OVERCOMING BARRIERS

OPTIMISING NUTRITIONAL THERAPY IN THE CRITICALLY ILL CHILD

R.D. EVELEENS

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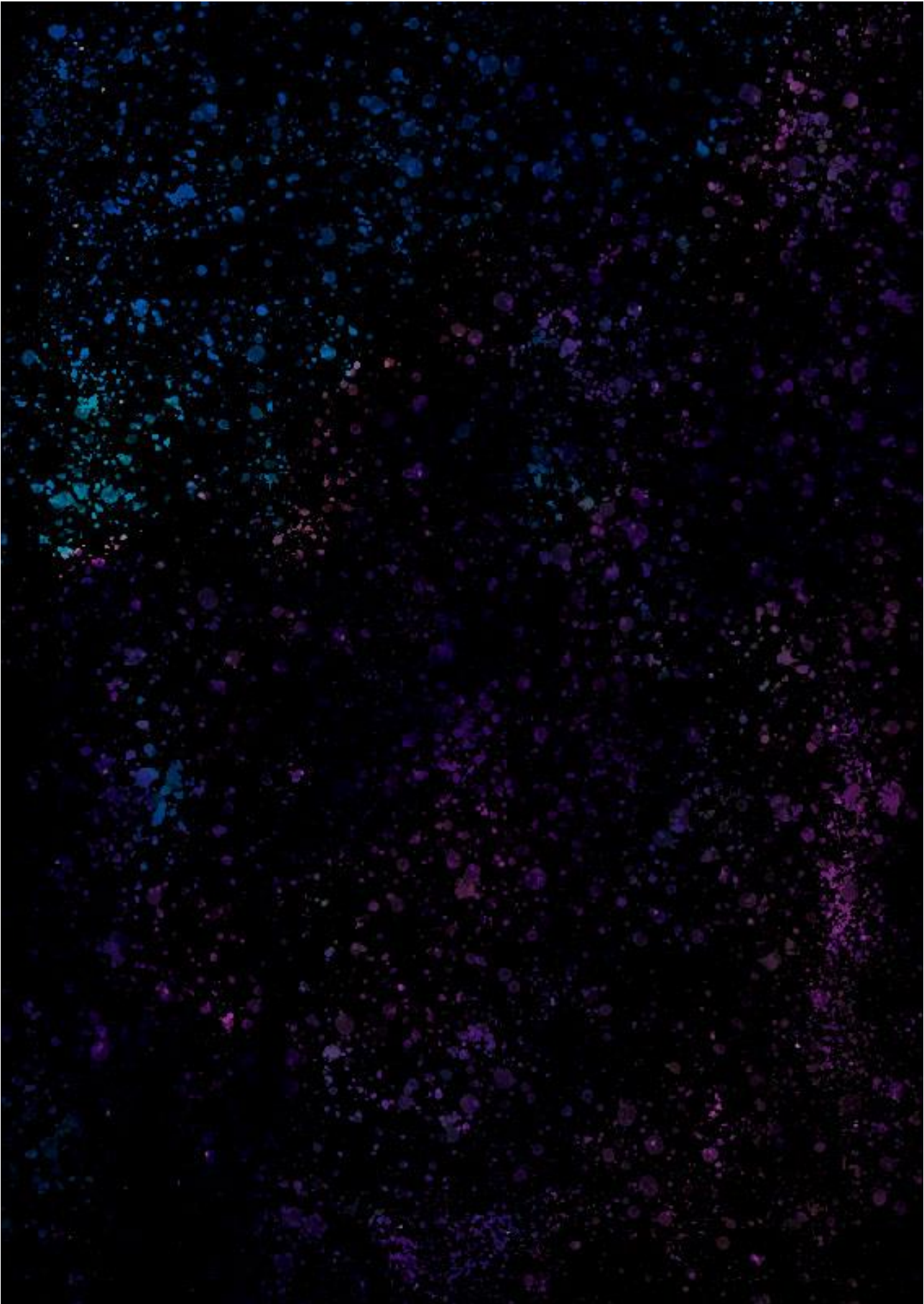
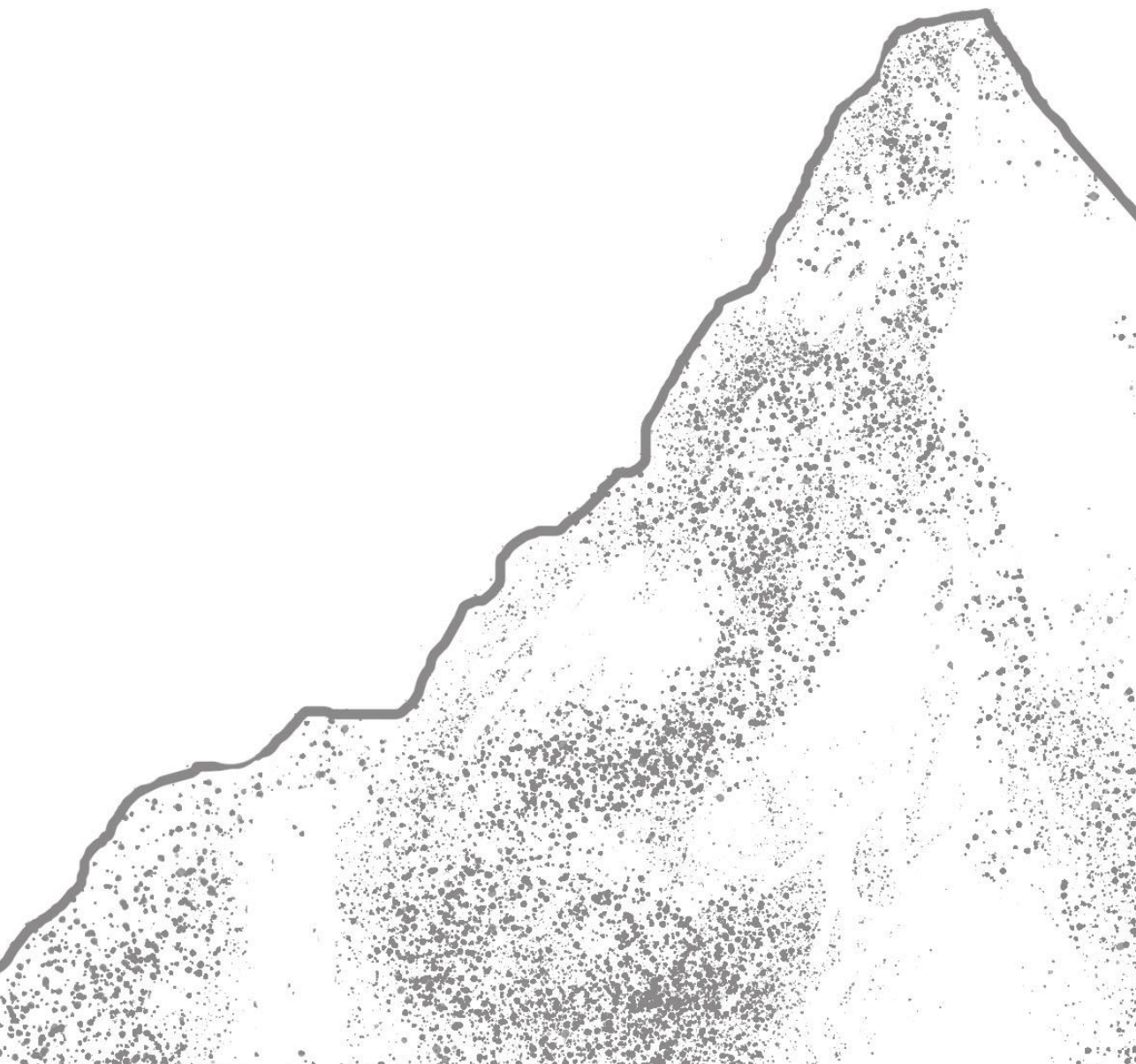


PART I

CHAPTER 1

GENERAL INTRODUCTION



Nutrition [noun]: "The process by which living things receive the food necessary for them to grow and be healthy" – Oxford dictionary

Introduction

Optimal nutrition during childhood is one of the essential prerequisites for normal growth, development and providing lifelong health. A healthy and well-balanced diet, rich in fruits, vegetables and whole grains, helps to protect against malnutrition in all its forms, as well as a range of diseases.[1] During critical illness the child is subjected to neuro-endocrine, immunologic and metabolic changes, commonly referred to as acute stress response, which temporarily inhibits the normal developmental process in order to survive.[2] Admission to the paediatric intensive care unit (PICU) may result in harmful consequences prolonging long after PICU admission. The goal of nutritional support is to provide an appropriate amount of feeding in order to accelerate recovery and to have beneficial effects on both short-term outcome and long-term physical, neurocognitive and mental health. Both undernutrition and overfeeding have been associated with impaired outcomes.[3-5] Critically ill infants and children are thought to be particularly vulnerable for development of nutritional deficiencies due to their limited body reserves and increased energy expenditure.

Acute stress response

The acute stress response to critical illness can be categorised into an acute, stable and recovery phase and the nutritional goals differ throughout the phases of the disease.[6] The first phase of critical illness, the acute phase, is characterised by (escalating) requirement of viral organ support after admission to the paediatric intensive care unit (PICU) and may last up to several days. This is followed by a stable phase, where stabilisation or weaning of vital organ response occurs. The final phase, the recovery phase, is characterised by normalisation of stress response and clinical mobilisation. The awareness of the changes in metabolism during the different phase of critical illness is fundamental in determining metabolic and nutritional support. Thereby, during the complete course of admission both underfeeding and overfeeding should be avoided. Although optimal nutrition is considered an essential therapy during critical illness, there is a lack of causal evidence favouring specific strategies.

Neuro-endocrine stress response

The neuroendocrine response to critical illness predominantly involves enhanced activation of the hypothalamic function without activation of the peripheral pathways. This evolves to a reduction in pulsatile secretion of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), prolactin, and luteinising hormone when the child enters the stable phase of illness.

Hypothalamic-pituitary-thyroid axis

Paediatric critical illness is typically presented with reduced plasma concentrations of triiodothyronine (T3), without physiological increase of TSH, as well as increase of inactive

hormone reverse T3 (rT3) and decreased or normal thyroxine (T4). This phenomenon is commonly referred to as non-thyroidal illness syndrome (NTIS) and holds a strong correlation with the severity of illness.[7,8] During acute stress non-thyroidal illness syndrome seems to be the result of increased peripheral inactivation of thyroid hormones and is a beneficial adaptation of the body to reduce energy expenditure and activate the innate immune response in order to survive. These plasma alterations can be variable and are believed to be adaptive in response to environmental factors, including nutritional support and inflammatory stimuli.[9-11]

Hypothalamic-pituitary-adrenal axis

The production of endogenous glucocorticoids, predominantly cortisol, are essential for normal homeostasis and play an essential role in the acute stress response.[12,13] Cortisol levels normally fluctuate throughout the day in a circadian rhythm. Due to illness related factors, such as inflammation, splanchnic nerve output, and central nervous system control affect the pulsatile release and negative feedback system.[14,15] In response to critical illness, corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) are increasingly released by the hypothalamus. This stimulates the release of ACTH from the pituitary into the circulation, which increases the rate of synthesis and secretion of cortisol from the adrenal cortex.[16] In critically ill children the increase in cortisol availability is temporary and low levels of ACTH and high levels of cortisol are associated with worsened recovery.[17]

Somatotropic Axis

Growth hormones (GH) play a pivotal role in paediatric growth during health and induces a metabolic effect in a physiologic response to food intake and circadian rhythm.[18] The release of GH is regulated by hypothalamic growth hormone releasing hormone (GHRH), the gut hormone ghrelin and the inhibitory hormone somatostatin. During stress the GH secretion is enhanced due to GH resistance in peripheral tissue, which is seen by a decrease in plasma concentrations of insulin-like growth factor I (IGF-I), which affects lipolysis and insulin antagonism.[19] During prolonged critical illness GH secretion and low IGF-I concentrations occurs, which is associated with enhances protein catabolism and preservation of fat tissue.[20]

Immunologic and metabolic stress response

The immunologic and metabolic stress response is mediated by catabolic hormones (glucagon, catecholamines and corticosteroids), insulin resistance and local mediators (cytokines, eicosanoid and oxygen radicals). The acute phase is characterised by an enhanced metabolic rate associated with increased release of endogenous substrates for energy metabolism and increased inter-organ substrate exchanges. Increased pro-inflammatory cytokines cause a release of catabolic hormones stimulating a release of glucose and due to depletion in glycogen storages as a result of low intake this glucose is mainly formed via gluconeogenesis in the liver, kidney and muscle, which is the production of glucose from non-carbohydrate sources (i.e. protein, triacylglycerol).[21-23] Peripheral insulin resistance

together with increased gluconeogenesis result in hyperglycaemia, which is often seen during critical illness. During this catabolic state the amount of protein degraded for gluconeogenesis can be measured by increased excretion of nitrogen from the body. Carbohydrates are the preferred energy substrate over fat; however, stress hormones and glucagon can activate lipolysis resulting in a release of fatty acids and glycerol from adipose tissue as an alternative form of energy into the bloodstream.[24,25] These fatty acids are produced into ketone bodies via ketogenesis by the liver. In most peripheral tissue cells these ketone bodies can be oxidised via the citric acid cycle in the mitochondria into energy.[26] Furthermore, ketone bodies can cross the blood-brain barrier and are a main source of energy during fasting for the central nervous system.[27] During stable and recovery phase the metabolic response shift towards an anabolic phase and is characterised by restoration of amino acid and lipid stores and normalization of nitrogen balance.[28]

Underfeeding and overfeeding

Acute phase

Observational studies have found that malnourishment and nutritional deficits, often as a result of feeding intolerance, prolonged fasting around procedures and fluid restriction, are associated with delayed wound healing, reduced immune response, malabsorption, bacterial overgrowth and increased morbidity and mortality, as well as neurological and psychological long-term development disorders.[3,29,30]

Two large observational studies involving 500 and 1200 critically ill ventilated children who received nutritional support via EN and PN presented an association between insufficient nutritional support and worse clinical outcomes. The first study found an association between improvement in 60 day mortality and higher enteral energy intake (energy goal achievement of >67% as compared with <33%).[3] The second study found a similar association between reaching higher protein goals via enteral route and lower mortality rates, in which the found beneficial effect of protein was independent of the energy intake (protein goal achievement of 20-60% or >60% as compared with <20%).[4] Due to the observational nature of these studies a cautious interpretation is necessary, as children who are less critical ill might tolerate EN better, and therefore already have an accelerated recovery. Without randomised controlled trials it is impossible to know if the impact on clinical outcome is caused by lower enteral intake, gastrointestinal dysfunction or other factors affected due to the underlying illness.

Overfeeding in its turn may lead to fatty liver disease, hyperglycaemia and increased respiratory burden due to the increase in CO2 production present by lipogenesis from carbohydrates. The risk of overfeeding is considerably prominent during the acute phase, especially when PN is provided to supplement nutrition in children with intolerance to feeding or other barriers. A small retrospective study actually showed that overfeeding (defined as >110% of measured REE) was associated with worse outcome as compared with children who received nutrition within or below (<90% REE) range.[5] Nonetheless, additional

investigation is warranted to find the balance between overfeeding and underfeeding during the acute phase.

Stable and recovery phase

During the stable and recovery phase the body can shift from catabolism to anabolism and nutritional support should focus on increasing protein and energy intake to enable recovery, growth and even catch-up development. The focus during this phase should be to allow restoration of lean body mass and prevent muscle loss as a result of prolonged immobilisation. There are indications based upon observational studies that during the stable and recovery phase nutritional requirements rise markedly and even increase above normal requirements of a healthy growing child.[31-34]

Identification of barriers in nutritional therapy

The gastrointestinal tract is the preferred route of nutritional support. Enteral nutrition (EN) is considered safe, cost effective and more physiologic compared to Parenteral Nutrition (PN). Guideline recommendations for caloric and protein targets are often not achieved via enteral route and discrepancies between the amount prescribed and delivered ranged up to 60%.[3,4,35,36] There have been numerous studies describing reasons for these discrepancies, with (perceived) feeding intolerance as a result of gastrointestinal dysfunction, fluid restriction, fasting around extubation and (bedside) procedures as most frequently reported.[37-39] To improve EN delivery these barriers need to be identify and addressed earlier during the course of PICU admission.

Gastrointestinal dysfunction

In order to provide optimal enteral nutrition, the "gut" needs to function appropriately. During critical illness the gut is subjected to numerous adverse influences such as ischemia, altered blood flow, lack of EN and medication resulting in gastrointestinal dysfunction. In addition, during critical illness the gastrointestinal function may be affected by impoverishment of the microbiome and intestinal inflammation. As such the metabolic utilisation and assimilation of amino acids, carbohydrates and fats and micronutrients may be altered. Failure of the gastrointestinal tract to digest and absorb nutrients is commonly referred to by the descriptive term "feeding intolerance" and is associated with adverse clinical outcomes.[40-42] Feeding intolerance may arise from a diversity of mechanisms including intestinal inflammation, altered enterocyte function and/or impaired gastrointestinal motility, including delayed gastric emptying.

Identification of feeding intolerance

Even though feeding intolerance is one of the most reported reasons for insufficient enteral intake in critically ill children, there is currently no consensus on when we should consider a child feeding intolerant. Table 1 presents an overview of symptoms used by clinicians to describe (perceived) feeding intolerance in critically ill children. Many of these symptoms are subjective.[43] The definition used in research are also vague and elusive. Without a more

uniform and objective definition we cannot provide insight on the possible magnitude, causes and consequences of feeding intolerance, or more importantly, adequately compare nutritional intervention in studies to overcome feeding intolerance as a barrier for optimal nutritional support.

Enteral feeding practices

Besides human milk, different types of EN formula including different protein and fat contents are available in children. These formulas can be classified into polymeric, semi-elemental (oligomeric), elemental (monomeric) or disease specialised. Traditionally human milk or polymeric standard enteral feeds are used as first line. However, when full EN to account for high nutritional requirements is not tolerated or possible because due to PICU barriers, a protein and energy-enriched or semi-elemental (hydrolysed) protein and energy-enriched formulas can be considered.[44]

Protein and energy-enriched formula may have an additional value in children with fluid-restriction i.e. after congenital heart surgery, or during recovery phase when energy requirements may rise remarkably. Previously, it has been shown that protein balances were positive in infants during the first days after PICU admission with the use of protein and energy-enriched formula compared to standard formula, however, this trial was not designed to provide evidence of the impact of these results on clinical outcome.[45] While this formula is recommended to be considered by the guidelines when energy and protein goals cannot be reached with standard formula, currently, little data are available on feeding tolerance, recovery and growth in critically ill children during stable and recovery phase.

Semi-elemental formulas are partially pre-digested (hydrolysed) and contain peptides of varying chain length, simple carbohydrates, and primarily medium chain triglycerides. These formulas have been used to treat non-critically ill children with feeding intolerance for many years and are also advised in critically ill children presenting with feeding intolerance, as they are believed to result in better absorption, are less allergenic and are better tolerated in patients with a malabsorptive state.[46] There is a lack of evidence for the use of this type of formula in critically ill infants. However. a recent RCT in 180 children above 1 year showed a decrease in feeding interruptions and abdominal distention with faster achievement of EN targets and improved weight gain with semi-elemental formula as compared with polymeric formula.[47]

Enteral feeding can be provided continuously via post-pyloric route or gastric or intermittently (bolus) via gastric route. Overall, gastric feeding can be considered safe in the majority of patients with no evidence favouring continuous or intermittent feeding in regards to feeding intolerance or achievement of nutrient targets.[48-50] Furthermore, post-pyloric feeding may be considered in children with a high risk for aspiration or if nutritional target are not achieved via gastric feeding.[51,52]

Table 1. Signs to define perceived feeding intolerance in critically ill children.

Sign/ Symptom	Comment
Gastric residual volume (GRV)	Most commonly used parameter, invalid marker of delayed gastric emptying, definitions highly variable and no evidence to support "high" GRV and prone to measurement error
Colour of gastric aspirate	Very subjective
Vomiting (emesis)	May be induced by coughing, opiates and other drugs, withdrawal syndrome
Diarrhoea	Definition problematic in infants and can be induced by infections, drugs, bowel ischemia, withdrawal syndrome
Stool output	May be useful if being fed enterally
Abdominal distention	Subjective unless girth measured accurately over time and may be induced by other factors; no clear threshold
Bowel sounds	No evidence relates to feed tolerance, are objective, but often poorly assessed
Raised serum lactate	Used commonly, different thresholds of tolerance used
Splanchnic NIRS (near-infrared spectroscopy)	No research in critically ill children in relation to feed tolerance

Adapted with permission from Tume et al.[43]

Supplemental parenteral nutrition

In critically ill children with insufficient enteral intake due to gastrointestinal dysfunction or PICU barriers, parenteral nutrition (PN) is often initiated to reach recommended target nutritional intake. PN usually contains numerous components, including macronutrients (carbohydrates, amino acids, lipids) and micronutrients (electrolytes, trace elements and vitamins). PN guidelines historically had to base their recommendation for optimal timing, amount and composition upon very few studies in paediatric critical care and all using intermediate or surrogate endpoints, such as inflammation markers or nitrogen balances, thereby PN appeared to positively influence those surrogate markers.[53,54] Furthermore, underfeeding has been associated with unfavourable outcome in many studies, thus based on expert consensus and observational studies, PN was advised during the acute, stable and recovery phase of critical illness to achieve early and high nutritional goals.[55]

It was not until the paediatric early versus late PN in critically ill children (PEPaNIC) randomised controlled trial (RCT) that the recommendations to reach high and early macronutrient goals via PN were reassessed.[56] This large multicentre RCT involving 1440 critically ill children showed that withholding supplemental macronutrients (amino acids, carbohydrates and lipids) via PN for seven days (late PN), as compared with initiating PN within 24 hours after admission (early PN), improved short-term outcome in critically ill children.[56,57] Children allocated to the late PN group, thus excepting lower than

recommended macronutrient intake, had a lower incidence of new acquired infections and shorter length of stay (PICU and hospital). This was independent of confounders such as illness severity, age and malnutrition upon admission. Moreover, secondary analyses of the PEPaNIC RCT showed that also term neonates and undernourished children who are thought to be more vulnerable to nutritional deficiencies benefited from the acute phase parenteral macronutrient restriction.[58,59]

In addition, recent studies have shown that restriction of parenteral macronutrients during the acute phase ameliorates the neuro-endocrine response shown by further reduction in plasma concentrations of TSH, total T4, T3, and the ratio of T3 (active) to reverse T3 (inactive), which was not seen in patients receiving early feeding.[11] Furthermore, the inactivation of T4 to reverse T3 and T3 to T2, altering the T3/reverse T3 ratio, might be a beneficial adaptation during acute illness as a result of caloric restriction associated with improved outcome in critically ill children.[11,17,60]

Except for the PEPaNIC RCT, there are no other interventional studies that have focused on optimal timing or amount of PN in critically ill children and, therefore, recent updated SCCM/ESICM[61], ESPNIC[44] and ESPGHAN/ESPEN/ESPR/CSPEN[62] guidelines advise to consider withholding parenteral macronutrients during the first week of paediatric critical illness, while continue to provide micronutrients in children.

