideline, the time frame of the individual literature search is given.

Titles and abstracts were screened by at least two authors from each chapter writing group independently to assess their eligibility for inclusion in the chapter. In cases with a large number of titles a preliminary screening was conducted by a single independent reviewer and titles that were obviously irrelevant were removed from the title list. Full-texts of articles that were deemed potentially relevant to the chapter were retrieved for further assessment. Decision on inclusion was reached by consensus among the authors of the chapter.

4. Assessment of quality of evidence [2]

The GRADE approach was used to assess the quality of evidence and to interpret findings. Authors of the individual chapters independently extracted data on methods, types of participants, interventions, and outcomes from the selected trials and then evaluated the level of evidence (LOE) and grade of recommendation (GOR). The SIGN classification was used to assign both the evidence level and the recommendation grade. The scales used to evaluate LOE and GOR are summarized in [Tables 1 and 2](#). Apart from the

Table 1
Rating scheme for the strength of the evidence [2].

Level of Evidence (LOE)	Type of evidence
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (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 or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2–	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case reports, case series
4	Expert opinion

Table 2
Rating scheme for the strength of the recommendations [2].

Grade of Recommendation (GOR)	Level of evidence
A	At least one meta-analyses, systematic reviews or RCT rated as 1++, and directly applicable to the target population; 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	A body of evidence including studies rated as 2++, directly applicable to the target population; or 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+
O	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points: Recommended best practice based on the clinical experience of the guideline development group

Table 3
Forms of recommendation [2].

Judgement	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

Table 4
Classification of the strength of consensus [2].

Classification	Definition
Strong consensus	Agreement of >90% of the participants
Consensus	Agreement of >75–90% of the participants
Majority agreement	Agreement of >50–75% of the participants
No consensus	Agreement of <50% of the participants

classical three class grading (A/B/O) the category ‘Good practice points’ (GPP) was also offered by this grading system (Table 2), enabling authors to make expert recommendations based on their experience for clinically relevant questions which are not covered by appropriate trials. In addition, a text recommendation (Table 3) was also formulated to give a potentially more definitive recommendation for guideline users; experts were instructed to focus on the recommendations ‘Conditional recommendation for’ and ‘Strong recommendation for’.

5. Achievement of consensus

One to three rounds of online voting using the software SurveyMonkey (SurveyMonkey Europe, 2 Shelbourne Buildings, 2nd Floor, Shelbourne Road, Ballsbridge, Dublin 4, Ireland) were

performed with each individual guideline to achieve consensus within all participants of the working group. The first round took place after finalization of each individual guideline by the individual group of authors. The feedback from online voting and its corresponding online discussion were used to modify and improve the initial recommendations in order to reach the highest degree of acceptance at the final (second or third) online voting. This process of modification lasted in individual guidelines till the end of 2017. The level of the strength of consensus is given with each individual recommendation (Table 4).

Conflict of interest

None declared.

References

- [1] Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. 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). *J Pediatr Gastroenterol Nutr* 2005;41(Suppl. 2):S1–87.
- [2] Bischoff SC, Singer P, Koller M, Barazzoni R, Cederholm T, van Gossum A. Standard operating procedures for ESPEN guidelines and consensus papers. *Clin Nutr* 2015;34:1043–51.