**Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) Metabolism, Endocrine and Nutrition section Position statement and Clinical Recommendations**

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**Take Home Message:**

There is a lack of high-quality evidence to guide nutrition in pediatric critical illness. This position statement and clinical recommendations summarises the existing evidence around 15 of the most important clinical questions, and where no evidence is available, suggests good clinical practice.**Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) Metabolism, Endocrine and Nutrition section Position statement and Clinical Recommendations**

**Abstract**

**Background:** Nutritional support is considered essential for the outcome of pediatric critical illness. There is a lack of methodologically sound trials to provide evidence-based guidelines leading to diverse practices in PICUs worldwide. Acknowledging these limitations, we aimed to summarize the available literature and provide practical guidance for the pediatric critical care clinicians around important clinical questions many of which are not covered by previous guidelines.

**Objective:** To provide an ESPNIC position statement and make clinical recommendations for the assessment and nutritional support in critically ill infants and children.

#### Design: The Metabolism, Endocrine and Nutrition (MEN) section of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) generated 15 clinical questions regarding different aspects of nutrition in critically ill children. After a systematic literature search, the Scottish Intercollegiate Guidelines Network (SIGN) grading system was applied to assess the quality of the evidence, conducting meta-analyses where possible, to generate statements and clinical recommendations, which were then voted on electronically. Strong consensus (>95% agreement) and consensus (>75% agreement) on these statements and recommendations was measured through modified Delphi voting rounds.

**Results:** The final 15 clinical questions generated a total of 7261 abstracts, of which 142 publications were identified relevant to develop 32 recommendations. A strong consensus was reached in 21 (66%) and consensus was reached in 11 (34%) of the recommendations. Only 11 meta-analyses could be performed on 5 questions.

**Conclusions:** We present a position statement and clinical practice recommendations. The general level of evidence of the available literature was low. We have summarised this and provided a practical guidance for the pediatric critical care clinicians around important clinical questions.

**Keywords:** Enteral nutrition; parenteral nutrition; child; pediatric; intensive care; guidelines

**Introduction**

Critical illness induces profound metabolic and endocrine changes in close interaction with the alterations in autonomic and immune systems. The metabolic and endocrine changes are characterized by catabolism, insulin resistance and shifts in substrate utilisation.1 These changes evolve during the course of illness, where the acute changes are assumed to be advantageous for survival. However, following the acute phase these changes might become harmful.1,2 Parallel to these changes, critically ill children frequently experience feeding difficulties, caused by (perceived) feed intolerance and feeding interruptions.3,4 This often leads to undernourishment with a cumulative macronutrient deficit during the course of their Pediatric Intensive Care Unit (PICU) stay.5,6 Malnutrition at PICU admission is frequent (15 to 25% prevalence rates) in developing countries; nutritional status deterioration is also an early and frequent phenomenon in this setting with almost one third of critically ill children presenting with nutritional indices decline.7-9 Muscle wasting is also a constant, intense and rapid phenomenon.10 Malnourishment and macronutrient deficits during critical illness have been associated with increased morbidity (infections, weakness, prolonged mechanical ventilation and delayed recovery) as well as increased mortality. However, overfeeding has also been shown to pose harm to critically ill children especially during the acute phase. As the metabolic and endocrine response evolves during the course of critical illness, possibly the nutritional support should also accommodate these changes and differ during the different phases of pediatric critical illness as well.

Although optimal nutrition is considered essential to improve outcomes in critically ill children, large well-designed randomized controlled trials (RCTs) with clinically relevant outcome measures are scarce.11,12 The limited evidence has led to a wide variation in nutritional practices worldwide, between individual clinicians, PICUs and countries.13,14 Yet the evidence is increasing, and the number of publications on nutritional support in pediatric critical illness in 2018 has doubled when compared with 2012 and tripled since 2007. In 2017 the American Society of Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) published their guidelines for the provision of nutritional support in the PICU.15 However, several important clinical topics remained unanswered.16 For instance, term neonates (defined as >37 weeks to 44 weeks gestational age) which comprise around 32% of the PICU population, were excluded from these recommendations.17 As a multidisciplinary research group within Europe, the ESPNIC Metabolism, Endocrinology and Nutrition (MEN) section therefore felt it was timely to address unanswered clinical questions and review new evidence to produce a position statement and recommendations on artificial nutrition in critically ill children.