Long-term developmental outcome

The improvements of medical devices and therapy has led to a substantial decrease in mortality rates over the past decades. Children, especially young infants, are in the fundamental phase of development. After admission to the PICU children may experience new or deteriorating impairments in their psychical, neurocognitive and mental health status for months or even years, which is defined as the post-intensive care syndrome (PICS).[63,64] Due to the increasing number of PICU survivors, it becomes increasingly important to consider long-term developmental physical and neurocognitive complications post-intensive care in addition to short-term improvements. Overall, studies investigating PICU survivors find lower scores for neurocognitive and mental health compared to the healthy population, with several risk factors identified to influence the degree of neurocognitive impairment including younger age at admission, need for high oxygen requirements and duration of mechanical ventilation, sedation and opioid therapy.[65] The consequences of the post-intensive care syndrome does not only cause growing health care costs but also reduces health-related quality of life.[66]

Both underfeeding and overfeeding have been associated with impaired growth, cognitive functioning and emotional and behavioural problems in non-critically ill children.[67,68] However, there is a lack of evidence regarding long-term developmental outcomes of optimal enteral and/or parenteral nutrition. Due to this increasing number of survivors together with a gaining knowledge on the long-term legacy of paediatric critical illness, it

seems imperative to incorporate long-term psychical and neurocognitive development before implementation or de-implementation of certain nutritional interventions.

AIMS AND OUTLINE OF THESIS

Part I: Introduction

Admission to the PICU has detrimental consequences on morbidity and mortality. Nutritional therapy plays an important role in accelerating recovery and maintaining normal physical and neurocognitive development. The aim of this thesis is to provide insight on optimal nutritional therapy for critically ill children concerning the route, timing and amount.

Part II: Identification of barriers in nutritional therapy

~the acute phase

The second part of this thesis is devoted to barriers in (enteral) nutritional therapy and aimed to find solutions to overcome these barriers. Chapter 2 aims to find PICU related barriers via a world survey and develops a tool to find and possible overcome these barriers on individual PICU sites. Non-invasive ventilation as a possible barrier for EN delivery is investigated in Chapter 3 and (perceived) feeding intolerance in critically ill children is systematically reviewed in Chapter 4. In Chapter 5 the amount of enteral intake during the acute phase of critical illness is associated with short-term clinical outcomes.

~the stable and recovery phase

The use of protein and energy-enriched or hydrolysed protein and energy-enriched enteral formulas during the recovery phase of critical illness are reviewed in Chapter 7. Chapter 8 aims to find associations between protein and energy-enriched formula and feeding intolerance. These findings are followed by Chapter 9 which aims to find similar associations with hydrolysed protein and energy-enriched formula.

Part III: Parenteral nutrition: macronutrients and micronutrient supplementation

The third part of the thesis aims to review the role of parenteral macronutrients and micronutrients as a nutritional therapy in Chapter 9, and to answer how to provide parenteral micronutrients in Chapter 10.

Part IV: Long-term developmental outcome of parenteral nutrition

Children are in the fundamental phase of development and before implementation of a nutritional therapy in clinical practise the long-term developmental, physical and neurocognitive consequences have to be investigated. The developmental outcomes of the nutritional intervention of omitting parenteral nutrition during the acute phase of critical illness two years (Chapter 11) and four years (Chapter 12) after PICU admission are investigated.

Part V: General discussion, future perspectives and summary

The final part of this thesis is dedicated to the general discussion and places the results in broader perspectives and areas of current and future research are described (Chapter 13). The thesis is summarised in Chapter 14.

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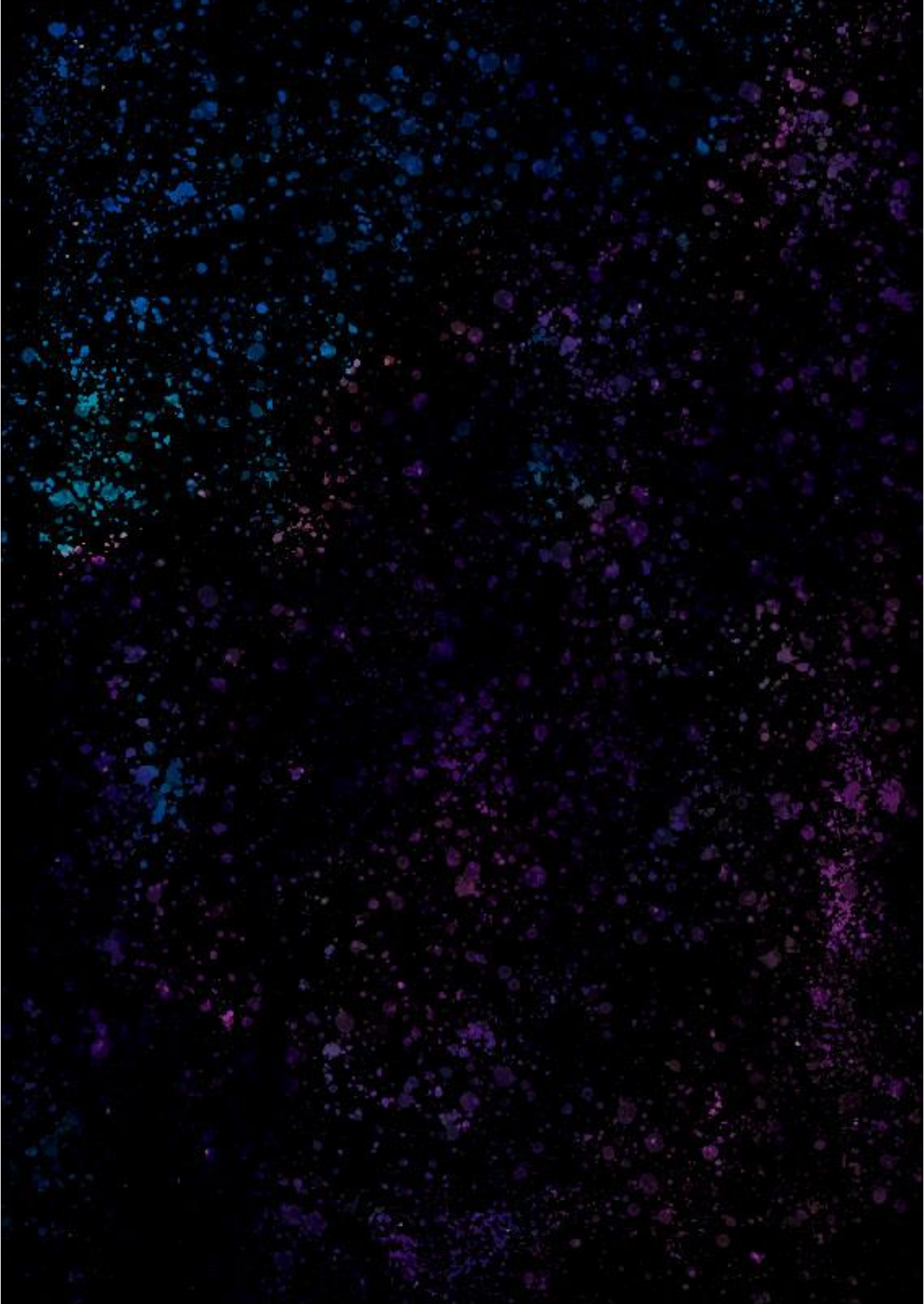
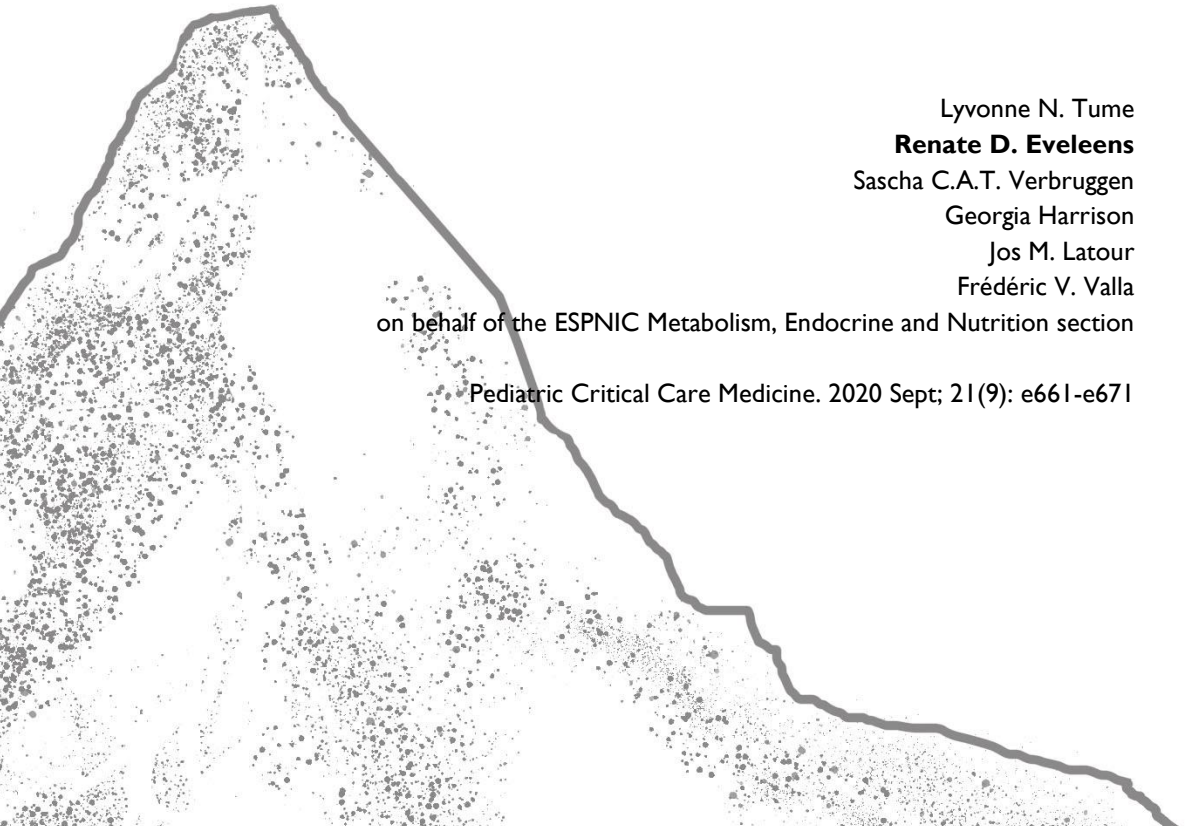


PART II

CHAPTER 2

BARRIERS TO DELIVERY OF ENTERAL NUTRITION IN PAEDIATRIC INTENSIVE CARE: A WORLD SURVEY



Lyvonne N. Tume
Renate D. Eveleens
Sascha C.A.T. Verbruggen
Georgia Harrison
Jos M. Latour
Frédéric V. Valla
on behalf of the ESPNIC Metabolism, Endocrine and Nutrition section

Pediatric Critical Care Medicine. 2020 Sept; 21(9): e661-e671

ABSTRACT

Objectives: To explore the perceived barriers by paediatric intensive care healthcare professionals (nurses, dieticians, and physicians) in delivering enteral nutrition to critically ill children across the world.

Design: Cross-sectional international online survey adapted for use in paediatric settings.

Setting: PICUs across the world.

Subjects: PICU nurses, physicians, and dietitians.

Interventions: The 20-item adult intensive care "Barriers to delivery of enteral nutrition" survey was modified for paediatric settings, tested, and translated into 10 languages. The survey was distributed online to paediatric intensive care nurses, physicians, and dieticians via professional networks in March 2019 to June 2019. Professionals were asked to rate each item indicating the degree to which they perceived it hinders the provision of enteral nutrition in their PICUs with a 7-point Likert scale from 0 "not at all a barrier" to 6 "an extreme amount."

Measurement and Main Results: Nine-hundred twenty paediatric intensive care professionals responded from 57 countries; 477 of 920 nurses (52%), 407 of 920 physicians (44%), and 36 of 920 dieticians (4%). Sixty-two percent had more than 5 years PICU experience and 49% worked in general PICUs, with 35% working in combined cardiac and general PICUs. The top three perceived barriers across all professional groups were as follows: 1) enteral feeds being withheld in advance of procedures or operating department visits, 2) none or not enough dietitian coverage on weekends or evenings, and 3) not enough time dedicated to education and training on how to optimally feed patients.

Conclusions: This is the largest survey that has explored perceived barriers to the delivery of enteral nutrition across the world by physicians, nurses, and dietitians. There were some similarities with adult intensive care barriers. In all professional groups, the perception of barriers reduced with years PICU experience. This survey highlights implications for PICU practice around more focused nutrition education for all PICU professional groups.

INTRODUCTION

Successfully achieving delivery of enteral nutrition (EN) to critically ill children is associated with improved clinical outcomes.[1,2] Yet, multiple barriers remain to achieving adequate nutrition enterally in the critically ill child. Some of these are common to all PICUs, but for some, the barrier is organization and unit specific.[3,4] Recently, a survey instrument was developed and validated for adult ICUs (AICUs)[5-7] to assess EN barriers in an ICU. This tool allowed clinicians to directly assess and address the perceived barriers in their ICU, with an aim to optimise EN delivery. In the adult survey, 20 known barriers to delivering EN identified in the literature are rated on a Likert scale relating to the perception of the item being a barrier. The aim of our study was to explore the barriers in providing optimal nutrition to children in PICU settings worldwide, as viewed by nurses, doctors, and dieticians using this survey tool, modified for the paediatric setting.

METHODS

A cross-sectional electronic survey design was used. The 20-item adult survey instrument[5-7] was examined and modifications were made based on previously identified paediatric barriers from the literature. The modified survey was then pilot tested in a single U.K. PICU with 62 PICU staff (physicians, nurses, and dieticians). All items from the adult survey were considered relevant and therefore no items were deleted; however, the wording of some items was revised for clarification. Four additional barrier items specific for PICU population were identified and added to the survey. Afterward, pilot testing with nine professionals in a second PICU (in France) using the same method yielded one additional barrier item, resulting in a new 25-item barrier of EN in PICU survey (Appendix). Added items were as follows: 1) severe fluid restriction; 2) conservative PICU feeding protocol; 3) feeding tube or pomp delivery problems; 4) enteral feeds withheld for bedside procedures; and 5) lack of staff knowledge and support around breastfeeding mothers.

In addition to the 25 barriers, basic demographic data was collected; PICU experience, PICU type and country, with one open-ended question asking if there were any other barriers not listed. The survey was translated from English by bi-lingual clinicians into 10 languages (French, Italian, Dutch, German, Latvian, Chinese, Spanish, Arabic, Polish, and Portuguese) using a recognised cultural adaptation process[8] and tested by local clinicians for face validity. SurveyMonkey (San Mateo, CA) was used for distribution. Given the nature of distribution of this survey, there was no anticipated survey response. However, we aimed for an equal spread across continents and near equal among professional groups (acknowledging that the dietician numbers would be lower based on the number of dietitians compared with physicians and nurses). The inclusion criteria were as follows: nurses, assistant nurses, dieticians, and doctors who are working in a PICU and make decisions around feeding in

critically ill children. The exclusion criteria were as follows: nonclinical nurses or staff who worked permanently outside clinical PICU setting. Neonatal and adult intensive care staff were excluded. If PICUs were mixed (neonates or adults), the introduction letter made it clear that the questions were to be answered regarding feeding in children 0 (term infants) to 17 years old.

Data Collection

The e-survey was sent out via established professional networks to PICU nurses, doctors, and dieticians via country leads and via organizational newsletters (The European Society of Paediatric and Neonatal Intensive Care [ESPNIC], the U.K. Paediatric Intensive Care Society [PICS], and the World Federation of Paediatric Intensive Care Societies in March 2019 to June 2019). Reminders were sent to country leads with low responses to improve response rates. No identifiable staff, patient, or PICU data were collected, and consent was implied by completing the survey. Country leads were responsible for ensuring ethical requirements were obtained according to their country regulation. In the United Kingdom (where data were gathered and analysed), this study was approved by the PICS study group and was approved as an audit by University Hospitals Bristol. Ethical approval was provided in the Netherlands by the Institutional Review Board of the Erasmus Medical Centre (MEC-2019-0065).

Data Analysis

The datasets (one for each language version) from SurveyMonkey were downloaded, checked, and combined into one dataset and imported into IBM SPSS Version 25 (IBM Corp., Armonk, NY) for analysis. All data were categorical data or ordinal data (Likert scale) and were first analysed descriptively and then inferential analysis undertaken to test relationships between categorical variables including continents/geographical regions, professional groups, PICU type regarding perceived barriers using chi-square tests. The Likert scale ranged from 0 (not at all) to 6 (an extreme amount). Median (interquartile range) refers to the full Likert scale. However, barriers were further categorised as not a barrier (respondents who scored 0), moderate barrier (respondents who scored 1–3), and important barrier (respondents who scored score 4–6) consistent with the adult survey analysis (5,6). For subgroup analysis, the Europe countries were classified into three European regions as in the End-of-life Practices in European Intensive Care Units: The Ethicus Study (9): northern (Ireland, Latvia, Lithuania, the Netherlands, Sweden, and United Kingdom); central (Austria, Belgium, Germany, France, Luxembourg, Poland, and Switzerland); and southern (Bulgaria, Italy, Portugal, Spain). When a statically significant level was obtained using chi-square test, differences between the variable were further compared using a z test with Bonferroni correction. A p value of less than 0.05 was considered significant and two-tailed tests were used.

RESULTS

There were 920 survey responses from 57 countries (Figure 1). Most respondents were nurses (52%) and physicians (44%), followed by dieticians (4%). Sixty-two percent of respondents had more than 5 years PICU experience, and half (49%) worked in a general PICU with 32% in a mixed cardiac and general PICU (Table 1).

The top five perceived barriers were as follows: 1) Enteral feeds being withheld in advance of procedures or operating department visits (43%); 2) No dietician coverage on weekends, evenings, or holidays (38%); 3) Not enough time dedicated to education and training on optimal feeding of patients (34%); 4) In stable resuscitated patients, other aspects of caretaking priority over nutrition (33%); and 5) Delays in obtaining small bowel access in patients intolerant of nutrition (31%). Table 2 presents the perceived importance of all barriers. However, these perceived barriers differed by professional group (Tables 3 and 4). Importantly, dietitians perceived severe fluid restriction as the most significant barrier (69%), whereas for physicians, it was withholding feeds before procedures (46%) and for nurses, it was insufficient dietician coverage on weekends, evenings, and holidays (44%).

Comparing different PICU types: general PICUs compared with units which admitted cardiac surgical children and combined PICU-neonatal ICUs (NICUs) showed little differences in perceived barriers (Table 5) with severe fluid restriction being rated highly as a barrier across all PICU types (general 27% vs general and cardiac 31% vs PICU and NICU 26%; p=0.354). The two highest perceived barriers were consistent among the PICU types: Not enough (or no) dietician coverage during weekends, evenings, and holidays (p=0.664) and not enough time dedicated to education and training on how to optimally feed patients (p=0.701). When we examined perceived barriers by years of PICU experience, in all groups, we found a reduction in perceived barriers as PICU experience increased (Appendix). This was statistically significant for seven barriers.

There were also significant differences in 14 perceived barriers when comparing continents (Appendix). Across all continents, the biggest perceived barrier was enteral feeds being withheld for procedures and operating department visits, and this was the highest perceived barrier in Southern America. A lack of knowledge around breastfeeding mothers was also significantly different between continents with the barrier perceived almost three times more in Northern America (48%) compared with Australasia (17%) (p=0.001). Most strikingly, was the perceived lack of dietician support and coverage in PICUs, which varied across countries, but even in units with a dietician (many had no dietitian input at all).

Table 1. Characteristics of the responders

Characteristics	**No. of surveys (N=920)**
Continent	
Europe	517 (56%)
Northern region	220 (24%)
Central region	171 (19%)
Southern region	126 (14%)
Asia	314 (34%)
Latin America	48 (5%)
North America	31 (3%)
Oceania	8 (1%)
Africa	2 (0%)
Type of PICU	
General	453 (49%)
General and Cardiac	319 (35%)
PICU and NICU combined	125 (14%)
Other or missing	23 (3%)
Primary clinical specialty	
Nurse	477 (52%)
Physician	407 (44%)
Dietitian	36 (4%)
Years of working experience	
0 – 5 years	356 (39%)
6 – 10 years	215 (24%)
11 – 15 years	133 (15%)
> 15 years	211 (23%)
Missing	5 (1%)

PICU, Paediatric intensive care unit; NICU, Neonatal intensive care unit

Table 2. Descriptive statistics of Barriers for Enteral Nutrition survey in 920 respondents

Item	Median [IQR], (range 0-6)	Not a barrier (0), %	Important barrier (4-6), %
Delivery of Enteral Nutrition to the Patient			
1. Delay in physicians ordering the initiation of EN.	2 [1-3]	11.9%	20.1%
2. Waiting for physician to order and check x-ray to confirm tube placement.	1 [0-2]	29.8%	13.6%
3. Frequent displacement of feeding tube, requiring reinsertion.	1 [1-1]	17.1%	12.1%
4. Delays in initiating motility agents in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	2 [1-3]	11.0%	19.1%
5. Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	3 [2-4]	5.1%	30.9%
6. In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over nutrition.	3 [1-4]	8.1%	33.0%
7. Nutrition therapy not routinely discussed on ward rounds.	1 [0-3]	30.1%	18.5%
8. Severe fluid restriction (especially post-operative cardiac surgery).	2 [1-4]	9.8%	29.2%
9. Conservative PICU feeding protocol.	2 [1-3]	23.2%	16.4%
10. Difficulty in delivering enteral feed due to feeding tube obstruction or pump delivery problems with thickened formula.	1 [0-2]	26.9%	10.8%
Dietitian Support (Only if dietitian present; N=728)			
11. Waiting for the dietitian to assess the patient.	2 [1-3]	17.2%	15.2%
12. Dietitian not routinely present on weekday patient rounds.	2 [1-4]	24.2%	29.6%
13. No or not enough dietitian coverage during evenings, weekends and holidays.	3 [1-4]	11.5%	38.4%
14. Not enough time dedicated to education and training on how to optimally feed patients.	3 [1-4]	9.7%	33.7%
PICU Resources			
15. Delays to preparing or obtaining non-standard enteral feeds	2 [1-3]	13.6%	15.7%
16. No or not enough feeding pumps on the unit.	1 [0-2]	49.7%	12.0%

Healthcare Professional Attitudes and Behaviour			
17. Non-PICU physicians (i.e. surgeons, gastroenterologists) requesting patients not be fed enterally.	2 [1-3]	12.1%	17.4%
18. Nurses failing to progress feeds as per the feeding protocol.	1 [0-2]	28.2%	10.3%
19. Enteral feeds withheld due to diarrhoea.	2 [1-3]	12.6%	13.0%
20. Fear of adverse events due to aggressively enterally feeding patients.	2 [1-3]	13.4%	18.4%
21. Enteral feeds withheld for bedside procedures, such as physiotherapy, turns, and administration of certain medications.	2 [1-3]	12.0%	20.5%
22. Enteral feeds being withheld in advance of procedures or operating department visits.	3 [2-4]	4.6%	42.7%
23. Lack of familiarity with current guidelines for nutrition in the PICU.	2 [1-3]	14.9%	22.9%
24. General belief among PICU team that provision of adequate nutrition does not affect patient outcomes.	1 [0-2]	36.1%	15.4%
25. Lack of staff knowledge and support around breastfeeding mothers	2 [1-3]	23.0%	19.7%

EN, Enteral Nutrition; PICU, Paediatric intensive care unit

Responders answered the questionnaire through Likert scale (range 0-6). Median [IQR] refers to the full Likert scale (0-6).

Not a barrier were the percentage of responders who answered with "not a barrier (0)".Important barrier is indicated by the percentage of responders who answered with "a lot (4)", "a great deal (5)", and "an extreme amount (6)"

Table 3. Top 3 barriers to deliver enteral nutrition in the PICU reported per clinical specialty

Primary Clinical Specialty		
Nurse (N=477)	**% Important barrier (score with 4-6)**	**Median [IQR], (range 0-6)**
1. No or not enough dietitian coverage during evenings, weekends and holidays.	44.0%	3 [2-4]
2. Enteral feeds being withheld in advance of procedures or operating department visits	40.3%	3 [2-4]
3. In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over nutrition.	33.5%	3 [2-4]
Physician (N=407)		
1. Enteral feeds being withheld in advance of procedures or operating department visits.	46.4%	3 [2-5]
2. Not enough time dedicated to education and training on how to optimally feed patients.	38.1%	3 [1-4]
3. Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	36.7%	3 [2-4]
Dietitian (N=36)		
1. Severe fluid restriction (especially post-operative cardiac surgery)	68.6%	5 [3-6]
2. No or not enough dietitian coverage during evenings, weekends and holidays.	41.2%	3 [1-5]
3. Enteral feeds being withheld in advance of procedures or operating department visits.	33.3%	3 [1-4]

PICU, Paediatric intensive care unit

Responders answered the questionnaire through Likert scale (range 0-6). Median [IQR] refers to the full Likert scale (0-6)

Important barrier is indicated by the percentage of responders who answered with “a lot (4)”, “a great deal (5)”, and “an extreme amount (6)”

Table 4. Differences in perceived important barriers by professional group

Item	Total group N=844	Physician N=407	Nurse N=477	Dietitian N=36	P-value
Delivery of Enteral Nutrition to the Patient					
1. Delay in physicians ordering the initiation of EN.	20.1%	21.1%	20.3%	5.6%	0.081
2. Waiting for physician to order and check x-ray to confirm tube placement.	13.6%	9.6%[a]	16.8%[b]	17.1%[a,b]	0.006
3. Frequent displacement of feeding tube, requiring reinsertion.	12.1%	10.6%	14.1%	2.9%	0.066
4. Delays in initiating motility agents in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	19.1%	15.5%[a]	22.5%[b]	14.3%[a,b]	0.023
5. Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	30.9%	36.7%[a]	26.7%[b]	20.0%[a,b]	0.002
6. In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over nutrition.	33.0%	31.9%	33.5%	37.1%	0.763
7. Nutrition therapy not routinely discussed on ward rounds.	18.5%	19.9%	18.3%	5.7%	0.144
8. Severe fluid restriction (especially post-operative cardiac surgery).	29.2%	27.8%[a]	27.5%[a]	68.6%	<0.001
9. Conservative PICU feeding protocol.	16.4%	15.7%	16.4%	22.9%	0.547
10. Difficulty in delivering enteral feed due to feeding tube obstruction or pump delivery problems with thickened formula.	10.8%	5.9%[a]	15.4%[b]	5.7%[a,b]	<0.001
Dietitian Support (Only if dietitian present; N=728)					
11. Waiting for the dietitian to assess the patient.	15.2%	10.6%[a]	18.9%[b]	14.7%[a,b]	0.008
12. Dietitian not routinely present on weekday patient rounds.	29.6%	25.7%	33.5%	20.6%	0.037
13. No or not enough dietitian coverage during evenings, weekends and holidays.	38.4%	31.0%[a]	44.0%[b]	41.2%[a,b]	0.002
14. Not enough time dedicated to education and training on how to optimally feed patients.	33.7%	38.1%	30.7%	29.4%	0.100
PICU Resources					
15. Delays to preparing or obtaining non-standard enteral feeds	15.7%	15.6%	16.1%	11.4%	0.757
16. No or not enough feeding pumps on the unit.	12.0%	6.9%	15.7%[a]	19.4%[a]	<0.001

Healthcare Professional Attitudes and Behaviour					
17. Non-PICU physicians (i.e. surgeons, gastroenterologists) requesting patients not be fed enterally.	17.4%	21.0%[a]	14.7%[b]	13.9%[a,b]	0.041
18. Nurses failing to progress feeds as per the feeding protocol.	10.3%	12.1%	9.4%	2.8%	0.136
19. Enteral feeds withheld due to diarrhoea.	13.0%	13.6%	11.9%	19.4%	0.385
20. Fear of adverse events due to aggressively enterally feeding patients.	18.4%	23.2%[a]	14.7%[b]	13.9%[a,b]	0.004
21. Enteral feeds withheld for bedside procedures, such as physiotherapy, turns, and administration of certain medications.	20.5%	22.0%	19.3%	19.4%	0.608
22. Enteral feeds being withheld in advance of procedures or operating department visits.	42.7%	46.4%	40.3%	33.3%	0.093
23. Lack of familiarity with current guidelines for nutrition in the PICU.	22.9%	26.4%	20.3%	19.4%	0.089
24. General belief among PICU team that provision of adequate nutrition does not affect patient outcomes.	15.4%	16.0%	15.3%	8.3%	0.468
25. Lack of staff knowledge and support around breastfeeding mothers	19.7%	17.3%	21.2%	28.6%	0.143

EN, Enteral Nutrition; PICU, Paediatric intensive care unit

Responders answered the questionnaire through Likert scale (range 0-6). Important barrier is indicated by the percentage of respondents who answered with “a lot (4)”, “a great deal (5)”, and “an extreme amount (6)”

The subscript letters “a” and “b” denote categories in which proportions did not significantly differ from each other.

Table 5. Differences in perceived important barrier by PICU type (N=897)

	General N=453	General-Cardiac N=319	PICU-NICU N=125	p-value
Delivery of Enteral Nutrition to the Patient				
1. Delay in physicians ordering the initiation of EN.	21.1%	19.7%	16.0%	0.435
2. Waiting for physician to order and check x-ray to confirm tube placement.	16.0%	11.9%	8.0%	0.043
3. Frequent displacement of feeding tube, requiring reinsertion.	12.4%	11.9%	11.3%	0.942
4. Delays in initiating motility agents in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	16.9%	20.1%	22.4%	0.286
5. Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	29.8%	32.0%	34.4%	0.574
6. In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over nutrition.	35.0%	31.7%	30.4%	0.494
7. Nutrition therapy not routinely discussed on ward rounds.	19.1%	15.0%	20.8%	0.234
8. Severe fluid restriction (especially post-operative cardiac surgery).	27.4%	31.4%	25.8%	0.354
9. Conservative PICU feeding protocol.	16.5%	17.4%	10.6%	0.198
10. Difficulty in delivering enteral feed due to feeding tube obstruction or pump delivery problems with thickened formula.	13.1%[a]	7.2%[b]	12.0%[a,b]	0.033
Dietitian Support (Only if dietitian present; N=728)				
1. Waiting for the dietitian to assess the patient.	16.5%	14.1%	12.2%	0.505
11. Dietitian not routinely present on weekday patient rounds.	28.2%	30.5%	33.3%	0.590
12. No or not enough dietitian coverage during evenings, weekends and holidays.	39.5%	36.3%	40.0%	0.664
13. Not enough time dedicated to education and training on how to optimally feed patients.	32.6%	34.2%	37.1%	0.701
PICU Resources				
14. Delays to preparing or obtaining non-standard enteral feeds	15.7%	16.4%	12.9%	0.661
15. No or not enough feeding pumps on the unit.	12.8%[a]	7.9%[a]	15.3%	0.035
Healthcare Professional Attitudes and Behaviour				

16. Non-PICU physicians (i.e. surgeons, gastroenterologists) requesting patients not be fed enterally.	18.3%	16.4%	16.1%	0.723
17. Nurses failing to progress feeds as per the feeding protocol.	9.9%	8.5%	12.9%	0.373
18. Enteral feeds withheld due to diarrhoea.	11.5%	13.8%	13.7%	0.579
19. Fear of adverse events due to aggressively enterally feeding patients.	15.0%[a]	20.2%[a,b]	26.6%[b]	0.008
20. Enteral feeds withheld for bedside procedures, such as physiotherapy, turns, and administration of certain medications.	22.7%	17.9%	21.0%	0.268
21. Enteral feeds being withheld in advance of procedures or operating department visits.	43.3%	44.3%	38.7%	0.555
22. Lack of familiarity with current guidelines for nutrition in the PICU.	23.4%	21.4%	25.8%	0.588
23. General belief among PICU team that provision of adequate nutrition does not affect patient outcomes.	15.0%	13.1%	20.2%	0.185
24. Lack of staff knowledge and support around breastfeeding mothers	19.0%	19.5%	23.4%	0.551

EN, Enteral Nutrition; PICU, Paediatric intensive care unit

Responders answered the questionnaire through Likert scale (range 0-6). Important barrier is indicated by the percentage of responders who answered with “a lot (4)”, “a great deal (5)”, and “an extreme amount (6)”.

The subscript letters ”a” and ”b” denote categories in which proportions did not significantly differ from each other.

Other or Missing PICU type were not included in the table and analyses.

Table 6. Differences in perceived important barrier across Europe (N=517)

Item	North Europe N=220	Central Europe N=171	South Europe N=126	P-value
Delivery of Enteral Nutrition to the Patient				
1. Delay in physicians ordering the initiation of EN.	18.2%	22.8%	20.6%	0.527
2. Waiting for physician to order and check x-ray to confirm tube placement.	10.9%	4.7%	6.3%	0.062
3. Frequent displacement of feeding tube, requiring reinsertion.	10.0%	14.9%	8.7%	0.187
4. Delays in initiating motility agents in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	21.0%	17.9%	23.0%	0.537
5. Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	36.5%	38.8%	30.2%	0.290
6. In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over nutrition.	25.5%	37.6%	34.9%	0.026
7. Nutrition therapy not routinely discussed on ward rounds.	10.5%	25.3%[a]	24.6%[a]	<0.001
8. Severe fluid restriction (especially post-operative cardiac surgery)	28.1%	30.8%	26.8%	0.740
9. Conservative PICU feeding protocol	8.4%	13.6%	18.3%	0.026
10. Difficulty in delivering enteral feed due to feeding tube obstruction or pump delivery problems with thickened formula	5.5%	14.8%	6.3%	0.003
Dietitian Support (Only if dietitian present; N=465)				
11. Waiting for the dietitian to assess the patient.	7.3%	17.9%[a]	19.4%[a]	0.004
12. Dietitian not routinely present on weekday patient rounds.	27.0%[a]	31.6%[a]	58.1%	<0.001
13. No or not enough dietitian coverage during evenings, weekends and holidays.	33.8%[a]	33.3%[a,b]	50.8%[b]	0.038
14. Not enough time dedicated to education and training on how to optimally feed patients.	29.9%	43.6%[a]	56.5%[a]	<0.001
PICU Resources				
15. Delays to preparing or obtaining non-standard enteral feeds	19.1%	12.9%	12.0%	0.112
16. No or not enough feeding pumps on the unit.	11.8%	12.9%	7.2%	0.274

Healthcare Professional Attitudes and Behaviour				
17. Non-PICU physicians (i.e. surgeons, gastroenterologists) requesting patients not be fed enterally.	17.3%	17.0%	25.6%	0.112
18. Nurses failing to progress feeds as per the feeding protocol.	10.9%	9.9%	8.0%	0.684
19. Enteral feeds withheld due to diarrhoea.	6.8%[a]	14.0%[a,b]	16.7%[b]	0.015
20. Fear of adverse events due to aggressively enterally feeding patients.	16.8%	22.2%	16.0%	0.394
21. Enteral feeds withheld for bedside procedures, such as physiotherapy, turns, and administration of certain medications.	13.2%[a]	28.1%[b]	18.4%[a,b]	0.001
22. Enteral feeds being withheld in advance of procedures or operating department visits.	42.3%[a]	43.3%[a]	57.6%	0.014
23. Lack of familiarity with current guidelines for nutrition in the PICU.	16.4%	31.6%[a]	28.0%[a]	0.001
24. General belief among PICU team that provision of adequate nutrition does not affect patient outcomes.	11.8%	17.0%	17.6%	0.231
25. Lack of staff knowledge and support around breastfeeding mothers	17.3%	21.6%	20.8%	0.516

EN, Enteral Nutrition; PICU, Paediatric intensive care unit

Responders answered the questionnaire through Likert scale (range 0-6). Important barrier is indicated by the percentage of respondents who answered with "a lot (4)", "a great deal (5)", and "an extreme amount (6)"

The subscript letters "a" and "b" denote categories in which proportions did not significantly differ from each other.

DISCUSSION

This is the largest survey undertaken to identify perceived barriers to the delivery of EN in PICU settings across the world. It is also only the second survey to include all three professional groups responsible for the delivery of EN in the ICU (nurses, physicians, and dieticians). With permission, we adapted and tested a new paediatric version of the survey tool validated for adult intensive care,[5-7] providing a new paediatric version of this quality improvement tool.

We identified the main perceived barriers of EN in PICU that were related to fasting for procedures, dietician coverage, inadequate education, care priorities, and delays in gained small bowel access. However, there was variability in perceived barriers between the professional groups. In PICU, the first observational study to describe barriers to EN[10] found severe fluid restriction in children with congenital heart disease the main barrier, followed by the interruption of feeds for procedures. In our study, only the dieticians perceived this as the most important barrier, and overall it ranked sixth. Interestingly, we did not find any significant difference between PICUs that admitted cardiac surgical children and those that did not, even though the fluid restriction for postoperative cardiac children is greater.

Cahill et al.[5] used the adult barriers survey to explore the views of 138 critical care nurses across five AICUs in the United States and Canada. Three of these are consistent with our top five PICU perceived barriers but ranked differently. However, another AICU survey[11] found different barriers: with the main barrier being insufficient nursing staff to deliver EN (60%) followed by a fear of adverse events by feeding aggressively (56%).

The problem of feed interruption is well recognised.[3,4,12] Mehta et al.[12], in a prospective observational study of 117 children, found interruptions occurred in 30% of PICU patients, and 58% of these interruptions were classed as avoidable. A Canadian survey of physicians and dieticians[3] also found fasting for procedures a major barrier. Fasting for procedures, both in the PICU (such as for extubation) or outside the PICU (for radiological procedures) and to the operating department, are considerable problems for most intensive care patients. No evidence exists regarding "safe" fasting times for critically ill children and specifically which procedures require fasting for. The fear driving the fasting is potentially having a "full stomach" and the risk of pulmonary aspiration associated with emergency reintubation (if the endotracheal tube became dislodged). Despite recent Early Rehabilitation after Surgery recommendations for "well" children being fasted preoperatively, which have considerably reduced fasting times,[13] there is no evidence for fasting times in critically ill children, being fed, often minimally and already intubated. New techniques, such as gastric antral ultrasound,[14,15] need to be examined in the PICU population, to determine a more accurate way to individualise fasting times to critically ill children, with a view to avoiding the blanket 6 hour fasting rule.

In a U.K.-wide survey of PICU physicians, nurses, and dieticians,[4] the top five barriers were as follows: severe fluid restriction (60%), the child being "too ill" to feed (17%), surgical postoperative orders (17%), nursing staff being slow in starting feeds (7%), and hemodynamic instability (7%) including children with hemodynamic instability requiring pressor support, those with fluid restrictions, and those with major degrees of injury severity.

More recently, a retrospective study of 444 children in six PICUs in the United States,[16] identified the biggest risk factors for delayed EN were noninvasive ventilation (NIV), followed by invasive ventilation, increasing severity of illness, impending procedures, and gastrointestinal disturbances within the first 48 hours. Interestingly, NIV was not listed as barrier in our survey (nor is it in the adult survey), and only two people mentioned being on NIV as a barrier in free-text responses. Children requiring noninvasive respiratory support are at risk of requiring escalation of care to intubation. Many early guidelines recommended avoiding or limiting EN in respiratory distress (American Bronchiolitis Guidelines); however, NIV is no longer a barrier to enteral feeding, in accordance with recent updated guidelines.[17]

Only 4% of the respondents were dieticians and the perceived inadequacy of dietician coverage in PICUs was identified by dieticians and physicians. Specialist dieticians and their educational level vary significantly across countries. Additionally, there are relatively few of these individuals compared with other healthcare professionals, with many European units reporting having no dietician at all.[18] Nutritional support teams (NSTs) (including a dietitian) have been shown to be beneficial in optimising nutrition in PICUs.[19] This has been shown in a Latin American and Spanish survey on nutrition in paediatric intensive care where 68% of the participant PICUs had a NST and the availability of an NST was associated with better nutritional practices.[19] A perceived lack of education around nutrition (and the optimal feeding of critically ill patients) is concerning. In the United Kingdom, "nutrition" is a required component of both specialist PICU nursing education and PICU medical trainees; however, how it is taught is variable. In some countries, specialist PICU training programs for doctors or nurses do not exist, and individuals train in adult critical care or anaesthesia, further contributing to their lack of knowledge around paediatric nutrition. In this context, the ESPNIC and its nutrition section has a major role to play in providing education for all professionals.

The lack of prioritization of nutrition over other aspects of care has been identified as a problem in a recent Australian AICU nursing survey.[20] In this study, nurses identified their main perceived role related to EN was the care, maintenance and management of EN and being an advocate for EN. When asked to rank their care priorities; however, nutrition support and management ranked sixth after physiologic monitoring of other systems, but before hygiene and psychologic support. They concluded that education (as well as reducing other barriers) could improve nurses' understanding of the importance of nutrition and thus improve the prioritization of nutrition within the competing demands of their workload.

Additionally, a survey investigating barriers in an Israeli hospital found the time it takes to prescribe nutritional therapy, lack of protocols, and awareness of the staff of the nutritional therapy as the main barriers and highlighted the importance of collaboration between the clinical specialties.[21] The role of a nutrition support nurse could also be a valuable aspect in a NST, especially in PICUs without a dietician. This nurse can act as an important player for patients and the healthcare organization by having enough knowledge, attitudes, and competences to fulfil the role of a clinical nutrition expert.[21]

We found delays in obtaining small bowel access was also reported as a barrier. Although the paediatric evidence does not show superiority in post-pyloric feeding as the primary feeding method, some units do utilise this method successfully in all patients.[23-25] However, most units reserve this method for children intolerant of gastric feeding.[23] In the only randomised controlled trial of EN via gastric versus post-pyloric feeding,[25] there was significant crossover and drop out reported in the post-pyloric arm because of inability to place the pyloric tube. Newer devices[26] may assist in ease of correct placement of these tubes in larger children, but others have simply implemented intensive nurse training to achieve high placement success.

One of the most common reasons for failure to deliver EN in PICUs is that of feed intolerance,[3-12] yet this was not a survey item, and its definition remains problematiC.[27,28] The Canadian Critical Care Nutrition network (https://www.criticalcarenutrition.com/resources/strategies-for-improving) developed the barriers survey as part of a larger nutrition improvement program focused around: auditing your own practice, standardising care, identifying barriers, improving nutrition knowledge, and having nutrition champions. Thus, this quality improvement survey tool sought to identify modifiable ICU organizational and healthcare team barriers to the delivery of EN, rather than patient-related factors such as this.

The differences in perceived barriers by professional groups is interesting and has not been examined before. All three groups perceived fasting prior to procedures and operating department visits as a significant problem. The lack of dietician input was identified by both physicians and dieticians (in the top three barriers), but not nurses. This shows some consistency among the three professional groups but reflects their specific professional role around nutrition. Future education and interventions to improve EN in PICUs must involve all three of these professional groups. This freely available survey (available in eleven languages on the ESPNIC website: https://espnic-online.org/Education/Professional-Resources) can now be used by PICUs to first identify barriers in their unit, and then target these barriers to improve the delivery of EN, as part of a unit-based quality improvement program. This survey tool was adapted to a PICU population and deliberately excluded neonatal wards, as the organizational, behavioural, clinical, and pathophysiological aspects could be different. It would be interesting to evaluate these aspects in future research.

There are some limitations to our study that warrant highlighting. First, due to our distribution method via professional networks and organizational websites and newsletters, we are unable to know a denominator and thus calculate a response rate or rule out possible selection bias. Second, because of this, we were also unable to control for the variation in response rates from different countries; thus, we had significantly more European responses. However, the strengths of our study are our extensive responses (920 across 57 countries) and in our inclusion of all three professional groups involved in the delivery of EN. Unfortunately, the responses from dietitians were lower, which prevented us making firm conclusions regarding this group. Furthermore, our translation into multiple languages ensured the survey did not just reach an English-speaking group, a bias in many other surveys.

CONCLUSIONS

This study has demonstrated that many perceived barriers to enteral feeding remain in PICUs internationally. These are similar, but not the same as those in AICUs. These barriers relate to organizational and staff factors as well as patient factors relating to their clinical status. Whether the barrier is real or not, if clinicians believe these, then this still inhibits the delivery of EN. Generating evidence to support or refute these perceived barriers is ongoing, but further education to improve awareness of the existing evidence and facilitate the implementation of best evidence into local unit guidelines is required. The use of local feeding guidelines with or without nutrition support teams have been shown to be effective in promoting EN and as such should be encouraged. Physicians, nurses, and dieticians must all be involved in this process and in actively addressing barriers in their PICU.

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APPENDIX

Figure S1. Countries of which the survey correcspondents work; 920 responses from 57 countries

Created with: https://www.amcharts.com/visited_countries/#

Argentina , Austria, Australia, Belgium, Bolivia, Brazil, Bulgaria , Canada, Chile, China, Cuba, Colombia, Ecuador, France, Germany, Guatemala, Honduras, Hong Kong, India, Iraq, Ireland, Israel, Italy, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia, Mexico, the Netherlands, Nicaragua, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Puerto Ricco, Republic Dominica, Reunion, Russia, Saudi Arabia, Singapore, Spain, South Africa, Surinam, Sweden, Switzerland, Taiwan, Thailand, Turkey, Unites States of America, Uruguay, Uzbekistan, United Kingdom, Vatican, Vietnam

Table S1. Differences in perceived important barrier divided by years of experience (N=920)

Item	0-5 years N=356	6-10 years N=215	11-15 years N=113	> 15 years N=211	P-value
Delivery of Enteral Nutrition to the Patient					
1. Delay in physicians ordering the initiation of EN.	21.1%	20.9%	23.3%	15.6%	0.288
2. Waiting for physician to order and check x-ray to confirm tube placement.	15.7%	16.3%	10.6%	9.0%	0.060
3. Frequent displacement of feeding tube, requiring reinsertion.	18.3%[a]	12.1%[a,b]	6.0%[b]	5.8%[b]	<0.001
4. Delays in initiating motility agents in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	24.4%[a]	15.0%[a,b]	18.9%[a,b]	14.8%[b]	0.013
5. Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	32.7%	29.3%	31.8%	29.0%	0.760
6. In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over nutrition.	34.6%	32.1%	36.8%	28.6%	0.359
7. Nutrition therapy not routinely discussed on ward rounds.	19.7%	20.9%	19.5%	13.8%	0.229
8. Severe fluid restriction (especially post-operative cardiac surgery)	27.9%	31.8%	30.2%	26.9%	0.672
9. Conservative PICU feeding protocol	19.3%[a]	16.9%[a,b]	17.4%[a,b]	10.1%[b]	0.040
10. Difficulty in delivering enteral feed due to feeding tube obstruction or pump delivery problems with thickened formula	14.9%[a]	11.2%[a,b]	7.5%[a,b]	5.8%[b]	<0.001
Dietitian Support (Only if dietitian present; N=465)					
11. Waiting for the dietitian to assess the patient.	20.1%[a]	15.0%[a,b]	16.2%[a,b]	6.5%[b]	0.002
12. Dietitian not routinely present on weekday patient rounds.	33.9%	28.7%	30.6%	22.2%	0.065
13. No or not enough dietitian coverage during evenings, weekends and holidays.	40.9%	37.1%	38.2%	34.7%	0.595
14. Not enough time dedicated to education and training on how to optimally feed patients.	34.6%	35.6%	34.2%	30.4%	0.746
PICU Resources					
15. Delays to preparing or obtaining non-standard enteral feeds	18.8%	14.0%	17.4%	11.1%	0.079
16. No or not enough feeding pumps on the unit.	13.8%	13.5%	10.6%	8.1%	0.188

Healthcare Professional Attitudes and Behaviour					
17. Non-PICU physicians (i.e. surgeons, gastroenterologists) requesting patients not be fed enterally.	19.4%	18.1%	20.5%	11.9%	0.099
18. Nurses failing to progress feeds as per the feeding protocol.	10.4%	9.8%	12.1%	10.0%	0.908
19. Enteral feeds withheld due to diarrhoea.	14.3%	14.9%	12.1%	9.5%	0.314
20. Fear of adverse events due to aggressively enterally feeding patients.	19.4%	19.6%	19.7%	15.2%	0.579
21. Enteral feeds withheld for bedside procedures, such as physiotherapy, turns, and administration of certain medications.	22.5%[a]	22.3%[a]	25.8%[a]	12.4%	0.007
22. Enteral feeds being withheld in advance of procedures or operating department visits.	41.6%	47.9%	50.0%	35.7%	0.022
23. Lack of familiarity with current guidelines for nutrition in the PICU.	23.9%	23.7%	25.8%	19.2%	0.531
24. General belief among PICU team that provision of adequate nutrition does not affect patient outcomes.	16.9%	15.8%	11.4%	15.2%	0.521
25. Lack of staff knowledge and support around breastfeeding mothers	18.5%	25.6%	17.6%	16.2%	0.070

EN, Enteral Nutrition; PICU, Paediatric intensive care unit

Responders answered the questionnaire through Likert scale (range 0-6). Important barrier is indicated by the percentage of responders who answered with “a lot (4)”, “a great deal (5)”, and “an extreme amount (6)”

The subscript letters ”a” and ”b” denote categories in which proportions did not significantly differ from each other.

Table S2. Differences in perceived important barrier across the world (N=918)

Item	Northern Americas N=31	Southern Americas N=48	Europe N=517	Austral asia N=322	P-value
Delivery of Enteral Nutrition to the Patient					
1. Delay in physicians ordering the initiation of EN.	29.0%	20.8%	20.3%	18.6%	0.572
2. Waiting for physician to order and check x-ray to confirm tube placement.	22.6%[a,b]	12.5%[a,b]	7.8%[b]	22.4%[a]	<0.001
3. Frequent displacement of feeding tube, requiring reinsertion.	12.9%	8.3%	11.3%	14.0%	0.564
4. Delays in initiating motility agents in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	19.4%	12.5%	20.5%	17.7%	0.496
5. Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes).	35.5%[a,b]	31.9%[a,b]	35.7%[b]	22.4%[a]	<0.001
6. In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over nutrition.	41.9%	35.4%	31.8%	33.9%	0.647
7. Nutrition therapy not routinely discussed on ward rounds.	35.5%[a]	27.1%[a,b]	18.8%[a,b]	15.2%[b]	0.014
8. Severe fluid restriction (especially post-operative cardiac surgery)	35.5%	29.8%	28.7%	29.2%	0.881
9. Conservative PICU feeding protocol	41.9%[a]	8.3%[b,c]	12.5%[c]	21.3%[a,b]	<0.001
10. Difficulty in delivering enteral feed due to feeding tube obstruction or pump delivery problems with thickened formula	16.1%[a,b]	4.2%[a,b]	8.8%[b]	14.6%[a]	0.017
Dietitian Support (Only if dietitian present; N=465)					
11. Waiting for the dietitian to assess the patient.	16.0%	5.0%	12.5%	19.6%	0.017
12. Dietitian not routinely present on weekday patient rounds.	44.0%[a]	12.5%[b]	33.4%[a]	25.9%[a,b]	0.005
13. No or not enough dietitian coverage during evenings, weekends and holidays.	56.0%[a]	22.5%[b]	36.4%[a,b]	41.4%[a,b]	0.024
14. Not enough time dedicated to education and training on how to optimally feed patients.	56.0%[a]	30.0%[a,b]	38.4%[a]	26.5%[b]	0.001
PICU Resources					
15. Delays to preparing or obtaining non-standard enteral feeds	25.8%	19.6%	15.3%	14.3%	0.326
16. No or not enough feeding pumps on the unit.	29.0%[a]	14.9%[a,b]	11.0%[b]	11.5%[b]	0.024

Healthcare Professional Attitudes and Behaviour					
17. Non-PICU physicians (i.e. surgeons, gastroenterologists) requesting patients not be fed enterally.	29.0%	14.9%	19.2%	13.7%	0.060
18. Nurses failing to progress feeds as per the feeding protocol.	22.6%	12.8%	9.9%	9.6%	0.134
19. Enteral feeds withheld due to diarrhoea.	19.4%	14.9%	11.4%	14.6%	0.376
20. Fear of adverse events due to aggressively enterally feeding patients.	35.5%[a]	21.3%[a,b]	19.0%[a,b]	15.6%[b]	0.044
21. Enteral feeds withheld for bedside procedures, such as physiotherapy, turns, and administration of certain medications.	22.6%	21.3%	19.8%	21.4%	0.932
22. Enteral feeds being withheld in advance of procedures or operating department visits.	45.2%[a,b]	53.2%[a,b]	46.3%[b]	35.4%[a]	0.008
23. Lack of familiarity with current guidelines for nutrition in the PICU.	38.7%[a]	29.8%[a,b]	24.2%[a,b]	18.3%[b]	0.019
24. General belief among PICU team that provision of adequate nutrition does not affect patient outcomes.	32.3%	12.8%	14.9%	14.9%	0.067
25. Lack of staff knowledge and support around breastfeeding mothers	48.4%	19.1%[a]	19.6%[a]	17.4%[a]	0.001

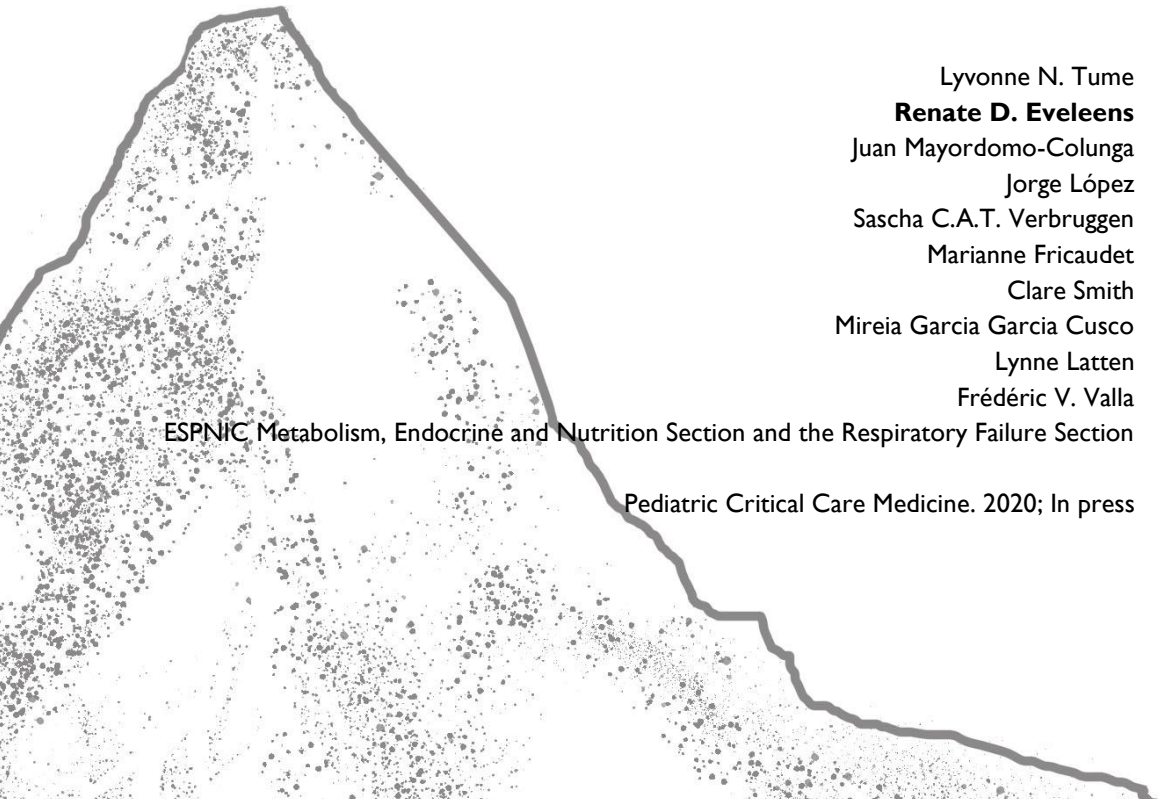
EN, Enteral Nutrition; PICU, Paediatric intensive care unit

Responders answered the questionnaire through Likert scale (range 0-6). Important barrier is indicated by the percentage of responders who answered with "a lot (4)", "a great deal (5)", and "an extreme amount (6)".

The subscript letters "a" and "b" denote categories in which proportions did not significantly differ from each other.

CHAPTER 3

ENTERAL FEEDING IN CHILDREN ON NONINVASIVE RESPIRATORY SUPPORT: A FOUR-CENTRE EUROPEAN STUDY



Lyvonne N. Tume
Renate D. Eveleens
Juan Mayordomo-Colunga
Jorge López
Sascha C.A.T. Verbruggen
Marianne Fricaudet
Clare Smith
Mireia Garcia Garcia Cusco
Lynne Latten
Frédéric V. Valla
ESPNIC Metabolism, Endocrine and Nutrition Section and the Respiratory Failure Section

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ABSTRACT

Objectives: To explore enteral feeding practices and the achievement of energy targets in children on non-invasive respiratory support, in four European PICUs. DESIGN: A four-centre retrospective cohort study.

Setting: Four PICUs: Bristol, United Kingdom; Lyon, France; Madrid, Spain; and Rotterdam, The Netherlands.

Patients: Children in PICU who required acute non--invasive respiratory support in the first 7 days. The primary outcome was achievement of standardised kcal/goal.

Measurements and main results: A total of 325 children were included (Bristol 104; Lyon 99; Madrid 72; and Rotterdam 50). The median (interquartile range) age and weight were 3 months (1–16 months) and 5kg (4–10 months), respectively, with 66% admitted with respiratory failure. There were large between-centre variations in practices. Overall, 190/325 (58.5%) received non-invasive respiratory support in order to prevent intubation and 41.5% after extubation. The main modes of non-invasive respiratory support used were high-flow nasal cannula 43.6%, bilevel positive airway pressure 33.2%, and continuous positive airway pressure 21.2%. Most children (77.8%) were fed gastrically (48.4% continuously) and the median time to the first feed after non-invasive respiratory support initiation was 4 hours (interquartile range, 1–9hr). The median percentage of time a child was nil per oral while on non-invasive respiratory support was 4 hours (2–13hr). Overall, children received a median of 56% (25–82%) of their energy goals compared with a standardised target of 0.85 of the recommended dietary allowance. Patients receiving step-up non-invasive respiratory support ($p < 0.001$), those on bilevel positive airway pressure or continuous positive airway pressure (compared with high-flow nasal cannula) ($p < 0.001$), and those on continuous feeds ($p < 0.001$) achieved significantly more of their kcal goal. Gastrointestinal complications varied from 4.8—20%, with the most common reported being vomiting in 54/325 (16.6%), other complications occurred in 40/325 (12.3%) children, but pulmonary aspiration was rare 5/325 (1.5%).

Conclusions: Children on non-invasive respiratory support tolerated feeding well, with relatively few complications, but prospective trials are now required to determine the optimal timing and feeding method for these children

INTRODUCTION

Enteral nutrition (EN) delivery in children on non-invasive respiratory support (NRS; highflow nasal cannula [HFNC], bilevel positive airway pressure [BLPAP], and continuous positive airway pressure [CPAP]) remains challenging. Clinical staff are concerned about the potential need for escalation of treatment and subsequent intubation and of the risk of aspiration. A large study of risk factors for delayed EN in the United States PICUs found that non-invasive ventilation was the most significant risk factor for delayed EN.[1] Furthermore, a single-centre U.S. study reported that enteral feeding was possible in these children, with 64% children receiving EN within 24 hours (54% orally, 30% transpylorically, and 7% gastric feeding).[2] This contrasts with a multicentre adult ICU study in France, which found three-fifths of patients receiving non-invasive ventilation fasted for the first 2 days.[3]

The use of NRS is increasing in children worldwide, in efforts to reduce the need for intubation and invasive ventilation.[4] Despite the lack of an accurate and clinically available method of predicting energy expenditure in children on NRS, they are likely to have a higher work of breathing (and higher energy expenditure) than those on invasive ventilation. As increasing evidence shows associations between the inadequate nutrition intake and the impaired clinical outcomes in invasively ventilated children,[7-10] the impact of this for children on NRS may be worse, particularly in infants and already malnourished children. Efforts to prevent faltering growth occurrence on PICU are recommended in both the ASPEN 2017 and ESPNIC 2020 guidelines. However, these are based on the studies in invasively ventilated children, rather than in children on non-invasive ventilation. We lack evidence in this subgroup of critically ill children; thus, we wanted to investigate practices with regard to EN in children receiving NRS across four European PICUs as a first step.

First, we wanted to examine the child's achievement of energy goals while on NRS. Second, we wanted to describe the time to initiate EN after NRS commencement, the duration of nil per oral times on NRS, the EN site and delivery method, and reported gastrointestinal complications on NRS. Then, we explored whether any associations existed between the main NRS modes, or whether step-up or down on EN delivery and percentage of energy targets achieved.

METHODS

Study population

A retrospective cohort study was undertaken to describe current practices around the enteral feeding of all consecutive children who met the study inclusion criteria in four European PICUs receiving some form of acute NRS: HFNC, CPAP, and BLPAP between 2018 and March 2019. We only included children 0–17 years old receiving acute NRS with

no limitation on the duration of NRS and collected data for the first 7 days of NRS and excluded children on chronic long-term respiratory support and preterm infants (< 37-wk gestational age).This period of NRS may have been before or after intubation and it may occur at any time point in the child's PICU stay.

Data collected included age, weight, gender, reason for PICU admission, primary diagnostic category, severity of illness score at admission (Paediatric Index of Mortality 2 [PIM2]), mode of NRS—step-up or down and specific type (CPAP, BLPAP, and HFNC) and starting pressures, flows, and Fio2 . Nutritional data collected included gastric tube type, route and feeding method, estimated (by equation) energy requirements at the initiation of NRS, hours nil per oral during the first 7 days, the time from initiation of NRS to the first enteral feed, and the child's total nutritional intake (kcal) during the first 7 days of NRS, along with any documented gastrointestinal complications (vomiting, diarrhoea, constipation, and high gastric residual volumes) and any documented aspiration. In all units, these data were retrieved from the electronic health records.

Four European centres participated (Bristol, United Kingdom; Lyon, France; Madrid, Spain; and Rotterdam, The Netherlands) and collected data on 50–100 patients per centre. Settings included the following: Bristol PICU is an 18-bedded combined general and cardiac PICU, Lyon is a 23-bedded general PICU, Rotterdam is a 24-bedded combined general and cardiac PICU, and Madrid is an 11-bedded combined general and cardiac PICU. All units deliver NRS regularly. Local unit protocols and practices was summerized in the appendix.

Ethical approval for the study was obtained separately in each country. In the United Kingdom, ethical approval was gained through the University of the West of England (August 2017), and in France, ethical approval was granted by Comite d'Ethique de Chu de Lyon (References 19–82). In The Netherlands, ethical approval was granted from Erasmus Medical Centre (MEC-2019-0182), and in Madrid, ethical approval was granted from Hospital General Universitario Gregorio Marañón (23/2017).

Outcomes

An important goal of our study was to examine the child's achievement of both their unit derived energy goal and a standardised energy goal (85% recommended daily allowance [RDA]) on NRS across the four sites. As no current recommendation exists on how much and how to feed NRS children, we used 85% of RDA as an assumption based on the mean of Schofield (in critically ill intubated sedated children) and RDA (healthy children).This was calculated as follows: ([total feeds given during NRS in mL, max 7 d] × [feed concentration in kcal/mL]) × 100/(number of days of NRS in days)/(85% RDA as goal in kcal/d). The definitions for other outcomes were defined and agreed by the four centres (Appendix).

Statistical Analysis

Data were collected in Microsoft Excel, checked, anonymised, and cleaned before combining into one database and exported directly into IBM SPSS v22 for analysis. Descriptive statistics were summarised by median (interquartile range [IQR]) and mean (SD) if appropriate and numbers (percentages). Data were tested for normality using the Shapiro-Wilk test. Nonparametric tests (Spearman rho) were used for testing associations between the non-normal variables with the primary outcome, and Mann-Whitney or Kruskall-Walis to test between the categorical variables and the non-normally distributed primary outcome. Stepwise multivariate linear regression analysis was used to identify if any patient or practice variables were associated with the percentage of achieved energy targets (% energy intake compared with 85% RDA goal). Investigated variables were age, PIM2 score, NRS initiation, main mode used, starting Fio2), inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), highest Fio2, IPAP, and EPAP, the child's feeding method, and route. Variables were included in the multivariate model if the univariate association with the outcome % achieved energy targets had a significance of $p \leq 0.1$. The multivariate models included the PICU site as a fixed effect to account for. Multicollinearity was assessed using Spearman correlation with a cut-off value of 0.5. The constant, unstandardised beta values with their corresponding standard errors, 95% CIs, and p values were reported for multivariate linear regression model. The normality assumption was not met for the main outcome variable energy achievement; however, due the large cohort group, it was considered acceptable under the central limit theorem.[5] Results are reported as standardised beta, standard error, or beta values, and corresponding 95% CI. All p values were two-sided and less than 0.05 were considered as statistically significant.

RESULTS

Three-hundred twenty-five children were included (104 in Bristol, 99 in Lyon, 72 in Madrid, and 50 in Rotterdam). The median (IQR) age and weight were 3 months (1–16 months) and 5 kg (4–10 kg), respectively, and weight for age z score 0.74 (–1.8 to –0.39) with 66% children admitted with respiratory failure (Table 1). The patient recruitment number and profile were significantly different between the centres (Table 2). The median duration of NRS was 3 days (IQR, 2–5 d) and 190/325 (58.5%) received NRS to prevent intubation and 41.5% as a step-down after extubation. Across the four units, the main mode of NRS used was HFNC 43.7%, BLPAP 33.2%, and CPAP 21.2%, with 1.8% patients on neurally adjusted ventilatory assist.

Overall, children received a median of 56% (25– 82%) of their energy goals (compared with a standardised 85% RDA) target while they were receiving NRS. However, large variability was seen across centres (Table 3). Across all centres, the median (IQR) time to first EN after NRS initiation was 4 hours (1–12hr) but varied between the centres. The median

percentage of time nil per oral while on NRS was 5 hours (IQR, 2–14.5). Of the children enterally fed, most children (93.8%) were fed via the gastric route, with 48.4% of these fed continuously. Only 6.2% were fed post-pyloric. Relatively few (10.8%) received normal oral/bottle and 17 (5.3%) were nil per oral (Table 3). Children receiving continuous feeds achieved significantly more of their energy goals than bolus feeds (mean 70.5% vs 47.8%, respectively ($p< 0.001$). Of the 6.2% children fed via the post-pyloric route, they received significantly more of their energy goal (mean 76.8% post-pyloric vs 57.6%; $p=0.012$); however, these factors were not significant in the multivariate model. Overall, children receiving HFNC achieved less of their mean energy goal achievement (42.1%) compared with those on BLPAP (68.5%) or CPAP (63.2%) ($p< 0.001$), but this was highly centre-dependent and not significant in the multivariate model. Children in whom NRS was initiated as "step-down" received less than those in whom it was "step-up" (mean 49% vs 61.9%, respectively; $p=0.001$) and this was significant only in univariate analysis ($p< 0.001$). In our multivariate analysis, only a higher age and bolus feeding were associated with lower achievement of standardised target energy goals (Table 4).

In terms of gastrointestinal complications, the rate varied between the centres from 4.8% to 20%. The most common reported gastrointestinal complication was vomiting in 54/325 (16.6%) and other reported complications occurred in only 40/325 (12.3%) children, with pulmonary aspiration rare 5/325 (1.5%) (Table 3). Overall, children received a median of 56.2% (24.7–79%) of their centre-predicted energy goal and 55.9% (24.9–81.8%) compared with a standardised energy goal of 0.85% RDA.

DISCUSSION

Our results showed significant differences in patient characteristics, NRS, and nutrition practices between the centres. Despite these differences, EN was commonly used and started early after NRS commencement; nutrition complications were infrequent and non-severe in most cases. However, target energy goals were rarely reached. This is the first study to examine practices around EN and NRS across four centres in Europe.

Delivering adequate nutrition in PICUs is challenging. An international study of 800 mechanically ventilated children in 31 PICUs showed only 37% of children received their prescribed energy intake.[6] On average, critically ill children receive less than half of their predicted energy requirements.[7] This is problematic, because inadequate nutrition delivery to critically ill children is associated with prolonged mechanical ventilation, impaired wound healing (and time to sternal closure in postoperative cardiac babies), increased healthcare acquired infections, increased mortality, and longer PICU stays.[8-15] However, in our study, energy achievement in children on NRS did not appear worse than those studies reporting this in invasively ventilated children.

Despite the variations between the four European centres, the time to initiation of EN was still better than previous studies. A North American cross-sectional analysis of barriers to delayed enteral feeding in six PICUs showed NIV as the predominant factor for EN delay,[1] with the odds ratio of delayed EN compared with those with no respiratory support that was 3.37 (95% CI, 1.69–6.72) and a median of 20 hours (IQR, 6–42hr) for EN initiation after PICU admission.[1] A single-centre U.S. retrospective study of 562 children on non-invasive ventilation found 64% were fed within the first 24 hours.[2] Compared with this, EN was initiated in 80% of our patients in less than 24 hours.

In our study, no NRS parameter was significantly associated with a lower achievement of energy targets, whereas Leroue et al[2] found BLPAP itself was a significantly factor for delayed EN with the reported median IPAP at initiation (16 cm H2 O). However, only 18% of children in this U.S. study received HFNC compared with nearly half (44%) of our sample. Surprisingly, in our study, the children receiving HFNC received significantly less of their energy goal compared with children on BLAP and CPAP. There was significant between-centre variation in the use of HFNC; however, when corrected for centre, there was no significant effect, and in the multivariate analysis, mode of NRS was not significant. Two centres (both having a cardiac surgical population) used significantly more HFNC and more step-down HFNC than the other two centres. It may be the impact these fluid restricted postoperative cardiac surgical children may have affected this on this finding of lower energy targets.

We found on univariate analysis that children receiving "step-down" NRS after extubation received significantly less of their energy goal compared with step-up NRS to prevent intubation. This was, however, not significant in the multivariate model. No other studies have examined this. This is also unexpected, as one might expect that the clinical team may be more cautious in starting EN in NRS initiated in children with respiratory distress to prevent intubation. A possible explanation is that one centre used significantly more step-down NRS than others, and this centre also had significantly more postoperative cardiac surgical patients, who were severely fluid-restricted, thus potentially affecting the EN allowance.

Few children in our study reached their nutritional targets during NRS: this may be partly due to the centre practices consisting of a progressive increase of EN during the first hours/days of PICU stay and ventilation support and affected also by the severe fluid restriction of children with cardiac failure and postoperative cardiac surgery. However, we did see a significantly higher achievement of energy goal in children continuously fed, compared with those fed by intermittent bolus feeds. However, this practice varied by centre, and future prospective studies are needed to investigate this further in children on NRS. In ventilated children, recent recommendations found neither method was superior, but this may be different in children on NRS. Similarly, in the few patients receiving post-

pyloric feeding (in only two centres), they achieved higher energy goals, but these are small numbers. In the same review,[16] they found no difference in energy goals by either method in invasively ventilated children.

Recent guidelines recommend targeting at least two-thirds of energy expenditure in invasively ventilated children within the first week.[17] Due to the difficulty of measuring energy expenditure in NRS children, no clear recommendation exists regarding children on acute NRS. The percentage of predefined energy goal reached differed significantly between the centres (14–82%), even when considering a standard goal (85% of RDA) or locally defined goals; this was mainly attributable to centres differences in patient recruitment and nutrition practices.

A study of adult on non-invasive ventilation and[18] airway complications found the rate of airway complications was higher in those adults receiving EN. However, vomiting alone and gastrointestinal complications were not reported. In our study, gastrointestinal complications were relatively low and mainly consisted of minor signs of feed intolerance: vomiting was less than 17% and others (non-severe) were less than 12%. Neither paediatric study examined gastrointestinal complications. Leroue et al[2] did record "new" pneumonia (reflecting aspiration) with an incidence of 9.6% (54/562). Our recorded aspiration occurrence was rare; however, these data may not be reliable when defined and collected retrospectively.

Our study suggests that enteral feeding can be initiated early after NRS commencement, with a low-to-moderate rate of complications. The ideal timing for initiation of EN and the optimal method for children on NRS, however, remain based on the experience and confidence of the team managing the child. Our study found large variations among the four European canters, both in NRS practices and EN initiation and titration.

This study has several limitations that warrant mentioning. There were significant differences in recruitment numbers between the centres and significant variations in both NRS and EN practices, along with a skewed population in terms of age, all of which may affect our findings. In addition, the retrospective nature of the data collection may have introduced selection bias, even though we had agreed definitions and used an agreed data extraction tool. Due to the observational nature of the study, EN initiation was biased by the clinical team local practice and protocols and we did not collect data on sedative use during NRS and the lack of a control group is also a weakness. Finally, we used estimated energy target prediction on the day NRS started as the goal and did not reassess this in the 7-day NRS period, and we only studied patients for the first 7 days of NRS. Despite these limitations, this is the first study to examine real practices around the issue of enteral feeding in children on NRS in a European context and provides us with new knowledge, giving us some idea of energy targets achieved in this group of children.

CONCLUSIONS

Despite variations between the centres in terms of NRS use, nutrition targets, and delivery practices, our study suggests that early enteral feeding is possible during NRS, even if energy targets are not met. We found a low–to-moderate incidence of gastrointestinal complications such as vomiting; however, documented aspiration was rare. Further conclusions regarding the association between different NRS methods and EN initiation cannot be drawn from this retrospective study. Further prospective trials are needed to determine both the optimal timing and feeding method for children on NRS using a consistent approach to enteral feeding.

Table 1. Patient demographics variation by centre and overall

Patient characteristic	Bristol	Lyon	Madrid	Rotterdam	Total
Number	104	99	72	50	325
Sex male	58 (55.8%)	46 (46.5%)	40 (55.5%)	26 (52.0%)	104/203 (51.2%)
Weight (kg)	5.9 (3.5-11.0)	4.0 (3.4-5.1)	5.5 (4.4-9.9)	9.6 (4.7-24.4)	5.0 (3.7-10.0)
Median (IQR) WAZ score	-1.3 (-2.3 - -0.27)	-.34 (-1.7 -0.7)	-3.0 (-1.6 – 0.5)	-0.86 (-1.95 – 0.21)	-0.74 (-1.8 -0.39)
PIM2 score	2.9 (1.7-8.3)	1.4 (1.1-3.7)	0.3 (0.2-1.7)	2.8 (1.6-7.8)	1.8 (1.0-4.5)
Age (months)	5.0 (1.0-18.3)	1.3 (0.8-3.5)	3.0 (1.5-16.0)	15.0 (3.0-78.1)	3.0 (1.0-16.1)
Cause of Admission	N 104	N 99	N 72	N 50	N 325
Circulatory failure	16 (15.4%)	0	1 (1.4%)	2 (4%)	19 (5.8%)
Trauma	1 (1%)	2 (2%)	0	2 (4%)	5 (15.4%)
Respiratory failure	49 (47.1%)	90 (90.1%)	55 (76.4%)	21 (42%)	215 (66.2%)
Neurological failure	4 (3.8%)	3 (3%)	0	2 (4%)	9 (2.8%)
Post op cardiac surgery	33 (31.7%)	0	12 (16.7%)	9 (18%)	54(16.6%)
Post op other	0	4 (4%)	0	4 (8%)	8 (2.5%)
Renal failure	1 (1%)	0	1 (1.4%)	6 (12%)	8 (2.5%)
Metabolic	0	0	1 (1.4%)	2 (4%)	3 (0.9%)
Sepsis	0	0	2 (2.8%)	0	2 (0.6%)
Other	0	0	0	2 (4%)	2 (0.6%)
Primary Diagnostic group	N 104	N 99	N 72	N 50	N 325
Gastroenterology	0	1 (1%)	0	6 (12%)	7 (2.2%)
Neurology	13 (12.5%)	5 (5%)	0	2 (4%)	20 (6.2%)
Oncology haematology	1 (1%)	3 (3%)	0	1 (2%)	5 (1.5%)
Respiratory infection	35 (33.6%)	84 (84.8%)	55 (76.4%)	14 (28%)	188 (57.8%)
Trauma	1 (1%)	1 (1%)	0	2 (4%)	4 (1.2%)
Cardiac failure	8 (7.7%)	0	2 (2.8%)	1 (2%)	11(3.4%)
Congenital heart disease	42 (40.4%)	0	11 (15.3%)	11 (22%)	64 (19.7%)
Metabolic/Endocrine	2 (2%)	0	2 (2.8%)	2 (4%)	6 (1.8%)
Sepsis	1 (1%)	0	2 (2.8%)	0	3 (0.9%)
Other	1 (1%)	5 (5%)	0	11 (22%)	17 (5.2%)

PIM, pediatric index of mortality; WAZ, weight-for-age Z-score

Table 2. Variation by centre in Non-Invasive Respiratory support practices

Variable	Bristol (N=104)	Lyon (N=99)	Madrid (N=72)	Rotterdam (N=50)	Total (M=325)
Total days NRS (max 7d)	2.0 (1.0-3)	4 (3-6)	3 (2-4)	2.0 (1.0-3.0)	3.0 (2.0-5.0)
NRS initiation	N=104	N=99	N=72	N=50	N=325
Step up	24 (23%)	82 (82.8%)	55 (76.4%)	29 (58.0%)	190 (58.5%)
Step down	80 (76.9%)	17 (17.1%)	17 (23.6%)	21 (42.0%)	135 (41.5%)
Main mode NIRS used	N=104	N=99	N=72	N=50	N=325
CPAP	16 (15.4%)	45 (45.4%)	3 (4.2%)	5 (10.0%)	69 (21.2%)
BIPAP	23 (22.1%)	24 (24.2%)	61 (84.7%)	0	108 (33.2%)
HFNC	64 (61.5%)	25 (25.2%)	8 (11.1%)	45 (90.0%)	142 (43.7%)
NAVA	1 (0.9%)	5 (5%)	0	0	6 (1.8%)
Starting Fio2	40 (30-50)	30 (25-40)	60 (40-100)	60 (40-100)	40 (30-60)
Starting IPAP	14 (11.5-15.3)	14 (13.3-14)	10 (8-12)	NA	12 (10-14)
Starting EPAP	6.5 (6-8)	7 (7-7)	6 (5-6)	5 (5-5.5)	7 (6-7)
Starting Flow (L/min)	10.0 (8-16)	10 (8-20)	12 (10-15)	15 (9-25)	12 (8-20)
Highest Fio2	40 (35-52.8)	40 (30-50)	60 (47.3-100)	100 (50-100)	45 (35-65)
Highest IPAP	16 (14-18)	14 (14-15)	12 (12-14)	NA	14 (12-15)
Highest EPAP	8 (6-8)	7 (7-7)	6 (6-8)	6.(5.5-6.5)	7 (6-8)
Highest flow (L/min)	12 (8-20)	10 (8-20)	12 (11.5-15)	15 (9-25)	12 (8-20)
Main patient interface used	N=103	N=99	N=72	N=48	N=322
Nasal mask	5 (4.9%)	65 (65.7%)	1 (1.4%)	3 (6.2%)	74 (23.0%)
Nasal cannula	73 (70.9%)	26 (26.3%)	51 (70.8%)	44 (91.7%)	194 (60.2%)
Face mask	6 (5.8%)	8 (8.0%)	2 (2.8%)	1 (2.1%)	17 (52.8%)
Full face mask	19 (18.4%)	0	18 (25.0%)	0	37 (11.5%)

Data in median (IQR) or numbers (%)

BIPAP, Bilevel Positive Airway pressure, CPAP, Continuous Positive Airway pressure; EPAP, Expiratory positive airway pressure; Fi02, Fraction of inspired oxygen, HFNC, High Flow Nasal Cannula, IPAP, Inspiratory positive airway pressure; NA, Not available; NAVA, Neurally Adjusted Ventilatory Assist; NRS, Non-invasive Respiratory Support

Table 3. Variation across centres in Enteral Nutrition Practices

Nutrition variable	Bristol	Lyon	Madrid	Rotterdam	Total	p-value
Feeding tube tip site	N 95	N 99	N55	N 40	N 289	<0.01
Gastric	85 (89.5%)	98 (99.0%)	40 (72.7%)	31 (77.5%)	254 (87.9%)	
Post pyloric	0	0	13 (23.6%)	5 (12.5%)	18 (6.2%)	
Gastrostomy	10 (10.5%)	1 (1.0%)	2 (3.6%)	4 (10%)	17 (5.9%)	
Feeding route	N 104	N 99	N 72	N 50	N 325	<0.01
Enteral	89 (85.6%)	99 (100%)	55 (76.4%)	30 (60%)	273 (84.0%)	
Oral	11 (10.6%)	0	16 (22.2%)	8 (16%)	35 (10.8%)	
NBM	4 (3.8%)	0	1 (1.4%)	12 (24%)	17 (5.2%)	
Main enteral feed method during NRS	N 88	N 99	N 55	N 30	272	<0.01
Continuous	2 (2.3%)	96 (97.0%)	46 (83.6%)	12 (40.0%)	156 (57.3%)	
Bolus/Intermittent	86 (97.7%)	3 (3.0%)	9 (16.3%)	18 (60.0%)	116 (42.6%)	
Energy targets used	85% RDA	85% RDA	85% RDA	Individualised*		
Energy goals and fasting	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
0.85% of RDA as energy goal (kcal/d)	497 (297-900)	340 (291-429)	467.5 (377.2-837.3)	817.9 (396.3-1355.8)	425.0 (314.5-850.0)	<0.01
At initiation of NIRS estimated energy requirements (kcal/d)	497 (297-900)	340 (291-429)	467.5 (377.2-837.3)	529.9 (241.3-974.3)	442.0 (320.0-782.0)	<0.01
Time (hours) first EN	3 (2-5)	3 (1-15)	6 (1-14)	11.5 (2.0-21.1)	4 (1-12)	<0.01
NBM hours during NRS	4 (2-6)	5 (1-16)	6 (1-16)	13.5 (4.5-24)	5 (2-14.5)	<0.01
Percentage of hours NBM during total NRS	12.5 (4.1-25)	6.4 (1.2-19.3)	9 (2.0-26.2)	37 (15.4-100)	11.8 (2.9-27.6)	0.02
Energy received compared to centre goal (%)	34.5 (17.6-59)	70.8 (51.9-85.2)	81.9 (50.5-95.8)	22.3 (0-72.7)	56.2 (24.7-79)	<0.01

Energy received compared to 0.85%RDA (%)	34.5 (17.6-59)	70.8 (51.9-85.2)	81.9 (50.5-95.8)	14.4 (0-53.2)	55.9 (24.9-81.8)	<0.01
Gastrointestinal effects						
Any vomiting (yes/no)	13/104 12.5%)	19/99 (19.2%)	15/72 (20.8%)	7/50 (14.0%)	54/325 (16.6%)	0.4
Any other	5/104 (4.8%)	11/99 (11.1%)	14/72 (19.4%)	10/50 (20.0%)	40/325 (12.3%)	<0.01
Gastrointestinal complications?						
If Any, other GI complications?	N 5 (4.8%)	N 11 (11.1%)	N 14 (19.4%)	N 10 (20%)	40 (12.3%)	<0.01
Regurgitation	0	11 (100%)	0	0	11 (27.5%)	
Diarrhoea	0/104	0/99	0/72	2 (20.0%)	2 (5.0%)	
High GRV	3 (60%)	0	0	7 (70.0%)	10 (25.0%)	
Abdominal distension	2 (40%)	0	5 (35.5%)	1 (10.0%)	8 (20.0%)	
Constipation	0	0	9 (64.3%)	0	9 (22.5%)	
Aspiration	0/104	5/99 (5.0%)	0/72	0/50	5/325 (1.5%)	<0.01

*Rotterdam energy goals for enteral nutrition are based on the Schofield equation for weight for the first day of admission and on the Recommended Dietary Allowances (RDA, Dutch Health Council) for the subsequent days. Data in median (IQR) or numbers (%)

EN, Enteral Nutrition; IQR, Interquartile Range; GI, Gastrointestinal; GRV, Gastric Residual Volume; NBM, Nil by mouth; NRS, Non-invasive Respiratory Support; RDA, Recommended Daily Allowance

Table 4. Impact of variables on the achievement of energy targets

		Univariate		Multivariate Adjusted R^2=0.126	
Variable	**Factor**	**Mean % energy target achievement**	**P value**	**β (95%CI)**	**p-value**
Centre	Bristol	43.7	<0.001	1.2 (-3.5 – 5.9)	0.609
	Lyon	70.4			
	Madrid	72.7			
	Rotterdam	32.4			
Age (months)		Rs -0.27	<0.001	-0.2 (-0.3 to -0.1)	0.001
PIM2		Rs -0.27	<0.001		
NRS initiation: Step up or Step down	Step up	62.0	0.001		
	Step down	49.0			
Main mode NRS used: CPAP, BLPAP, HFNC	HFNC	42.2	<0.001		
	CPAP	63.2			
	BLPAP	68.7			
Starting Fio2		Rs -0.07	0.231		
Starting IPAP		Rs -0.16	0.101		
Starting EPAP		Rs -0.09	0.238		
Highest Fio2		Rs -0.05	0.445		
Highest IPAP		Rs -0.17	0.096		
Highest EPAP		Rs 0.02	0.781		
Feeding method (continuous vs bolus)	Continuous	70.6	<0.001	-21.5 (-30.9 to -12.1)	<0.001
	Bolus	47.9			
Feeding route (gastric or post-pyloric)	Gastric	57.8	0.012		
	Post-pyloric	76.8			

All values univariate with P<0.1 were placed in the multivariate model including centre as fixed variable, except for highest IPAP which could not be included due to the large number of missing data and feeding route due to the high correlation with feeding method. Excluding variables were: PIM2, main NRS mode and NRS initiation. BLPAP, Bilevel Positive Airway pressure; CPAP, Continuous Positive Airway Pressure; FiO2, Fraction of Inspired Oxygen; HFNC, High Flow Nasal Cannulae; NRS, Non-invasive respiratory support; PIM2 Paediatric Index of Mortality 2 Score.

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APPENDIX

Table S1. Nutritional protocols across sites

Practices	**Bristol**	**Lyon**	**Madrid**	**Rotterdam**
EN protocol	Yes	Yes	Yes	Yes
Time to initiate EN	Within 24 hours of admission	Within 24 hours of admission	Within 24 hours of admission	Within 24 hours of admission
Default feeding site	Gastric	Gastric	Transpyloric	Gastric
Default Feeding method	Bolus 3 hourly	Continuous	Continuous	Continuous
Formula	Breast milk (infants) or age-based formula (no fibre)	Breast milk (infants) or age-based formula (with fibre) Polymeric as first line, semi-elemental if patient history	Breast milk (breast feeding infants) or age-based formula (energy enriched indicated by fluid restriction). No fibre	Breast milk (infants) or polymeric age-based formula (with fibre) Energy enriched indicated by fluid restriction or ventilated patients. Semi-elemental indicated by intolerance
Energy goals used	Based on IV fluid allowances and after this energy requirements based on Estimated Average Requirement (EAR) UK (1991).	Use Schofield in sedated intubated children RDA in extubated children 85% RDA in NIV children	Indirect calorimetry in sedated intubated patients. Schofield (weight and height) for the non-intubated patients	predicted REE according to Schofield equation (200% in infants declining to 130% REE in adolescents)
Feed advancement	Start at 5ml/3 hourly and increased by 2ml per Kg every 3-hourly feed until the maximum dose is achieved	Reach energy target within 2 to 4 days, daily stepwise increase	Start at 1 ml/kg (max. 10 ml) per hour first 3 hours and increased by 5 ml every 3-hourly feed until the maximum dose is achieved	Stepwise incline targeting 100% predicted REE at the end of the first week

Practices	Bristol	Lyon	Madrid	Rotterdam
Definition of intolerance	GRV >5mls/kg	Vomiting, abdominal pain GRV: not monitored	Vomiting, abdominal pain or distension. GRV: is monitored 3 times a day but it is not a criterion to stop enteral feeding	Large GRV >50% of intake Vomiting >2 times or diarrhoea ≥ 4 times in 24hours Signs for ischemia such as abdominal distention or pain and emesis or bloody stool
Reasons for stopping feeds	Lactate >2mmol/l GRV above threshold	Hemodynamic instability, vomiting	Hemodynamic instability, signs of feeding intolerance.	Signs of feeding intolerance. GRV is subtracted from next feeding
Prevention constipation	Children >12 months who are sedated and paralysed for >48hours get a high fibre feed & regular stool softening agents (Lactulose).	Fibre enriched formulas as first line choice, sedation sparing protocols, early feeding and mobilisation	Early feeding, early mobilisation and Macrogol at 4th day after PICU admission (constipation protocol)	Fibre enriched formulas as first line choice, regular stool softening agents (Macrogol; polyethylene glycol).

EN, Enteral Nutrition; GRV, Gastric Residual Volume; REE, Resting Energy Expenditure; RDA, Recommended Daily Allowance; NIV, Non-invasive ventilation

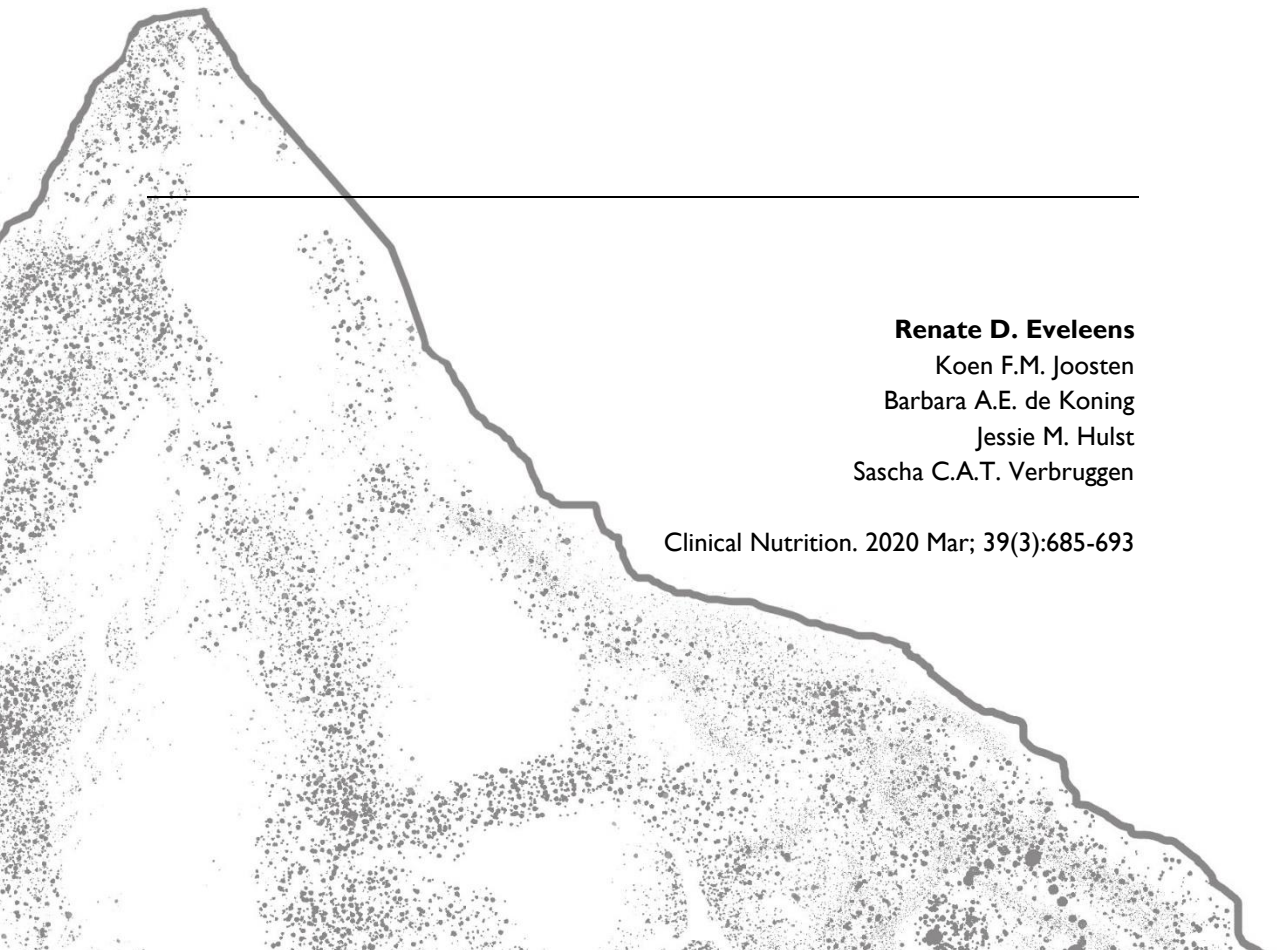
Table S2. Definition of terms

Term	Defined as
Patient age	In months to one decimal place
Patient weight	In Kg to one decimal place
Cause of PICU admission	Main reason for PICU admission: Drop down box options: Post-op cardiac surgery Post-op other surgery Respiratory failure Neurological failure Circulatory failure Trauma Metabolic Renal Failure Sepsis Other
Primary diagnostic group	Primary diagnostic group of patient: Drop down box options: Gastroenterology Neurology Oncology haematology Respiratory infection Trauma Cardiac failure Congenital heart disease Metabolic/Endocrine Sepsis Other
Total hours NRS	Up to a maximum of 7 days
PIM 2 score	All using standard PIM 2 scoring
Date patient started NRS	
Date patient stopped NRS	
Total days NRS	Defined from the dates above: up to a maximum of 7 days
Total hours NIV	Within the period above: Up to a maximum of 168 hours
Total hours HFNC	Within the period above: Up to a maximum of 168 hours
NRS initiation	Drop down box options: Step up or Step down
Main mode used	The NRS mode used for the majority of the time spend on NRS Drop down box options: HFNC, CPAP, BLPAP or NAVA
Second mode	If a secondary mode used, what was this Drop down box options: HFNC, CPAP, BLPAP or NAVA
Starting Fio2	Starting Fio2
Starting IPAP	If on BLPAP inspiratory pressure at start
Starting EPAP/PEEEP	For CPAP/BLPAP the lower pressure at start
Starting flow	For HFNC in l/min
Highest Fio2	Highest Fio2 recorded during NRS
Highest IPAP	If on BLPAP highest inspiratory pressure during NRS support
Highest EPAP/PEEP	For CPAP/BLPAP the highest value of the lower pressure during NRS support
Highest flow	For HFNC the highest flow during NRS support

Term	Defined as
Main patient interface used	Drop down box options: Face mask, nasal cannulae, full face mask,
Secondary interface used	Drop down box options: Face mask, nasal cannulae, full face mask,
Feeding tube insitu at NRS	Was a feeding tube insitu at the start of NRS Yes or No options
Type	Type: Drop down box options: Gastric, post-pyloric, gastrostomy
Feeding tube site	Options: nasal, oral or gastrostomy
Main feeding method	Main feeding method used whilst on NRS Drop down box options: Continuous, bolus or Not applicable e.g. Nil per oral
Enteral or normal oral feeding	Options: normal oral feeding/diet or enteral feeds
Feed formula used	Brand name
Concentration	Kcal/ml of this feed
0.85 of RDA as energy goal	85% of the RDA energy goal calculated by: Based on expert opinion only we defined this using the mean between invasively ventilated children (Scofield +/- = 65% RDA) and RDA
kcal requirements	At initiation of NRS estimated kcal requirements
Predictive equation used	Predictive equation or formula used to calculate these requirements
Any vomiting	Any recorded vomiting episodes during NRS (yes or No)
If yes, number	If yes, the number of recorded vomiting episodes
Any other GI complications?	If yes please record along with number of episodes
Any recorded aspiration?	Any recorded aspiration episodes (yes or No)
NPO during whole NRS	Nil per oral during whole NRS (1st 7 days) Yes or No
Time to first EN	Hours from initiation of NRS to first EN
NPO time	Total Nil per oral time during 1st 7 days of NRS
% NRS time NPO	Percentage of time nil per oral per time on NRS (in 1st 7 days)
Total mls feed	Total mls of feed given during 1st 7 days of NRS
Any supplemental PN	Was any supplemental PN started specifically due to poor enteral intake during 1st 7 days of NRS (not for other reasons)
Total kcal in	total (kcal) feed given during NRS: (kcal/mL) x (total feeds in mL) during the 1st 7 days of NRS
Total kcal in per hours of NRS	(kcal/mL) x (total feeds in mL)/ days of NIV (based on hours)
Total kcal in days of NRS	(kcal/mL) x (total feeds in mL) / days of NIV
% energy goal	kcal received compared to centre goal (%)
% standard goal	kcal received compared to standardised goal of 0.85% RDA (%)

CHAPTER 4

DEFINITIONS, PREDICTORS AND OUTCOMES OF FEEDING INTOLERANCE IN CRITICALLY ILL CHILDREN: A SYSTEMATIC REVIEW



Renate D. Eveleens
Koen F.M. Joosten
Barbara A.E. de Koning
Jessie M. Hulst
Sascha C.A.T. Verbruggen

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ABSTRACT

Background & aims: Clinicians and researchers often use feeding intolerance (FI) as main cause for insufficient enteral nutrition (EN). However, there is no uniform definition for FI. A uniform definition is essential for future studies focusing on predictors and outcomes of FI and enteral nutrition. A systematic review was performed to investigate the definitions, prevalence, predictors and outcomes of FI in critically ill children.

Methods: The databases Medline, Embase, Cochrane CENTRAL, Web of Science were searched. Inclusion criteria were interventional, observational or case-control studies (>10 patients) in which a definition of FI was reported in critically ill children (0-21 years).

Results: FI was defined in 31 unique studies performed in 2973 critically ill children. FI was most commonly defined as presence of gastrointestinal (GI) symptoms and/or large gastric residual volume (GRV) (n=21), followed by discontinuation of EN due to GI symptoms (n=7) and inadequate delivery of EN (n=3). Median prevalence of FI was 20.0% [IQR 7.4%-33.0%]. Large GRV, abdominal distention, diarrhoea and vomiting/emesis, were the predominantly reported GI symptoms to define FI. FI was associated with severity of illness, mortality and nosocomial infections.

Conclusions: Feeding intolerance is inconsistently defined in the current literature, but appears to be a prevalent concern in critically ill children. FI is most frequently defined by the presence of GI symptoms. A standardised definition is needed for both clinical and research purpose to determine the consequences of FI in relation to short-term and long-term outcomes. The new proposed definition for FI entails the inability to achieve enteral nutrition target intakes in combination with the presence of GI symptoms indicating GI dysfunction.

INTRODUCTION

The preferred route to administer nutritional support in the paediatric intensive care unit (PICU) is through enteral nutrition (EN) and achieving adequate energy and protein target intakes via enteral nutrition is associated with improved outcome. In clinical practice nutritional targets are often not reached during critical illness.[1,2] Failure to achieve enteral target intakes in the PICU can be caused by a diversity of reasons, of which fear for poor gut function, interruptions around procedures, fluid restriction and feeding intolerance (FI) are frequently reported.[2,3]

Although FI is declared a main reason for insufficient enteral intake, it is inconsistently defined among the different PICUs.[3] A standardised definition is essential from a clinical and scientific perspective, providing insight into possible causes and consequences of difficulties with enteral intake in critically ill children. Furthermore, such a definition is needed to compare interventions in studies to optimise enteral intake during critical illness.

A systematic review was performed to evaluate the definitions and to investigate the prevalence, predictors and outcomes of FI in critically ill children. Our primary aim was to evaluate all the reported definitions in research. Furthermore, the prevalence of FI, and associated predictors and outcomes of the different definitions were evaluated. Finally, we aimed to propose a definition for further validation.

METHODS

The study protocol and objectives were established a priori (PROSPERO protocol number: CRD42018092967) and performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[4]

Eligibility criteria

Studies were included if the following eligibility criteria were met: 1) the study had an interventional, observational cohort or case-control design; 2) study participants were admitted to a paediatric intensive care unit (PICU); 3) investigators provided a definition of 'feeding intolerance' or derivative terms (combination of the following terms: (in)tolerance, enteral, nutritional, GI, difficulties, complications). All studies reporting a definition were included, feeding intolerance was not necessarily the main topic of investigation. Studies were excluded if they: 1) were case reports or case series including <10 patients; 2) included infants <35 weeks of gestational age or included patients >21 years old.

Strategy

The search was conducted in the following databases: Medline Ovid, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google scholar. The search strategy was first developed by a Biomedical Information Specialist of the Medical Library of the Erasmus Medical Centre in Medline and adapted for the other databases. The search was limited to English language, and data published as conference abstract, letter, note or editorial were excluded. The search was performed on 11 January 2018 and updated on 07 Sept 2018. It included a citation review of all eligible articles (Appendix). All articles were independently screened on title and abstract by two reviewers and followed by full-text screening (RE, SV). When reviewers disagreed a third investigator made the final decision (KJ).

Data extraction and risk of bias assessment

Data were extracted from eligible articles by two reviewers (RE; SV). The following data were extracted: 1) study design and setting; 2) inclusion criteria; 3) population; 4) study objective; 5) interventions; 6) definition of FI; 7) incidence or prevalence of FI; 8) predictors and/or presumed causes of FI; and 9) clinical outcome measures (mortality, infection, mechanical ventilation, use of vasoactive agents, or other adverse events). Only data of unique studies were extracted to report the definitions or prevalence. However, secondary analysis of previous published populations were included in the predictors and outcomes sections of this systematic review.

The risk of bias was assessed by description of study design, feeding route, description of nutritional policy and the clearness in the definition of FI. The investigated PICU population was reported to determine the clinical heterogeneity of the studies, which potentially could result into bias. Methodological quality of nonrandomised studies was evaluated using the STROBE checklist.[5] Quality of randomised trials were assessed with the Cochrane risk of bias tool.[6] This tool assesses the different types of bias for RCTs, divided into selection, performance, detection, attrition, reporting and other bias.

Statistical analysis

Descriptive statistics are reported as number (percentages), mean (standard deviation (SD)) if normally distributed or as median (interquartile range (IQR)) if not normally distributed. A random effect meta-analysis was used to calculate the pooled prevalence of FI and the 95% confidence intervals (CI) using R studio version 3.4.1 (Boston, USA). Heterogeneity was clinically and statistically assessed using Cochran's Q homogeneity and I-squared inconsistency statistics. Due to the clinical heterogeneity of the definition categories, separate analyses were performed for the different FI definitions. The Agresti-Coull (AC) binominal CI was used if only one prevalence per definition was reported.

RESULTS

A total of 3572 unique studies were identified and after reviewing title and abstract 101 potentially relevant studies remained (Figure 1). After full-text screening 39 articles met the full eligibility criteria,[7-45] of which 10 were identified with possible overlapping participants.[7-14,29,45] After contact with the authors, the two primary studies with the largest population and a clear definition of FI were selected for the data pooling analyses.[7,45] Therefore, 31 unique studies, reporting definitions of FI on 2973 critically ill children, were included in the analysis. Of these studies, 9 studies were RCTs, 5 non-randomised interventional trials, 8 were prospective observational and 9 retrospective observational studies. The majority of the included studies were performed in a mixed PICU population and reported a median participant size of 60 (range 20–526). In all studies, EN was the main topic of investigation, whereas in 17 studies (54%) FI was the main objective of the study.

Risk of bias assessment

The majority of the studies included a mixed PICU population. Two studies were performed in term neonates; one with neonates receiving venoarterial extracorporeal membrane oxygenation (VA-ECMO) treatment[19] and one receiving prostaglandin medication.[20] Other studies with non-mixed population included infants with respiratory diagnosis,[24,40] post-surgery for congenital heart diseases (CHD),[21,22,24] and children with a hypoplastic left heart syndrome (HLHS).[23]

In the nine RCTs, FI was either the primary or secondary objective of the study.[24-28,30,43-45] The risk of bias from the randomization process (selection bias), selective reporting or incomplete outcome data was generally low, however, in three studies there might be selection bias because of exclusion or switching of patients to the other treatment arm after the randomization process due to the inability to place a post-pyloric tube.[25,43,44] There was potential performance and detection bias in four studies due to the inability to blind the participants, clinicians and investigators[25,26,43,45] and one study did not report if investigators were blinded for outcome data (detection bias).[24]

The methodological quality varied among the observational and non-randomised interventional studies but was overall medium to poor. The highest score obtained from the STROBE checklist[5] was 12 of a maximum of 22 points. Most studies did not report the method section according to the checklist and information on selection and inclusion of participants, methods of data assessment, bias, quantitative variables and/or detailed statistical plan were missing.

EN was provided in the majority of studies via the combination of gastric, post-pyloric and oral route. Ten studies (32%) investigated exclusive gastric feeding and four (13%) post-pyloric feeding. In three studies no information on feeding route was provided. Also, not all

studies provided information on patient characteristics. Three studies (10%) did not report an age range in method or result section.[15,18,26] Detailed description of nutritional policy was reported in 23 studies (74%). The majority of the studies reported exclusion criteria, which were expected limited admission duration (range 12 h to 5 days), GI-disorders or surgery, congenital or genetic abnormalities, renal or liver failure. Seven studies (23%) excluded children if GI symptoms or pro-kinetic agents were present at baseline.[22,24,37,39,44-46]

Definitions of feeding intolerance

There was a wide variety in definitions used to determine FI, which were classified into three main categories:

1) Discontinuations of EN due to gastrointestinal (GI) symptoms (n=7 studies);
2) Presence of GRV and/or GI symptoms, divided in
    a. GRV and GI symptoms (n=12 studies)
    b. Only GI symptoms (n=6 studies)
    c. Only GRV (n=3 studies);
3) Inability to achieve enteral target intake (n=3 studies).

Gastrointestinal symptoms

Table 1 presents an overview of the reported GI symptoms used to describe FI in the studies from category 1 (discontinuations of EN due to gastrointestinal (GI) symptoms) and category 2 (Presence of GRV and/or GI symptoms), which were reported in 28 studies (90%) in total. Most reported symptoms were diarrhoea, large GRV, abdominal distention and vomiting. Twenty studies (65%) reported large GRV as a marker for feeding intolerance (category 1, 2a and 2c), but this was defined inconsistently among the studies. Four studies reported large GRV as >50% of previous 4 h of feeding[7,42,46]. All other cut-off values for large GRV were used only once per study, i.e. 100–150% of previous 4 h of feeding, > 300% of previous 3 h of feeding, >66% of previous feeding, >125% after 4 h feed challenge, > 2 ml/kg per 3 h, >3 ml/kg/day, >5 ml/kg per 4–5 h, >10 ml/kg per 4 h, >100 ml per 4 h or >150 ml per hour. In the remaining six studies large GRV was not specified. No values or definitions were provided in the majority of the studies regarding the other GI symptoms. Diarrhoea was specified in eight studies as having more than 3, 4 or 6 loose stools per day or exciding the amount of 2.5 L per day.[15,24,25,37,40,44-46] Four studies mentioned a threshold value for abdominal girth, which were ≥2 times increase,[34,38] >3 cm increase[20] or ≥15% increase.[40] Emesis or vomiting was defined in two studies as having two or more episodes of spitting-up gastric content.[34,38]

Enteral target intake

Inability to achieve enteral target intake was used to determine FI in the remaining three studies (10%) (category 3) and GI-symptoms were not part of the definitions. In one study FI was defined by not reaching 75% of target intake (estimated energy expenditure * 1.3) within 48 h of initiation of EN.[30] A second study defined intolerance as the inability to reach

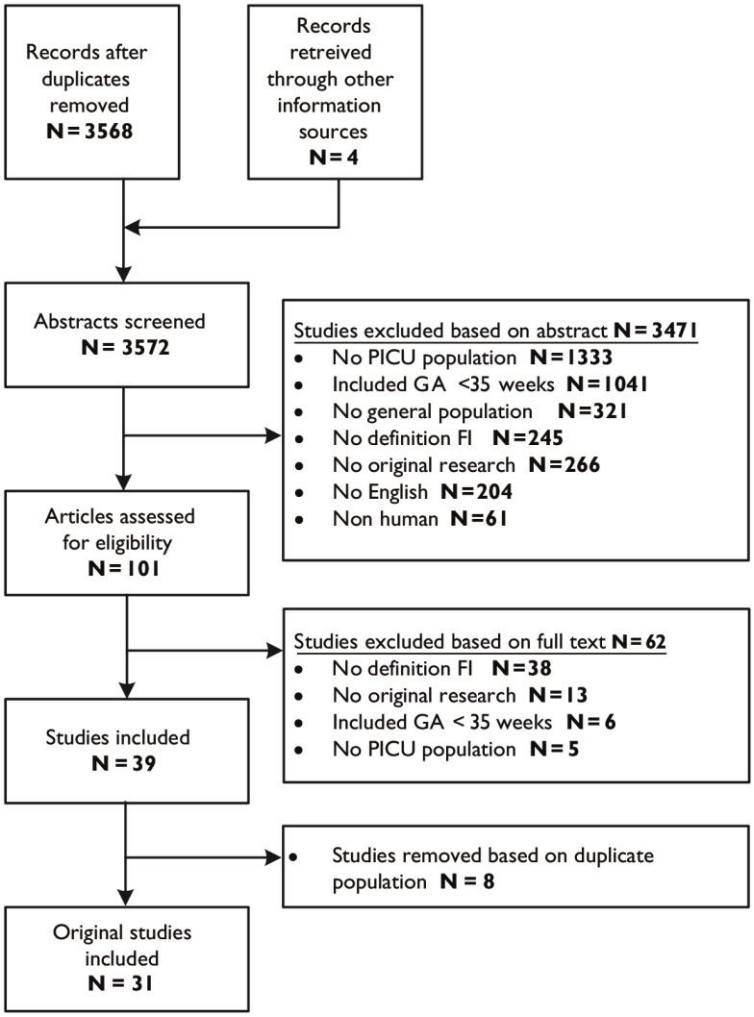

Figure 1. Flow chart depicting search for eligible studies for inclusion in systematic review about feeding intolerance in critically ill children.

Table 1. Number of times gastrointestinal symptoms were used to define feeding intolerance (N=28 studies)

Definition category	**Category 1**	**Category 2**	**Category 1 and 2**
	Discontinuation of EN due to GI symptoms	*GRV and/or GI symptoms*	*All GI symptoms reported*
Diarrhoea	5	17	22
Large GRV	5	15	20
Vomiting/emesis	5	15	20
Abdominal distention	5	13	18
Constipation	3	2	5
Aspiration	2	3	5
GI-bleeding	1	3	4
Abdominal discomfort	-	3	3
NEC	1	1	2
Reflux	-	2	2
Hemoccult positive stool	-	1	1
Absent bowel sounds	-	1	1

EN: enteral nutrition; GI, gastrointestinal; GRV, gastric residual volume; NEC, necrotising enterocolitis

Table 2. Prevalence of FI with use of different definitions

Definition of FI	Number of studies[a]	Number of patients	Number of FI patients	Binominal proportion (95% CI)[b]	Pooled proportion (95% CI)[b]	Heterogeneity I^2 % (95% CI)
1. EN discontinued due to GI symptoms	6	1026	119	NA	0.15 (0.07-0.30)	91 (87-96)
2a. GI symptoms including large GRV	7	854	238	NA	0.22 (0.09-0.44)	85 (71-92)
2b. GI symptoms without large GRV	1	59	7	0.12 (0.05-0.23)	NA	NA
2c. Large GRV	2	83	35	NA	0.42 (0.30-0.54)	NA
3. Insufficient enteral intake	1	50	0	0.00 (0.00-0.09)	NA	NA
Total	17	2072	339	NA	0.19 (0.11-0.30)	90 (86-93)

EN, Enteral nutrition; FI, feeding intolerant GI, gastrointestinal; GRV, gastric residual volume

[a]Subanalyses of studies with a reported prevalence; [b]Pooled proportion calculated when >1 study was included and binominal proportion when one study was included;

Table 3. Causes of feeding intolerance investigated in 8 randomised interventional trials

Author, year	Definition of FI	N	Population	Study design	Objective	Causes of FI
Cui et al., 2018 [24]	Large GRV (> 3 times feeding volume delivered in 3h), intolerable vomiting, diarrhoea (>4 stools or > 10g/kg/d) or GI bleeding	52	CHD, post-surgery 4 weeks - 12 months	PE-formula vs standard formula gastric EN	Compare nutrition effects and tolerance of the 2 different formulas in infants after congenital heart surgery.	Tolerable diarrhoea higher in PE-formula group 69.2% vs 33.3% No difference in other parameters
Fayazi et al., 2016 [43]	Large GRV (>100 ml after 4 hours)	60	Mixed 5 – 17 years	Intermitted vs continuous gastric EN	Compare intermitted vs continuous feeding in terms of time to reach caloric goal and complications	FI higher in intermittent feeding group (p=0.02) No significant difference in vomiting and diarrhoea
Jacobs et al., 2013 [30]	Achieved energy goal less than 75% of estimated energy expenditure x 1,3 within 48 hours of initiation of EN	26	Respiratory failure 1 - 18 years	Eicosapentaenoic acid, y-linolenic acid and antioxidants vs standard formula via gastric or post-pyloric route	Pilot study to determine feasibility of eicosapentaenoic acid, y-linolenic acid and antioxidants feeding	Achievement of energy goal comparable for both formulas (28-30 hours)
Simakachorn et al., 2011 [27]	Inability to reach target caloric intake (70 kcal * kg * day)	94	Mixed diagnosis receiving antibiotics 1 - 3 years	Probiotic vs standard formula via oral or gastric route	Demonstrate the tolerance and safety of an enteral formula containing a synbiotic blend and to investigate its effect on the intestinal microbiota	1) Median time to reach target caloric goal comparable between probiotic (4.13d) vs standard (4.36d) formula (p=0.999) 2) No difference in abdominal distention (p=0.83), vomiting (p=0.59), and diarrhoea (p=0.39)

Van Waardenburg et al., 2009 [28]	Large GRV (> 50% of 4h feeding volume delivered), distension, vomiting or diarrhoea (>4 watery stools per day leading to a negative fluid balance or hemodynamic consequences)	20	Respiratory failure 4 weeks – 12 months	PE-formula vs standard formula via gastric or post-pyloric route	Compare nutritional effects of PE-formula to standard formula (delivery, energy/nitrogen balances, amino acid profiles). Secondary aims were assessing tolerance and safety	No vomiting, distention, diarrhoea in both groups. GRV higher in PE-group vs standard group (9.8±2.8 vs 4.7±2.4 ml/kg; p<0.01)
Meert et al., 2004 [25]	Aspiration, vomiting, diarrhoea (> 3 liquid stools in a 24h period) or abdominal distention	74	Mixed <18	Gastric vs post-pyloric EN	Evaluate the effect of feeding tube position on nutrient delivery and feeding complications	Presence of each symptom did not differ between gastric and post-pyloric EN group (NS)
Horn et al., 2003 [45]	Number of stools, diarrhoea (>3 stools in a 24h period) or vomiting	45	Mixed 0 – 13 years	Intermittent vs continuous gastric EN	Assessing tolerance of continuous vs intermitted feeding	The number of stools per day and the prevalence's of diarrhoea and vomiting did not differ between the two groups (NS)
Lyons et al., 2002 [26]	Abdominal distention, diarrhoea, gastroesophageal reflux, pulmonary aspiration or emesis	59	Mixed Mean age 8.9 (±1.5) months	Continuation of post-pyloric feeding during extubation	Examine the safety and efficacy of continuous feeding compared with interrupted post-pyloric feeding at the time of extubation.	No difference between continuation vs withholding EN prior to extubation (NS)

CHD, Congenital heart disease; EN, Enteral nutrition; FI, Feeding Intolerance; GA, gestational age; GI, gastro-intestinal; GRV, gastric residual volume; NEC, necrotising enterocolitis; NPO, Nil per os; PE, protein and energy enriched; RCT, randomised controlled trial

Table 4. Feeding intolerance associated with outcome in 3 non randomised studies

	Definition of FI	N	Population	Study design	Objective	Clinical outcomes of FI
Sánchez et al., 2000* [14]	EN discontinued due to abdominal distention, large GRV (>50% of 4h feeding volume delivered), vomiting or diarrhoea	152	Mixed 3 days – 17 year	Prospective, receiving post-pyloric EN	Assess the use and complications of post-pyloric EN	- Pulmonary infections (25% vs 8.6%; p<0.05) - Altered hepatic function (100% vs 9.5%; p<0.01) - Hypokalaemia (19 vs 5.5%; p<0.05) - Hypocalcaemia (19% vs 9.5; p<0.05)
Panadero et al., 1998* [13]	Vomiting, abdominal distension, large GRV, diarrhoea or pulmonary aspiration	41	Mixed 8 days – 12 year	Prospective, receiving post-pyloric EN	Analyse the utility and complications of post-pyloric EN	Mortality higher in FI patients 30% vs 13% (NS)
Wolf et al., 1997 [15]	Abdominal distention, large GRV (>150ml/h) or diarrhoea (>2.5L/d) resulting in ≥ 24h EN discontinuation.	91	Severe burned children	Retrospective, receiving post-pyloric EN	Determine if FI is associated with sepsis and increased mortality in children with severe burns	FI associated with sepsis (p<0.001) FI associated with mortality (p<0.05)

* Studies are secondary analysis of previous published studies with possible overlay in population.
EN, Enteral nutrition; FI, Feeding Intolerance; GRV, gastric residual volume

Table 5. Feeding intolerance associated with energy delivery investigated in 4 non randomised studies

Author, year	Definition of FI	N	Population	Study design	Objective	Outcomes of FI
Martinez et al., 2017 [34]	Large GRV (>3ml/kg or >150 ml), ≥ 2 increases in abdominal girth, ≥ 2 emesis episodes, ≥ 3 loose stools or subjective abdominal discomfort in a 24h period	20	Mixed >1 year	Prospective cohort with acetaminophen absorption test, receiving gastric EN	Explored the feasibility of performing the acetaminophen absorption test and examined its correlation with FI	GRV did not predict delayed vs normal gastric emptying (p=0.964) Other FI signs did not predict gastric emptying (p=0.824)
Canarie et al., 2015 [33]	Large GRV, vomiting, abdominal distention, constipation, diarrhoea	444	Mixed < 21 years	Prospective cross-sectional, receiving oral, gastric or post-pyloric EN	Reviewed nutritional practices in six medical-surgical PICUs and determined risk factors associated with delayed EN	Risk factor for delayed EN (OR,2.05; 95% CI 1.14-3.68)
Canarie et al., 2015 [33]	Large GRV, vomiting, abdominal distention, constipation, diarrhoea	444	Mixed < 21 years	Prospective cross-sectional, receiving oral, gastric or post-pyloric EN	Reviewed nutritional practices in six medical-surgical PICUs and determined risk factors associated with delayed EN	Risk factor for delayed EN (OR,2.05; 95% CI 1.14-3.68)
Mayer et al., 2002 [39]	Large GRV (> 125% of 4h feeding volume delivered)	23	Mixed 1 month – 16 years	Prospective interventional, receiving gastric EN	Determine the relationship between amylin levels and gastric emptying	Delayed gastric emptying in FI patients using paracetamol absorption test (p≤0.01)

EN, Enteral nutrition; FI, Feeding Intolerance; GRV, gastric residual volume

120 ml/kg/day of continuous enteral feeds without interruption.[23] The third study defined FI as the inability to reach target caloric intake (70 kcal * kg * day) in children aged 1–3 years.[27]

Prevalence of feeding intolerance

Prevalence of FI was reported in 17 studies (55%) and ranged from 0.0 to 57.1% with a median prevalence of 20.0% [IQR 7.4–33.0]. Due to the clinical heterogeneity within the category definitions, a pooled prevalence was calculated per group category (Table 2). The pooled percentage of children with feeding intolerance was 15% (95% CI 7–30%) in six studies with the FI definition EN discontinuation, 22% (95% CI 9–44%) in seven studies with the FI definition of GI symptoms including large GRV and 42% (95% CI 30–54%) in two studies defining FI with large GRV. However, the heterogeneity of the pooled prevalence was considered large in the definitions, with an I-squared of 91% in studies which used discontinuation of EN and 85% in studies using GI symptoms and GRV.

Predictors associated with feeding intolerance

Causes and predictors of FI were mentioned in 23 studies (74%) and are presented in Table 3 and Appendix. Eight studies were randomised controlled trials (RCTs) with a primary focus on FI (Table 3), 10 studies had a prospective design and 5 studies a retrospective design (Appendix). In the 8 RCTs that were identified, various nutritional interventions were compared in critically ill children. In one study comparing intermittent versus continuous gastric feeding a significant higher prevalence of FI was found in the intermittent group ($p=0.02$) [43]. The other studies comparing gastric versus post-pyloric[25] and intermittent versus continuous feeding, did not find differences in FI.[26,45] Also studies comparing standard frmula with formulas that were enriched with either pre- and probiotics,[27] with immunomodulators[30] or with protein and energy did not report differences in FI.[24,46]

Clinical outcome measures associated with feeding intolerance

There were three observational studies associating clinical outcomes with FI and no interventional trials (Table 4).[13-15] In one study mortality was higher in children with FI (30% versus 13%); however this was not significant.[13] A retrospective study in 91 severely burned children receiving post-pyloric EN did find a significant association between feeding intolerance and mortality ($p<0.05$).[15] In 2 studies, FI in critically ill children was also associated with pulmonary infections ($p<0.05$)[14] and sepsis ($p<0.001$).[15] The association of FI and enteral energy delivery was investigated in four non randomised studies and are reported in Table 5. FI was associated with lower energy delivery[37] and delayed achievement of full EN.[33,39]

DISCUSSION

Our systematic review revealed several nutritional studies in critically ill children with a focus on the descriptive term "feeding intolerance". However, the methodological quality of these studies was moderate to poor. As hypothesised, FI was inconsistently defined, which precludes any firm conclusions on prevalence, predictors and outcomes. FI was most commonly based on a wide variety of gastrointestinal symptoms. FI was sometimes addressed as not reaching target intakes, however, in other studies this was the outcome determinant of FI. It is remarkable that there is no standardised definition for FI, especially considering the substantial impact it presumably is declared to have on morbidity and mortality during critical illness.[14,47] Unfortunately, no overall prevalence could be calculated to assess the burden if FI in critically ill children. Aside from inconsistency in the use of determinants for a definition the overall poor description of how these determinants were assessed was of greater concern, leading to a high risk of bias in almost all studies included in our review. This resulted in a large statistical heterogeneity of our pooled prevalence within the definitions (I-squared 85% and 91%).[48] Despite the substantial heterogeneity of the definitions, the current literature search showed that FI is prevalent (median prevalence 20.0%) in the PICU.

The variety of definitions used in the studies, in combination with the risk of bias of the studies describing them, precluded making even cautious conclusions on potential predictors of feeding intolerance. However, there appeared to be an association between FI and severity of illness.[17,39] Our review further showed that current literature does not provide causation in relation to feeding intolerance. No studies were identified which compared polymeric versus (semi)-elemental formulas. This is remarkable as these formulas are advised in nutritionally vulnerable patients who are unable to achieve adequate nutrition from standard oral diets.[49,50] Despite the high burden and prevalence, no studies investigated motility agents or other treatment for FI. Thus, the current literature does not provide any evidence that feeding intolerance can be influenced by feeding route, mode or the type or composition of enteral nutrition.

Considering feeding intolerance as an aggregate of symptoms of yet another organ failing during critical illness is, again taking the methodological issues into consideration, supported by a few studies which associated feeding intolerance with increased morbidity and even mortality.[13-15] Whether GI dysfunction in itself can determine outcome independent of nutrient intake is an important question. It is unclear if the impact on clinical outcome is caused by the consequences of FI as expression of organ (intestinal) failure, or if it reflects an underlying severity of illness. The studies in our systematic review that defined FI as an inability to achieve enteral target intake did not make associations with outcome. There are two large observational cohorts who have showed that enteral intake below two-third of what was prescribed during the first 10 days of admission in the PICU impaired clinical

outcome in critically ill children.[51,52] Unfortunately, these studies did not describe any GI symptoms or gave a description of feeding intolerance otherwise and where therefore not included in our systematic review.

Diverse pathophysiological pathways leading to FI might play a part in the variations in definitions and prevalence at the PICU. Both the GI morphology and function can be altered and aside from nutritional processing the intestines have other immunological, endocrine and barrier functions.[22,53,54] The aetiology of abnormal GI function in critically ill children is largely unknown, but is most likely multifactorial. GI peptides and neurohormones play an important role in the motor function and increased levels of GI peptides (CCK, PYY) have been associated with GI dysfunction .[55,56] A study in cardiac surgery patients found an association between GI symptoms as definition of feeding intolerance, and intestinal barrier function (I-FABP, citrulline, claudin 3). Plasma biomarkers reflecting the epithelial barrier function, together with pro- and anti-inflammatory cytokines, were altered in relation with severity of illness.[22] There is a high need for studies investigating the potential mechanisms of FI during critical illness and unravel the largely unknown aetiology.

A recently published narrative review discusses the need for a consistent definition of FI among the international PICU community.[57] Unfortunately, the evidence from the current paediatric literature is insufficient to provide such definition. Therefore, we want to propose a definition, which can be used for further validation (Table 6). The term feeding intolerance implies a patient who does not tolerate full enteral nutrition due to gastrointestinal symptoms. Thus, in our opinion the descriptive definition of FI should start with the inability to achieve enteral target intakes and secondly should include GI symptoms which indicate GI dysfunction according to expert clinicians and researchers. As previously reported, the evidence of insufficient enteral intake is sparse, however, an intake below two-third of target has been associated with poor clinical outcome.[51,52] Furthermore, the new SCCM-ASPEN clinical guidelines suggest to achieve an energy delivery of at least two-thirds of the prescribed daily requirement by the end of the first week in the PICU.[58] Therefore, this could be a starting point for a proposed definition. We would like to state that the GI symptoms are a direct symptom of the pathophysiological mechanism causing FI, and therefore reflect problems with gastric emptying, motility, enterocyte dysfunction and nutrient absorption or are related to intestinal inflammation or dysfunction of enteric endocrine system. Frequently described GI symptoms (≥10 times) were large GRV, abdominal distention, diarrhoea and vomiting, and these have to be considered in the definition. Also, serious adverse GI symptoms, such as intestinal ischemia and bloody stool have to be taken into account.[41] Usually no cut-off thresholds for frequency and/or volumes of symptoms were reported. Without reporting these thresholds in the definition, besides the issues with inter- and intra-observer reliability, validation will be difficult. The impact of each individual symptom is uncertain, but will probably vary between symptoms. Also, no attempts were made to report the sensitivity or specificity of the symptoms in the included

studies of our review. In our review, large GRV was often reported as one of the GI symptoms, which is comparable with the systematic review performed in adults.[47] The implications of GRV measurements in standard practice are debated. Recent studies found no association between GRV measurements and clinical outcome and current guidelines on critically ill children start to challenge the use of GRV as a marker for feeding intolerance.[59-62] Due to the previously mentioned limitations, further validation of any proposed definitions is needed in critically ill children.

Taking all these concerns into consideration, we propose the definition for enteral feeding intolerance as presented in Table 6, to be used as clinical and research tool. This definition includes the combination of the inability to achieve target intake and the presence of GI-symptoms. For this definition it is essential that EN is indicated and attempted. Additional research is needed for validation of this proposed definition, including cut-off thresholds for enteral target intake and GI symptoms. Furthermore, the impact of each individual criterion needs to be investigated.

There are several limitations of our systematic review that need to be addressed. As described before, the methodological quality of the included studies was overall moderate to poor and conclusions based on these studies need to be made with considerations. Furthermore, our systematic review might be subjected to bias, as a large proportion of our included studies were retrospective observational studies. Our primary aim was to report the most commonly used definitions of FI, and if possible, provide a universal and standard definition. Unfortunately, the evidence from the current paediatric literature is insufficient to provide such definition and we therefore proposed a definition for further validation based on expert opinion. Despite our elaborate literature search, no causal relationship could be addressed in regard with short-term or long-term effects of FI.

CONCLUSIONS

Feeding intolerance is inconsistently defined in the current literature, but appears to be a realistic and prevalent problem in critically ill children. FI is mostly defined in studies by the presence of gastrointestinal symptoms, without describing associations between predictors and outcome with FI. We would propose that a definition for FI should include the inability to achieve enteral nutrition target intakes in combination with the presence of GI symptoms indicating GI dysfunction.

Table 6. Proposed definition for enteral feeding intolerance in critically ill children in whom EN is indicated and attempted; registered over a 24h period

1)	**Insufficient enteral intake**	Defined as enteral intake two-third of prescribed daily target or EN is withheld for ≥ 48 hours or EN is not increased for ≥ 48 hours Excluding interruptions due to procedures
AND		
2)	**Presence of at least one of the following criteria**	
a	GI-symptoms	
	Large GRV	Defined as ≥ 50% of the EN delivered in the last 4 hours
	Presence of vomiting	Defines as ≥ 2 times with gastric content in 24h period
	Presence of diarrhoea	Defined as ≥ 4 times loose stool with negative fluid balance in 24h period
b	Severe GI-symptoms with concern for intestinal ischemia	- Abdominal distention - Abdominal pain - Melena - Haematochezia

Critically ill children must both fulfil the first and second criteria to be classified as feeding intolerant according to this definition.
EN, enteral nutrition; GI, gastro-intestinal; GRV: gastric residual volume

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APPENDIX

Supplement file 1. Search strategy in different databases.

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('critically ill patient'/de OR 'critical illness'/de OR 'intensive care'/de OR 'intensive care unit'/de OR 'coronary care unit'/exp OR 'medical intensive care unit'/exp OR 'neurological intensive care unit'/exp OR 'pediatric intensive care unit'/exp OR 'surgical intensive care unit'/exp OR 'artificial feeding'/de OR 'enteric feeding'/de OR 'digestive tract intubation'/exp OR 'nose feeding'/de OR 'artificial ventilation'/de OR 'digestive tube'/de OR 'enterostomy tube'/exp OR 'esophagus tube'/exp OR 'jejunostomy tube'/exp OR 'nasobiliary tube'/exp OR 'nasogastric tube'/exp OR 'stomach tube'/exp OR 'nutritional support'/de OR (((critical*) NEAR/3 (ill*)) OR (intensive* NEAR/3 care*) OR ((artificial* OR enter* OR nose OR tube OR support*) NEAR/3 (feed* OR nutrition*)) OR ((digestiv* OR duoden* OR esophag* OR oesophag* OR stomach* OR gastr* OR enterostom* OR jejunostom* OR nasobiliar* OR nasogastric* OR Nasojejun*) NEAR/3 (intubat* OR tube*)) OR picu OR icu OR ((mechanic* OR artificial* OR controlled* OR support*) NEAR/3 (respirat* OR ventilat*))):kw,ab,ti) AND ('nutritional intolerance'/de OR 'stomach emptying'/de OR 'gastric residual volume'/de OR 'caloric intake'/exp OR (((nutrition* OR food OR feeding* OR feed OR gastrointestin* OR enter*) NEAR/6 (intoleran* OR toleran*)) OR ((enter* OR tube) NEAR/3 fail*) OR ((stomach OR gastric*) NEAR/3 (empty* OR residu*)) OR ((energy OR calor* OR enteral*) NEAR/3 (intake* OR goal*))):kw,ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR pediatrics/exp OR childhood/exp OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/de OR 'child care'/exp OR 'childhood disease'/exp OR 'pediatric ward'/de OR 'pediatric hospital'/de OR 'pediatric intensive care unit'/exp OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR picu):kw,ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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(Critical Illness/ OR Critical Care/ OR Intensive Care Units/ OR Coronary Care Units/ OR Intensive Care Units, Pediatric/ OR Respiratory Care Units/ OR Nutritional Support/ OR Enteral Nutrition/ OR Intubation, Gastrointestinal/ OR Respiration, Artificial/ OR (((critical*) ADJ3 (ill*)) OR (intensive* ADJ3 care*) OR ((artificial* OR enter* OR nose OR tube OR support*) ADJ3 (feed* OR nutrition*)) OR ((digestiv* OR duoden* OR esophag* OR oesophag* OR stomach* OR gastr* OR enterostom* OR jejunostom* OR nasobiliar* OR nasogastric* OR Nasojejun*) ADJ3 (intubat* OR tube*)) OR picu OR icu OR ((mechanic* OR artificial* OR controlled* OR support*) ADJ3 (respirat* OR

ventilat*))).kw,ab,ti.) AND (Gastric Emptying/ OR Energy Intake/ OR (((nutrition* OR food OR feeding* OR feed OR gastrointestin* OR enter*) ADJ6 (intoleran* OR toleran*)) OR ((enter* OR tube) ADJ3 fail*) OR ((stomach OR gastric*) ADJ3 (empty* OR residu*)) OR ((energy OR calor* OR enteral*) ADJ3 (intake* OR goal*))).kw,ab,ti.) AND (exp Child/ OR exp Infant/ OR exp Adolescent/ OR exp "Pediatrics"/ OR "Child Nutrition Sciences"/ OR "Infant nutritional physiological phenomena"/ OR "Child Development"/ OR exp "Child Health Services"/ OR exp "Child Care"/ OR "Hospitals, Pediatric"/ OR exp "Intensive Care Units, Pediatric"/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR picu).kw,ab,ti.)

Cochrane CENTRAL

((((critical*) NEAR/3 (ill*)) OR (intensive* NEAR/3 care*) OR ((artificial* OR enter* OR nose OR tube OR support*) NEAR/3 (feed* OR nutrition*)) OR ((digestiv* OR duoden* OR esophag* OR oesophag* OR stomach* OR gastr* OR enterostom* OR jejunostom* OR nasobiliar* OR nasogastric* OR Nasojejun*) NEAR/3 (intubat* OR tube*)) OR picu OR icu OR ((mechanic* OR artificial* OR controlled* OR support*) NEAR/3 (respirat* OR ventilat*))):ab,ti) AND ((((nutrition* OR food OR feeding* OR feed OR gastrointestin* OR enter*) NEAR/6 (intoleran* OR toleran*)) OR ((enter* OR tube) NEAR/3 fail*) OR ((stomach OR gastric*) NEAR/3 (empty* OR residu*)) OR ((energy OR calor* OR enteral*) NEAR/3 (intake* OR goal*))):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR picu):ab,ti)

Web of science

TS=(((((critical*) NEAR/2 (ill*)) OR (intensive* NEAR/2 care*) OR ((artificial* OR enter* OR nose OR tube OR support*) NEAR/2 (feed* OR nutrition*)) OR ((digestiv* OR duoden* OR esophag* OR oesophag* OR stomach* OR gastr* OR enterostom* OR jejunostom* OR nasobiliar* OR nasogastric* OR Nasojejun*) NEAR/2 (intubat* OR tube*)) OR picu OR icu OR ((mechanic* OR artificial* OR controlled* OR support*) NEAR/2 (respirat* OR ventilat*)))) AND ((((nutrition* OR food OR feeding* OR feed OR gastrointestin* OR enter*) NEAR/5 (intoleran* OR toleran*)) OR ((enter* OR tube) NEAR/2 fail*) OR ((stomach OR gastric*) NEAR/2 (empty* OR residu*)) OR ((energy OR calor* OR enteral*) NEAR/2 (intake* OR goal*)))) AND ((adolescen* OR infan* OR newborn* OR (new NEAR/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR

prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR picu))) AND DT=(article) AND LA=(english)

Google scholar

"critical|critically ill|illness"|"intensive care"|"artificial|enteral|nose|tube feeding|nutrition"|"digestive|duodenal|esophageal|gastric intubation|tube" "nutrition|food|feeding|feed|gastrointestinal intolerance|tolerance" adolescents|infants|children

Table S1. Predictors associated with of feeding intolerance investigated in 14 non randomised studies

Author, year	Definition of FI	N	Population and age range	Study design	Objective	Associated predictors of FI
Haney et al., 2018 [40]	EN discontinued due to increased abdominal girth (>15 % increase), vomiting or diarrhoea (>4 stools) in a 24h period	106	Respiratory failure 37 weeks – 21 years	Retrospective, no information on EN route	Investigate the impact of early EN in patients with respiratory failure	No association with use of motility agents or degree of respiratory failure and FI FI higher in patients receiving vasoactive agents (33% vs 9%; p=0.02)
Qi et al., 2017 [21]	EN discontinued due to vomiting, GI bleeding, diarrhoea, constipation or large GRV	360	Congenital heart disease, post-surgery 1 month – 6 years	Retrospective, receiving oral, gastric or post-pyloric EN	Determine the causes of interruptions in postoperative EN in CHD patients and discuss clinical counter measures	Interruptions higher in younger patients (age 1 - 12 months vs 1 - 6 years; p=0.053)
Toms et al., 2015 [23]	Intake less than 120 ml/kg/d from continuous enteral feeds or per os feeds without interruption	50	Hypoplastic left heart syndrome GA > 35 weeks	Retrospective, receiving oral or gastric EN pre-operative vs NPO	Determine if preoperative trophic feeds can improve outcomes after Norwood palliation.	Infants with pre-operative tropic feeds achieved postoperative PO feeds 8 days sooner than NPO pre-operative group (p=0.01)
Sánchez et al., 2009 [17]	Abdominal distention, large GRV or diarrhoea	209	Mixed 3 days – 17 years	Prospective, receiving post-pyloric EN	Analyse relationship between the clinical severity at the time of starting post-pyloric EN and the onset of GI complications	- Risk of mortality and large GRV and/or abdominal distention (PRISM p=0.4; PELOD p=0.8; PIM2 p=0.5) - Risk of mortality and diarrhoea (PRISM p=0.04; PELOD p=0.06; PIM2 p=0.42)
Lopez-Herce et al., 2008* [11]	Abdominal distention, large GRV (>50% of 4h feeding volume delivered), diarrhoea or NEC	526	Mixed 21 days – 22 years	Prospective, receiving post-pyloric EN	Study risk factors for GI complications related to EN	Higher in patients with shock 30.7% vs non-shock 9.1% (p=0.004)

Sánchez et al., 2007* [12]	EN discontinued due to abdominal distensions and/or increased abdominal pressure, large GRV (>50% of 4h), diarrhoea (> 5 loose stools in 24h period), NEC	526	Mixed 3 days – 17 years	Prospective, receiving post-pyloric EN	Compared the tolerance of early (<24ht) and late post-pyloric EN	Early EN (<24h) associated with less abdominal distention (3.5%) vs late EN (7.8%) p=0.05 No association between early of late EN and diarrhoea (p=0.55), NEC or GI-bleeding
Petrillo-Albarano et al., 2006 [18]	EN discontinued due to abdominal distention, aspiration, vomiting, diarrhoea or constipation	184	Mixed	Retrospective, receiving gastric EN	Assess whether implementation of an early, aggressive, EN protocol improves time to goal feedings and results in fewer GI complications	Not significantly different after implementation of feeding protocol 30% vs 19% (p=0.10)
Lopez-Herce et al., 2006* [10]	Abdominal distention, large GRV (>50% of 4h feeding volume delivered), diarrhoea (> 5 loose stools in 24h period), NEC	526	Mixed 3 days – 17 years	Prospective, receiving post-pyloric EN	Analyse the tolerance of post-pyloric EN in children with renal failure compared with other critically ill children	Higher in patients with acute renal failure 24.5% vs 9.9% (p=0.01)
Sánchez et al., 2006* [8]	EN discontinued due to abdominal distention, severe diarrhoea, NEC or large GRV (>50% of 4h feeding volume delivered)	350	Post-cardiac surgery vs mixed 3 days – 17 years	Prospective, receiving post-pyloric EN	Assess the utility of post-pyloric EN after cardiac surgery	No difference between post cardiac surgery and mixed patients (NS)
Hanekamp et al., 2005 [19]	EN discontinued due to gastric retention, bilious vomiting, aspiration, NEC-related symptoms, such as blood-stained stool, abdominal distention or number of positive blood cultures during ECMO	67	Term neonates with VA-ECMO	Retrospective, receiving gastric EN or post-pyloric EN	Evaluate over a 5-yr period the feasibility and tolerance of a protocol of routine EN in neonates requiring ECMO	No association between Apgar scores, gestational age, time to beginning of enteral nutrition, vasoactive drugs, morphine dosage, and type of feeding tube and FI (p=0.63)

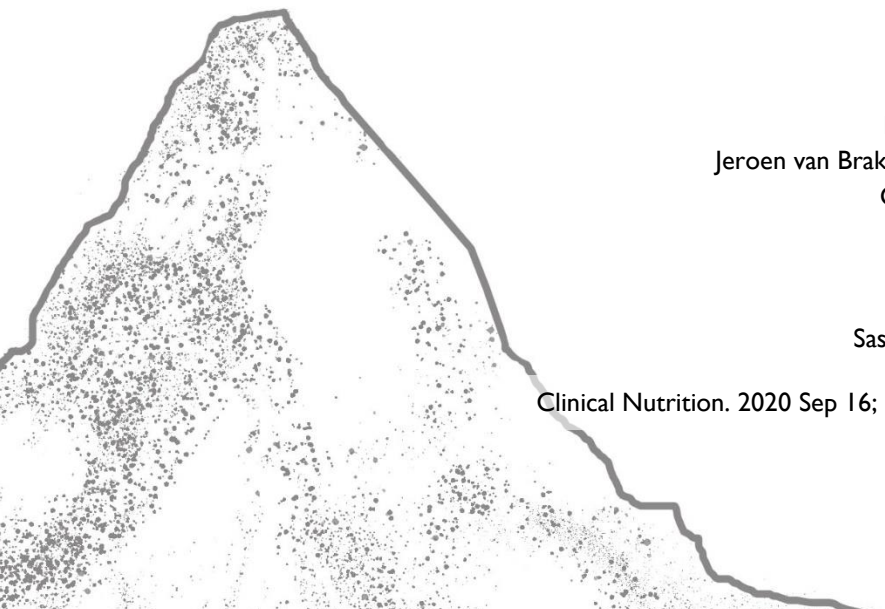
Sánchez et al., 2005* [9]	EN discontinued due to abdominal distensions, large GRV (>50% of 4h feeding volume delivered), diarrhoea or NEC	42	Mixed 2.5 months – 15 years	Prospective, receiving post-pyloric EN	Analyse anthropometric and biochemical nutritional status and evaluate the short-term effects of EN	No association between FI and anthropometric or biochemical parameters
Rogers et al., 2003 [32]	Large GRV (100-150% of 4h feeding volume delivered), vomiting, abdominal distention or diarrhoea	42	Cardiac vs mixed 0 - 198 months	Prospective, receiving EN, not specified	Asses adequacy of nutrition support and identify barriers impeding the delivery of estimated energy requirement	Higher in patients with cardiac diagnosis 57.1% vs non-cardiac diagnosis 38.9% (p=0.04)
Mayer et al., 2002 [39]	Large GRV (> 125% of 4h feeding volume delivered)	23	Mixed 1 month – 16 years	Prospective interventional, receiving gastric EN	Determine the relationship between amylin levels and gastric emptying	Higher risk of mortality score in FI patients 21% vs 6.6% (p=0.006) Higher serum amylin concentration in FI patients (47.0 pmol/l vs 22.7 pmol/l, p<0.0001)
Panadero et al., 1998* [13]	Vomiting, abdominal distension, large GRV, diarrhoea, pulmonary aspiration	41	Mixed 8 days – 12 years	Prospective, receiving post-pyloric EN	Analyse the utility and complications of post-pyloric EN	Higher in post-surgery patients 33% vs 0% (P<0.001). Age, diagnosis, type of formula, medication not significant

* Studies are secondary analysis of previous published studies with possible overlay in population.

ECMO, extracorporeal membrane oxygenation; EN, Enteral nutrition; FI, Feeding Intolerance; GA, gestational age; GI, gastro-intestinal; GRV, gastric residual volume; NEC, necrotising enterocolitis; NPO, Nil per os; PE, protein and energy enriched; RCT, randomised controlled trial

CHAPTER 5

ACHIEVING ENTERAL NUTRITION DURING THE ACUTE PHASE IN CRITICALLY ILL CHILDREN: ASSOCIATIONS WITH PATIENT CHARACTERISTICS AND CLINICAL OUTCOME



Renate D. Eveleens
Jessie M. Hulst
Barbara A.E. de Koning
Jeroen van Brakel, Dimitris Rizopoulos
Gonzalo Garcia Guerra
Ilse Vanhorebeek
Greet van den Berghe
Koen F.M. Joosten
Sascha C.A.T. Verbruggen

Clinical Nutrition. 2020 Sep 16; S0261-5614(20)30461-1

ABSTRACT

Background & aims: In the absence of methodologically sound randomised controlled trials (RCTs), current recommendations for timing and amount of enteral nutrition (EN) in critically ill children are based on observational studies. These studies have associated achievement of a higher EN intake in critically ill children with improved outcome. Inherent to the observational design of these underlying studies, thorough insight in possible confounding factors to correct for is essential. We evaluated the associations between EN intake and 1) patient and daily clinical characteristics and 2) clinical outcomes adjusted for these patient and clinical characteristics during the first week of critical illness with a multivariable mixed model.

Methods: This secondary analysis of the multicentre PEPaNIC RCT investigated a subgroup of critically ill children with daily prospectively recorded gastrointestinal symptoms and EN intake during the first week with multivariable analyses using two-part mixed effect models, including multiple testing corrections using Holm's method. These models combined a mixed-effects logistic regression for the dichotomous outcome EN versus no EN, and a linear mixed-effects model for the patients who received any EN intake. EN intake per patient was expressed as mean daily EN as % of predicted resting energy expenditure (% of EN/REE). Model 1 included 40 fixed effect baseline patient characteristics, and daily parameters of illness severity, feeding, medication and gastrointestinal symptoms. Model 2 included these patient and daily variables as well as clinical outcomes.

Results: Complete data were available for 690 children. EN was provided in 503 (73%) patients with a start after a median of 2 (IQR 2-3) days and a median % of EN/REE of 38.8 (IQR 14.1-79.5) over the first week. Multivariable mixed model analyses including all patients showed that admission after gastrointestinal surgery (-49%EN/REE; p=0.002), gastric feeding (-31% EN/REE; p<0.001), treatment with inotropic agents (-22%EN/REE; p=0.026) and large gastric residual volume (-64%EN/REE; p<0.001) were independently associated with a low mean EN intake. In univariable analysis, low mean EN intake was associated with new acquired infections, hypoglycaemia, duration of PICU and hospital stay and duration of mechanical ventilation. However, after adjustment for confounders, these associations were no longer present, except for low EN and hypoglycaemia (-39%EN/REE; p=0.018).

Conclusions: Several patient and clinical characteristics during the first week of critical illness were associated with EN intake. No independent associations were found between EN intake and clinical outcomes such as mortality, new acquired infection and duration of stay. These data emphasise the necessity of adequate multivariable adjustment in nutritional support research and the need for future RCTs investigating optimal EN intake.

INTRODUCTION

Critically ill children are vulnerable to become undernourished, which has been associated with increased mortality, prolonged hospital stay, as well as neurological and psychological development disorders.[1-4] However, feeding a critically ill child is a challenge and nutritional targets are often not achieved.[1-3] Different studies in various paediatric intensive care unit (PICU) settings have shown that the actual delivery of enteral nutrition (EN) is usually much less (40–75%) than is prescribed and reported barriers are the lack of feeding protocols, fluid restriction and stopping EN in anticipation of procedures.[1,5,6] One of the main factors for not reaching caloric goals is (presumed) intolerance to EN, where intolerance itself is also associated with adverse outcomes.[1,7] We recently performed a systematic review to seek the definition of feeding intolerance in critically ill children.[8] Unfortunately, feeding intolerance was highly inconsistently defined throughout the literature and most often based upon a wide variety of gastrointestinal symptoms. This inconsistency precludes any firm conclusions on its prevalence, predictors and outcomes and its relationship with enteral intake.

Despite the recognised difficulties to feed, current paediatric critical care guidelines agree to start EN early (<24–48 h) and to target caloric goals between 67% and 100% of Resting Energy Expenditure (REE) at the end of the first week.[9,10,11] In the absence of methodologically sound randomised controlled trials (RCTs) these recommendations for timing and amount of EN in critically ill children are based upon large observational studies which showed associations between early achievement of nutritional goals and improved outcome.[9,12-15] However, the observational design of these studies calls for cautiousness in assuming a causal relationship between higher EN intake and improved outcomes, as children who tolerate EN might be less critically ill and inherently have a better outcome. Up to now, observational nutritional studies commonly interpreted associations with outcomes from univariable analyses or with limited adjustments for confounders.[9,12-15] No RCTs are currently scheduled to investigate the impact of achieving enteral intake targets with clinical outcome in a paediatric intensive care setting.[16] Multivariable adjustment with relevant confounding factors is deemed imperative for interpreting observational studies with clinical outcome based on the hypotheses that predictors, clinical outcomes and EN intake are correlated. Therefore, we aimed to first explore the patient and clinical characteristics independently associated with amount of EN achieved during the first week of PICU admission, followed by an investigation of the associations between EN intake and clinical outcomes with multivariable mixed models.

METHODS

Subjects

For this study we included a subgroup of critically ill children who participated in the multicentre PEPaNIC RCT (University Hospital KU Leuven, Leuven, Belguim; Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands; Stollery Children's Hospital, Edmonton, Canada; ClinicalTrials.gov: NCT01536275), and for whom gastrointestinal symptoms and EN intake were recorded daily during the first week. The method and outcomes of the PEPaNIC RCT have been published previously.[1718] In brief, the PEPaNIC RCT was a multicentre trial involving 1440 critically ill children (term - 17 years) investigating short- and long-term outcome of late parenteral nutrition (PN) (initiation after one week) as compared with early PN to complete insufficient EN (initiation within 24 h).[17,18] The 723 patients assigned to the early PN group received PN within the first 24 h after PICU admission according to the local standard care. For the 717 patients in the late PN group, PN was withheld for the first 7 days. If at day 8 the required caloric goal was not reached, supplemental PN was started. In both groups EN was provided according to local protocol with an intended start 6 h after admission if possible. All children received micronutrients intravenously until the amount of EN provided was above 80% of the caloric target. The institutional ethical review boards of the participating centres approved the study and written informed consent was obtained from the parents or legal guardians (Belgium: ML8052; The Netherlands: NL38772.000.12; and Canada Pro00038098). Children with inborn metabolic diseases requiring specific diets or patients with short bowel syndrome or other medical condition requiring home PN for over 7 days prior to admission were excluded in the PEPaNIC RCT.

Nutritional protocol

The local EN protocol, including caloric goal achievement, differed per research centre. The initiation and incline of EN, the type and methods, as well as the use of gastroprokinetics were prescribed via standing orders in each centre and prospectively collected in the study database for each patient.[17] Nutritional and fluid practises of the three research centres which were valid during the PEPaNIC trial is presented in the appendix.

In Leuven, Belgium, enteral intake was assessed based upon fluid allowance. For patients who required fluid restriction, total fluid intake was 50 ml/m2/h on days 1 and 2 and 60 ml/m2/h on day 3, corresponding generally with an enteral intake of 50 kcal/m2/h and 60 kcal/m2/h, respectively. Patients not requiring fluid restriction received 100 kcal/kg/d for the first 10 kg bodyweight, 50 kcal/kg/d for the next 10 kg, and 20 kcal/kg/d for the bodyweight > 20 kg. Gastric feeding was considered first choice and provided continuously over 10 h including a 2 h rest in children and via slow bolus in infants.

In Rotterdam, The Netherlands, the energy goals for EN were based on the body weight and calculated with the Schofield equation[19] for the first day of admission and on the Recommended Dietary Allowances (Dutch Health Council) for the remaining duration of admission.[20] This translated to up to 2 times predicted resting energy expenditure (REE) in neonates to 1.5 times REE in adolescents. In patients who required fluid restriction or who were intubated, a protein and energy enriched formula or human milk was started as first choice and provided via post-pyloric tube and in non-ventilated patients standard formula was indicated.

In Edmonton, Canada, energy expenditure of patients was assessed by indirect calorimetry upon admission to the PICU when possible, and used for estimating patient specific caloric goals for the first day of admission. If indirect calorimetry measurement was not possible, the prescribed caloric goal was set on 65% of basal metabolic rate estimated by the equation of the Food and Agriculture Organisation – World Health Organisation.[21] For the subsequent days, caloric goals were assessed daily by a dietitian based on clinical information and acute phase response. In general, the caloric goal was 65% of Basal Metabolic Rate (BMR) when the patient was intubated, BMR when patient has been extubated and Total Energy Expenditure (REE adjusted for activity) when the patient had been extubated and ambulatory. Furthermore, type of feeding and location of feeding tube was prescribed at the discretion of the dietician and local protocol; common practise was to prescribe feeding via post-pyloric tube, especially in hemodynamic unstable patients and patient receiving (non-invasive) ventilatory support.

Each centre aimed to reach the caloric target from day 2 onwards via EN. When EN was below 80% of the target, supplemental PN was provided to reach the local goal in the early PN group. Initiation and incline of EN was based on the discretion of the clinical team in both study groups and (supplemental) PN was prescribed by the study team to reach the daily caloric goal in the early PN group only.

Data collection

Data on patient characteristics and gastrointestinal symptoms were prospectively collected and registered in the PEPaNIC RCT database. Characteristics investigated were demographics (early PN randomisation, age, sex, weight or BMI Z-score (defined as weight-for-age Z-score in children <1 year old and BMI-for-age Z-score in children ≥1 year old, as described previously[4]), emergency admission, diagnosis upon admission, centre, STRONGkids, PeLOD score (Paediatric Logistic Organ Dysfunction score), PIM 3 (Paediatric Index of Mortality) and Paediatric Risk of Mortality III (PRISM) score). Prior medical conditions and co-morbidities upon admission were also extracted (syndrome or genetic abnormality, malignancy, chronic disease, mechanical ventilatory or hemodynamic support and infection upon admission). At each day of admission, the nutritional intake, including initiation of EN and the total caloric and protein intake through enteral and

parenteral route were recorded. Daily gastrointestinal symptoms recorded were vomiting or aspiration (yes/no), abdominal distension (yes/no), diarrhoea (≥4 times loose stool; defined watery or mushy) and large gastric residual volume (GRV; ≥50% of delivered EN over 24 h). Furthermore, clinical and feeding characteristics and treatment with 12 different medications were also collected daily. