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EXPERT STATEMENT

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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Abstract

Background: Nutritional support is considered essential for the outcome of paediatric 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 paediatric 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 paediatric critical care clinicians around important clinical questions.

Keywords: Enteral nutrition, Parenteral nutrition, Child, Paediatric, Intensive care, Guidelines

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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 (15–25% 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 paediatric 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 paediatric 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 > 37–44 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.

Take-home message

There is a lack of high-quality evidence to guide nutrition in paediatric critical illness. This position statement and clinical recommendations summarise the existing evidence around 15 of the most important clinical questions, and where no evidence is available, suggest good clinical practice.

Methodology

Selection of members

The working group was composed of a multidisciplinary team of 11 European specialists (five paediatric intensivists, two nurses and four 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, gastrointestinal 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 four 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 I^2 0–91% (p value 0.13–0.83), and two meta-analyses with a I^2 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 haemodynamic support resulted in a lower risk of mortality (RR 0.41 [95%CI 0.20–0.86]). Accordingly, the grading of the 32 recommendations was 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 are 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 are 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 [21]. 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 haemodynamic 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, 22]. 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 g/kg/day or higher during the acute phase of disease to benefit clinical outcomes [15]. The intake of 1.5 g/kg/day or higher has shown to prevent cumulative negative protein balance [23, 24]. 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 [25].

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

Table 1 Summary of recommendations for nutritional support for children during critical illness

Question	Recommendation	SIGN recommendation grade	Consensus	References used in synthesis of recommendations
In critically ill children, should nutritional status be assessed and what is the optimal method to assess nutritional status?	1.1: The assessment of nutritional status is recommended in critically ill children at admission and throughout their PICU admission	GCP	Strong consensus	[31-57]
	1.2: It is recommended to perform anthropometric measurements on admission and regularly during admission, and to express these measurements in z-scores, including weight, height/length mid upper arm circumference and head circumference in young children	GCP	Strong consensus	[6, 10, 48–55]
In critically ill children, when should enteral nutrition be commenced and how should it be increased?	2.1: It is recommended to commence early enteral nutrition within 24 h of admission unless contraindicated	D	Strong consensus	[58, 61, 64–69, 71]
	2.2: It is recommended to increase enteral nutrition in a stepwise fashion until goal for delivery is achieved using a feeding protocol or guideline	D	Strong consensus	[59, 60, 62, 63, 71, 72, 74–76]
In critically ill children on haemodynamic support (vasoactive medications, extracorporeal life support ECLS) does enteral feeding compared to no enteral feeding affect outcomes?	3.1: Early enteral nutrition is recommended in term neonates who are stable on ECLS	D	Consensus	[77–80]
	3.2: Early enteral nutrition is recommended in children who are stable on ECLS	D	Strong consensus	[82]
	3.3: Early enteral nutrition is recommended in term neonates who are stable on pharmaceutical haemodynamic support	GCP	Consensus	[83, 85, 86]
	3.4: Early enteral nutrition is recommended in children who are stable on pharmaceutical haemodynamic support	D	Strong consensus	[83, 85, 86]
	3.5: Early enteral nutrition is recommended in children after cardiac surgery	C	Consensus	[87–94]
In critically ill term neonates with umbilical arterial catheters and/or PGE1 infusions, does enteral feeding impact on adverse events?	4.1: Enteral nutrition should be considered in term neonates with umbilical arterial catheters	D	Strong consensus	[95, 96, 100]
	4.2: Enteral nutrition should be considered in critically ill term neonates on PGE1 infusion if managed in a critical care unit with adequate observation and monitoring	D	Strong consensus	[97–99]
In critically ill children what are their energy requirements?	5.1 In the acute phase, energy intake provided to critically ill children should not exceed resting energy expenditure	C	Strong consensus	[26, 101–104]
	5.2. After the acute phase, energy intake provided to critically ill children should account for energy debt, physical activity, rehabilitation and growth	GCP	Strong consensus	[105–113]
In critically ill children, what is the most accurate method of determining or predicting energy expenditure?	6.1 Measuring resting energy expenditure using a validated indirect calorimeter should be considered to guide nutritional support in critically ill infants and children after the acute phase	GCP	Strong consensus	[114 –119]
	6.2 Schofield equation (for age and gender and using an accurate weight) is recommended to estimate resting energy expenditure	C	Strong consensus	[120–125]
In critically ill children, what are the macronutrient requirements?				
What is the recommended glucose intake?	7.1. Parenteral glucose provision should be sufficient to avoid hypoglycemia but not excessive to prevent hyperglycemia	D	Strong consensus	[126, 127]

Table 1 (continued)

Question	Recommendation	SIGN recommendation grade	Consensus	References used in synthesis of recommendations
What is the recommended lipid intake or type?	7.2: When parenteral nutrition is used, composite lipid emulsions, with or without fish oil, should be considered as the first-choice treatment	GCP	Strong consensus	[128]
What is the recommended protein/amino acid intake?	7.3a: For critically ill infants and children on enteral nutrition a minimum enteral protein intake of 1.5 g/kg/d can be considered to avoid negative protein balance	B	Strong consensus	[23, 24, 106–108, 129, 130]
	7.3b: There is insufficient evidence available to support the use of additional protein/amino acid intake during the acute phase of illness (Strong consensus)	D	Strong consensus	[131-137]
In critically ill children, do different feed formulas (polymeric vs. semi-elemental feed, standard vs. enriched formula) impact on clinical outcomes?	8.1 Polymeric feeds should be considered as the first choice for enteral nutrition in most critically ill children, unless there are contraindications	GCP	Strong consensus	
	8.2 Protein and energy-dense formulations may be considered to support achievement of nutritional requirements in fluid-restricted critically ill children	B	Consensus	[138, 139]
	8.3 Peptide-based formulations may be considered to improve tolerance and progression of enteral feeding in children for whom polymeric formulations are poorly tolerated or contra-indicated	GCP	Strong consensus	[141]
In critically ill children, does pharmaconutrition (glutamine, lipids and/or micronutrients) impact on clinical outcomes?	9.1 There is insufficient evidence to recommend the use of pharmaconutrition in critically ill children	B	Strong consensus	[81, 141-148]
In critically ill children, does continuous feeding compared to intermittent bolus gastric feeding impact on outcomes?	10.1: There is no evidence to suggest that either continuous or intermittent/bolus feeds are superior in delivering gastric feeds in critically ill children	B	Strong consensus	[70, 149 152]
In critically ill children, does gastric feeding compared to post-pyloric feeding impact on clinical outcomes?	11.1: Gastric feeding is as safe as post pyloric feeding in the majority of critically ill children	C	Strong consensus	[83, 150, 151, 153]
	11.2: Gastric feeding is not inferior to post pyloric feeding in the majority of critically ill children	D	Strong consensus	[150, 151, 153]
	11.3 Post-pyloric feeding can be considered for critically ill children at high risk of aspiration or requiring frequent fasting for surgery or procedures	GCP	Strong consensus	
In critically ill children does routine Gastric Residual Volume (GRV) to guide enteral feeding impact on outcomes?	12.1: Routine measurement of GRV in critically ill children is not recommended	D	Strong consensus	[154]
In critically ill children, do prokinetics impact on clinical outcomes?	13.1: There is insufficient evidence to support the use of prokinetics in critically ill children to improve gastric emptying and feed tolerance	GCP	Strong consensus	[144, 145]
In critically ill children, when should Parenteral Nutrition (PN) be started?	14.1: Withholding parenteral nutrition for up to one week can be considered in critically ill term neonates and children, independent of nutritional status, while providing micronutrients	B	Consensus	[8, 9, 22, 25–27, 156]
In critically ill children, does the use of a feeding protocols impact on clinical outcomes?	15.1: Enteral feeding protocols are recommended to improve time to initiation of EN and nutritional intake	C	Strong consensus	[30, 59, 60, 62, 72, 74–, 76, 87, 90, 157–, 162]
	15.2: Enteral feeding protocols are recommended for high-risk populations to improve nutritional intake and reduce adverse events	D	Strong consensus	[30, 59, 60, 62, 72, 74–76, 87, 90, 157–162]

Table 2 Comparison between American and European guidelines on paediatric intensive care nutrition support

ESPNIC Recommendations (European Society of Paediatric and Neonatology Intensive care)	SCCM and ASPEN recommendations (Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition)
Q1: In critically ill children, should nutritional status be assessed and what is the optimal method to assess nutritional status?	**Q1A. What is the impact of nutritional status on outcomes in critically ill children?** **Q1B. What are the best practices to screen and identify patients with malnutrition or those at risk of nutritional deterioration in the PICU?**
R1.1: The assessment of nutritional status is recommended in critically ill children at admission and throughout their PICU admission	R1A. Based on observational studies, malnutrition, including obesity, is associated with adverse clinical outcomes including longer periods of ventilation, higher risk of hospital-acquired infection, longer PICU and hospital stay, and increased mortality. We recommend that patients in the PICU undergo detailed nutritional assessment within 48 h of admission. Furthermore, as patients are at risk of nutritional deterioration during hospitalization, which can adversely affect clinical outcomes, we suggest that the nutritional status of patients be re-evaluated at least weekly throughout hospitalization
R1.2: It is recommended to perform anthropometric measurements on admission and regularly during admission, and to express these measurements in z-scores, including weight, height/length mid upper arm circumference and head circumference in young children	R1B. Based on observational studies and expert consensus, we recommend that weight and height/length be measured on admission to the PICU, and z scores for body mass index for-age (weight-for-length < 2 years), or weight-for-age (if accurate, height is not available), be used to screen for patients at extremes of these values. In children < 36-months, head circumference must be documented. Validated screening methods for the PICU population to identify patients at risk of malnutrition must be developed. Screening methods might allow limited resources to be directed to high-risk patients who are most likely to benefit from early nutritional assessment and interventions
Q2: In critically ill children, when should enteral nutrition be commenced and how should it be increased?	**Q6B. When should EN be initiated?** **Q4A. Is EN feasible in critically ill children?** **Q4B. What is the benefit of EN in this group?** **Q5A. What is the optimum method for advancing EN in the PICU population?**
R2.1: It is recommended to commence early enteral nutrition within 24 h of admission unless contraindicated	R6B. Based on expert opinion, we suggest that EN be initiated in all critically ill children, unless it is contraindicated. Based on observational studies, we suggest early initiation of EN, within the first 24–48 h after admission to the PICU, in eligible patients. We suggest the use of institutional EN guidelines and stepwise algorithms that include criteria for eligibility for EN, timing of initiation, and rate of increase as well as a guide to detecting and managing EN intolerance
	R4A. Based on observational studies, we recommend EN as the preferred mode of nutrient delivery to the critically ill child. Observational studies support the feasibility of EN, which can be safely delivered to critically ill children with medical and surgical diagnoses, and to those receiving vasoactive medications. Common barriers to EN in the PICU include delayed initiation, interruptions due to perceived intolerance, and prolonged fasting around procedures. Based on observational studies, we suggest that interruptions to EN be minimized to achieve nutrient delivery goals by the enteral route
	R4B. Although the optimal dose of macronutrients is unclear, some amount of nutrient delivered as EN has been beneficial for gastrointestinal mucosal integrity and motility. Based on large cohort studies, early initiation of EN (within 24–48 h of PICU admission) and achievement of up to two thirds of the nutrient goal in the first week of critical illness have been associated with improved clinical outcomes
R2.2: It is recommended to increase enteral nutrition in a stepwise fashion until goal for delivery is achieved using a feeding protocol or guideline	R5A. Based on observational studies, we suggest the use of a stepwise algorithmic approach to advance EN in children admitted to the PICU. The stepwise algorithm must include bedside support to guide the detection and management of EN intolerance and the optimal rate of increase in EN delivery
Q3: In critically ill children on haemodynamic support (vasoactive medications, extracorporeal life support ECLS) does enteral feeding compared to no enteral feeding affect outcomes?	**Q4A. Is EN feasible in critically ill children?**

Table 2 (continued)

ESPNIC Recommendations (European Society of Paediatric and Neonatology Intensive care)	SCCM and ASPEN recommendations (Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition)
R3.1: Early enteral nutrition is recommended in term neonates who are stable on ECLS	NA
R3.2: Early enteral nutrition is recommended in children who are stable on ECLS	NA
R3.3: Early enteral nutrition is recommended in term neonates who are stable on pharmaceutical haemodynamic support	
R3.4: Early enteral nutrition is recommended in children who are stable on pharmaceutical haemodynamic support	R4A. Based on observational studies, we recommend EN as the preferred mode of nutrient delivery to the critically ill child. Observational studies support the feasibility of EN, which can be safely delivered to critically ill children with medical and surgical diagnoses, and to those receiving vasoactive medications
R3.5: Early enteral nutrition is recommended in children after cardiac surgery	
Q4: In critically ill term neonates with umbilical arterial catheters and/or PGE1 infusions, does enteral feeding impact on adverse events?	**NA**
R4.1: Enteral nutrition should be considered in term neonates with umbilical arterial catheters	NA
R4.2: Enteral nutrition should be considered in critically ill term neonates on PGE1 infusion if managed in a critical care unit with adequate observation and monitoring	NA
Q5: In critically ill children what are their energy requirements?	**Q2C. What is the target energy intake in critically ill children?**
R5.1 In the acute phase, energy intake provided to critically ill children should not exceed resting energy expenditure	R2C. Based on observational cohort studies, we suggest achieving delivery of at least two thirds of the prescribed daily energy requirement by the end of the first week in the PICU. Cumulative energy deficits during the first week of critical illness may be associated with poor clinical and nutritional outcomes. Based on expert consensus, we suggest attentiveness to individualized energy requirements, timely initiation and attainment of energy targets, and energy balance to prevent unintended cumulative caloric deficit or excesses
R5.2. After the acute phase, energy intake provided to critically ill children should account for energy debt, physical activity, rehabilitation and growth	
Q6: In critically ill children, what is the most accurate method of determining or predicting energy expenditure?	**Q2A. What is the recommended energy requirement for critically ill children?** **Q2B. How should energy requirement be determined in the absence of IC?**
R6.1 Measuring resting energy expenditure using a validated indirect calorimeter should be considered to guide nutritional support in critically ill infants and children after the acute phase	R2A. Based on observational cohort studies, we suggest that measured energy expenditure by indirect calorimetry (IC) be used to determine energy requirements and guide prescription of the daily energy goal
R6.2 Schofield equation (for age and gender and using an accurate weight) is recommended to estimate resting energy expenditure	R2B. If IC measurement of resting energy expenditure (REE) is not feasible, we suggest that the Schofield or Food Agriculture Organization/World Health Organization/United Nations University equations may be used "without" the addition of stress factors to estimate energy expenditure. Multiple cohort studies have demonstrated that most published predictive equations are inaccurate and lead to unintended overfeeding or underfeeding. The Harris-Benedict equations and the RDAs, which are suggested by the Dietary Reference Intakes, should not be used to determine energy requirements in critically ill children
Q7.1: What is the recommended glucose intake?	NA
R7.1. Parenteral glucose provision should be sufficient to avoid hypoglycaemia but not excessive to prevent hyperglycaemia	NA
Q7.2: What is the recommended lipid intake or type?	NA
R7.2: When parenteral nutrition is used, composite lipid emulsions, with or without fish oil, should be considered as the first-choice treatment	NA

Table 2 (continued)

ESPNIC Recommendations (European Society of Paediatric and Neonatology Intensive care)	SCCM and ASPEN recommendations (Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition)
Q7.3: What is the recommended protein/amino acid intake?	**Q3A. What is the minimum recommended protein requirement for critically ill children?** **Q3B. What is the optimal protein delivery strategy in the PICU?** **Q3C. How should protein delivery goals be determined in critically ill children?**
R7.3a: For critically ill infants and children on enteral nutrition a minimum enteral protein intake of 1.5 g/kg/d can be considered to avoid negative protein balance	R3A. Based on evidence from RCTs and supported by observational cohort studies, we recommend a minimum protein intake of 1.5 g/kg/d. Protein intake higher than this threshold has been shown to prevent cumulative negative protein balance in RCTs. In critically ill infants and young children, the optimal protein intake required to attain a positive protein balance may be much higher than this minimum threshold. Negative protein balance may result in loss of lean muscle mass, which has been associated with poor outcomes in critically ill patients. Based on a large observational study, higher protein intake may be associated with lower 60-d mortality in mechanically ventilated children
	R3B. Based on results of randomized trials, we suggest provision of protein early in the course of critical illness to attain protein delivery goals and promote positive nitrogen balance. Delivery of a higher proportion of the protein goal has been associated with positive clinical outcomes in observational studies
R7.3b: There is insufficient evidence available to support the use of additional protein/amino acid intake during the acute phase of illness (Strong consensus)	R3C. The optimal protein dose associated with improved clinical outcomes is not known. We do not recommend the use of RDA values to guide protein prescription in critically ill children. These values were developed for healthy children and often underestimate the protein needs during critical illness
Q8: In critically ill children, do different feed formulas (polymeric vs. semi-elemental feed, standard vs. enriched formula) impact on clinical outcomes?	**NA**
R8.1 Polymeric feeds should be considered as the first choice for enteral nutrition in most critically ill children, unless there are contraindications	NA
R8.2 Protein and energy-dense formulations may be considered to support achievement of nutritional requirements in fluid-restricted critically ill children	NA
R8.3 Peptide-based formulations may be considered to improve tolerance and progression of enteral feeding in children for whom polymeric formulations are poorly tolerated or contra-indicated	NA
Q9: In critically ill children, does pharmaconutrition (glutamine, lipids and/or micronutrients) impact on clinical outcomes?	**Q8. What is the role of immunonutrition in critically ill children?**
R9.1 There is insufficient evidence to recommend the use of pharmaconutrition in critically ill children	R8. Based on available evidence, we do not recommend the use of immunonutrition in critically ill children
Q10: In critically ill children, does continuous feeding compared to intermittent bolus gastric feeding impact on outcomes?	**NA**
R10.1: There is no evidence to suggest that either continuous or intermittent/bolus feeds are superior in delivering gastric feeds in critically ill children	NA
Q11: In critically ill children, does gastric feeding compared to post-pyloric feeding impact on clinical outcomes?	**Q6A. What is the best site for EN delivery–gastric or small bowel?**
R11.1: Gastric feeding is as safe as post pyloric feeding in most critically ill children	R6A. Existing data are insufficient to make universal recommendations regarding the optimal site to deliver EN to critically ill children. Based on observational studies, we suggest the gastric route be the preferred site for EN in patients in the PICU. The post-pyloric or small intestinal site for EN may be used in patients unable to tolerate gastric feeding or those at high risk for aspiration. Existing data are insufficient to make recommendations regarding the use of continuous vs intermittent gastric feeding
R11.2: Gastric feeding is not inferior to post pyloric feeding in the majority of critically ill children	

Table 2 (continued)

ESPNIC Recommendations (European Society of Paediatric and Neonatology Intensive care)	SCCM and ASPEN recommendations (Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition)
R11.3 Post-pyloric feeding can be considered for critically ill children at high risk of aspiration or requiring frequent fasting for surgery or procedures	
Q12: In critically ill children does routine Gastric Residual Volume (GRV) to guide enteral feeding impact on outcomes?	**NA**
R12.1: Routine measurement of GRV in critically ill children is not recommended	NA
Q13: In critically ill children, do prokinetics impact on clinical outcomes?	**NA**
R13.1: There is insufficient evidence to support the use of prokinetics in critically ill children to improve gastric emptying and feed tolerance	NA
Q14: In critically ill children, when should Parenteral Nutrition (PN) be started?	**Q7A. What is the indication for and optimal timing of PN in critically ill children?** **Q7B. What is the role of PN as a supplement to inadequate EN?**
R14.1: Withholding parenteral nutrition for up to one week can be considered in critically ill term neonates and children, independent of nutritional status, while providing micronutrients	R7A. Based on a single RCT, we do not recommend the initiation of PN within 24 h of PICU admission R7B. In children tolerating EN, we suggest stepwise advancement of nutrient delivery via the enteral route and delaying commencement of PN. Based on current evidence, the role of supplemental PN to reach a specific goal for energy delivery is not known. The time when PN should be initiated to supplement insufficient EN is also unknown. The threshold for and timing of PN initiation should be individualized. Based on a single RCT, supplemental PN should be delayed until 1 wEEk after PICU admission in patients with normal baseline nutritional state and low risk of nutritional deterioration. Based on expert consensus, we suggest PN supplementation in children who are unable to receive any EN during the first week in the PICU. In patients who are severely malnourished or at risk of nutritional deterioration, PN may be supplemented in the first week if they are unable to advance past low volumes of EN
Q15: In critically ill children, does the use of a feeding protocols impact on clinical outcomes?	**NA**
R15.1: Enteral feeding protocols are recommended to improve time to initiation of EN and nutritional intake	NA
R15.2: Enteral feeding protocols are recommended for high-risk populations to improve nutritional intake and reduce adverse events	NA
NA	**Q5B. What is the role of a nutrition support team or a dedicated dietitian in optimizing nutrition therapy?**
NA	5B. Based on observational studies, we suggest a nutrition support team, including a dedicated dietitian, be available on the PICU team, to facilitate timely nutritional assessment, and optimal nutrient delivery and adjustment to the patients

NA not applicable, *EN* enteral nutrition, *IC* indirect calorimetry, *PN* parenteral nutrition, *RCT* randomized controlled trial, *RDA* recommended daily allowance

outcome in critically ill children [26, 27]. 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 paediatric 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 [28] 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 [29, 30].

Conclusion

This ESPNIC position statement with recommendations provides 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.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05922-5) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

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