**Methodology**

**Selection of members**

The working group was composed of a multidisciplinary team of 11 European specialists (5 pediatric intensivists, 2 nurses and 4 dietitians) in nutritional support for critically ill children, who are members of the MEN section of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC). Four members (LT/CJ/KJ/SV) were well trained and experienced in the development and methodology of systematic reviews and development of recommendations. A biostatistician (JvR) was added to the multi-disciplinary team specifically for the expertise in meta-analyses, but did not participate in development of the recommendations or the voting process.

**Question development and search strategy**

The working group met initially, in June 2017, to discuss the project, and generate 15 broad clinical questions. The systematic literature search was performed by biomedical information specialists (EK, SG, GdJ and WB; see acknowledgements) of the Erasmus Medical Centre Library (Rotterdam, The Netherlands) in four databases (Embase.com; Medline Epub (Ovid); Cochrane Central; Web of Science) and included all articles published from 1997 until May 2018 and updated in November 30 2018. Supplement file 1 describes the search terms used per question.

Inclusion and exclusion criteria were agreed by the group. Inclusion criteria were RCTs, case-control, before and after and cohort studies including critically ill term neonates and children (aged ≥37 weeks gestational age – 18 years). We only included manuscripts written in English or French, which excluded three papers, one in Russian two in Chinese. Publications describing studies in pre-term infants were excluded, unless the question specifically related to neonatal PICU patients and no evidence existed in term neonates (Question 4). In addition to reviews, animal studies, case reports, editorials, commentaries, conference abstracts and letters were excluded. Separate publications presenting outcomes from the same study population were included, but seen as one study, and the study that provided the most complete data to answer the question was included. For each of the 15 questions, key search words were defined, and specific search combinations were developed for the four databases (Supplementary file 1).

**Selection of studies**

In order to select the eligible studies, the results from each database were combined and exported to Endnote, followed by removal of duplicates and exportation to a Word document, allowing at least two working group members to separately undertake the screening of the abstracts in a standardized way. Abstracts were screened for eligibility by the group members, and those which were thought to be eligible were automatically exported as final abstract. Areas of disagreement were resolved by discussion. Abstracts that determined to be eligible by one of the two members were discussed with a third reviewer before decision of inclusion or exclusion. If eligibility criteria were met, full manuscripts were procured. Similarly, if a disagreement on the eligibility of the paper occurred, a discussion took place with a third reviewer. We also examined reference lists from included articles for suitable studies. A PRISMA diagram is shown in Supplementary file 2.

**Data extraction and assessment of study quality and evidence grading**

Data from eligible papers were extracted by two reviewers with the primary reviewer not an author on the paper. In addition, the risk of bias was assessed by two reviewers independently using the SIGN critical appraisal checklists available for each study design (<https://www.sign.ac.uk/checklists-and-notes.html>) (Supplementary file 3). Any disagreement with grading was discussed and the two lead authors (LT/FV) reviewed all the evidence grading. The classification of the literature into levels of evidence was performed according to the SIGN grading system (Supplementary file 3).

**Data analysis including meta-analyses**

In some questions, the data were combined statistically in a meta-analysis if they met the following criteria: there was more than one study, the combined studies (in one analysis) were either randomised trials or observational studies, the population and the intervention were sufficiently similar to combine and the outcomes were the same, or for continuous outcome variables, if we had data on the distribution of the variable. To perform the meta-analyses, we a priori defined clinically relevant outcome variables on which the meta-analyses would be performed. These were mortality, new infections, gastro-intestinal complications (vomiting aspiration / diarrhoea / NEC-ischemia), length of ventilation and length of stay (PICU / hospital). Anticipating a broad inconsistency of these outcome variables we chose a pragmatic meta-analysis. The risk of bias tables are presented in Supplementary File 4 For dichotomous outcomes, we used a random effects model for the relative risk of the intervention to compute a pooled relative risk and its 95% CI. The Hartung–Knapp–Sidik–Jonkman method was used to estimate the between-study variance, and a continuity correction of 0.5 was applied in case of zero cell frequencies. The heterogeneity of combined study results was assessed using the inconsistency statistic and tested using Cochran's Q test. The meta-analyses were performed using R version 3.6.1 with the package meta.

**Consensus methodology and grading of the recommendations**

Based on the results from the systematic review and meta-analyses, a first draft of recommendations was composed, including the supporting text and grade of recommendation. The classification of the grades of recommendation (A-D, Good Clinical Practice) was undertaken according to the SIGN grading system (Supplementary file 3).18 In May 2018, a second meeting took place to discuss all questions and review the evidence quality and recommendations. The group generated the position statement and a draft guideline with a total of 32 recommendations, which was followed by a round of electronic voting to gain consensus using a Delphi method in June 2018.19,20 The survey involved voting on each recommendation on 3-point scale with categories: disagree, agree and unsure. This was created and distributed via a proprietary electronic online platform hosted by the University of Southampton (<https://www.isurvey.soton.ac.uk/>) and checked by one of the authors (LM) without identifying features to ensure anonymity. In round 2, we provided the group results and asked the group to re-vote. We defined strong consensus as agreement of >95%, consensus as agreement of 75 - 95% and no consensus as agreement <75%. Feedback received during the first round of online voting was used to modify and improve the recommendations in order to reach a higher degree of consensus at the final online voting in September 2018. Any recommendations with an agreement equal to or lower than 95% were discussed at a consensus meeting which took place on 31 October 2018. Following a revised meta-analysis, a last and final meeting of a core group of 4 members took place in November 2019, which was followed by a final round of electronic voting. The AGREE reporting checklist for guideline development was followed (Supplementary File 5). The ESPNIC process for endorsement of guidelines was undertaken.

**Results**

A total of 7261 abstracts were screened. Subsequently 142 publications were reviewed, and data were extracted (Supplementary file 2) and included in the development of 32 recommendations (Table 1). The general level of evidence was low: out of the 142 publications, 5 (3.5%) were graded 1+ according to the SIGN grading system, 27 (18.9%) were graded 1-, six (4.2%) were graded 2++, 20 (14.0%) were graded 2+, 82 (58.0%) were graded 2-, one (0.7%) was graded 3 and one (0.7%) was graded 4. Furthermore, the data were suitable for meta-analysis for only 11 (sub)questions, all of which had dichotomous outcome measures. All forest plots of the meta-analyses have been provided in supplement file 6. Overall, heterogeneity of the studies suitable for meta-analysis varied with *I2* 0-91% (p-value 0.13-0.83), and two meta-analyses with a *I2* of higher than 50%, 53% and 55% respectively for the impact of gastric versus post-pyloric feeding on aspiration and intermittent versus continuous feeding on diarrhoea. The pooled relative risk showed a significant difference between groups in only 1 out of these 11 meta-analyses. Enteral feeding versus no enteral feeding in children on hemodynamic support resulted in a lower risk of mortality (RR 0.41 [95%CI 0.20 - 0.86]). Accordingly, the grading of the 32 recommendations were as follows: five recommendations were graded as B, five as C, 12 as D and 10 were GCP.

A strong consensus was reached in 21 (66%) and consensus was reached in 11 (34%) of the recommendations. A detailed discussion of the clinical questions, the recommendations with evidence grading, and level of consensus achieved in presented in Supplementary file 7 with a full reference list. The table of evidence is presented in Supplementary file 8. A summary of all recommendations is shown in Table 1. A summary of comparisons between our recommendations and those presented by ASPEN/SCCM is shown in Table 2.

**Discussion**

This position statement with clinical recommendations provides new guidance based on new evidence, as well as reinforcing most of the existing 2017 ASPEN Guidelines. These ASPEN PICU nutrition guidelines published in 2017, were based on a literature search from January 1995 to March 2016 and consisted of 17 recommendations. These ESPNIC clinical recommendations are based on an updated literature search until November 2018. Both the American (ASPEN) and our European guidelines provide expert opinion which is essential in this setting where limited data is available. Our recommendations are predominantly consistent with the ASPEN guideline recommendations (Table 2) which helps assist in the uptake and implementation of guidelines into practice.161 Implementation of evidence into clinical practice remains problematic, in 2017 a European survey of 59 PICUs found that 69% of PICUs still had no local feeding guidelines.13 Additionally, this position statement generated new clinical guidance as half of our clinical questions differed from the ASPEN guidelines. These included guidance on feeding neonates with arterial umbilical arterial catheters; the type of enteral formula to be used; the amount or type of each macronutrient to provide; the value of gastric residual volume to assess feeding tolerance; the use of prokinetics to enhance feeding tolerance and the use of feeding protocols to improve outcomes. Furthermore, these new ESPNIC recommendations covered in more detail the indications for enteral nutrition in various subgroups of patients in clinicians are in general uncertain on how to progress feeding (i.e. term neonates and children on hemodynamic support and after cardiac surgery).13 In addition, our position statement provides a different stand on two recommendations as compared with the ASPEN guidelines, based on new available research. In contrast with the ASPEN guidelines we recommend to consider withholding parenteral nutrition during the first week in neonates and children, independent of their nutritional state.8,15,150 Furthermore, there was also strong consensus in our working group that there is insufficient evidence to recommend a protein/amino acid intake of 1.5 gr/kg/day or higher during the acute phase of disease to benefit clinical outcomse.15 The intake of 1.5 gr/kg/day or higher has shown to prevent cumulative negative protein balance.96,97 However, future research should consider that the exact threshold is unknown, and might overestimate protein/amino acid requirements during acute critical illness, thus further work should therefore also investigate low protein/amino acid intakes during that phase.131

Overall, as expected, the general level of evidence was low, and the meta-analyses provided little value because of the heterogeneity in interventions and outcomes, population and the type of study designs (few RCTs). This resulted in few studies able to be pooled for this analysis. Despite these limitations, we formulated 32 recommendations which can guide PICU healthcare professionals. There are a few key messages to be taken from our position statement. Although hardly any methodologically sound studies exist, recent developments have shown that nutritional interventions in our PICUs are capable of impacting on the short and long-term outcome in critically ill children.92,152 Despite the lack of effect shown of protocols on mortality and NEC in the meta-analysis, as the level of this evidence was low, all individual studies did show positive effect on other variables such as time to initiate feeding and achievement of energy goals, but it was not possible to pool these in a meta-analysis. Therefore, despite this, we still recommend PICUs use feeding protocols which provide guidance on the assessment of nutritional status, and the start and advancement of feeding. A final key messages from this position statement is to encourage the enteral feeding of critically ill neonates and children early wherever possible, unless clear contraindications exist. Although starting early EN is recommended, no evidence exists to support high nutritional intake during the acute phase of critical illness and withholding supplemental PN during the first week in PICU may be considered when enteral nutrition is insufficient.

**Limitations**

We acknowledge that these clinical recommendations are based at times on sparse pediatric evidence. Moreover, for many questions and clinical recommendations we could not be age-specific, although the (patho)physiology of nutritional and metabolic changes during critical illness is age-dependent. For instance, the recommendations specifically for neonates were partially based upon studies in preterm neonates as no evidence existed in term neonates. The threshold of >37 weeks in our recommendations is recognized as rigid and we cannot exclude that some of our recommendations also apply for late preterm (>34 weeks) or early term (>36 weeks) neonates. Similarly, the same arguments can be raised for adolescents, where for certain (older) adolescents, recommendations from adult guidelines might be suitable. However, the mean age in adult ICUs is 60.9 years 162 and it therefore cannot be assumed that critically ill young adults are similar in their (patho)physiologic response to nutritional and metabolic changes to elderly patients. We further acknowledge that, as a priori anticipated, pragmatic meta-analyses were required due to the inconsistencies in the outcome variables. Another limitation is that our consensus voting was based only on the views of our study team of 11 experts. Finally, as already elaborated on in our discussion, aside from several novel features our recommendations have an overlap with the American (ASPEN) guidelines published in 2017. A future collaboration between the American and European societies might improve upcoming guidelines and help implement the recommendations worldwide. Despite these limitations, this work has provided an updated summary of the existing evidence, including questions around term neonates, which are not dealt with by other recommendations or guidelines, yet comprise a significant amount of the European PICU population.

**Conclusion**

This ESPNIC position statement with recommendations provide a ‘best-available-evidence’ guide for clinicians working in PICU to provide nutritional support in this setting. The lack of methodologically sound trials and the heterogeneous character of studies available were important barriers in the generation of these recommendations. Many recommendations are based on expert consensus and have a low level of evidence. Nonetheless, our recommendations support the use of a formal nutritional assessment and a feeding protocol in all PICUs.

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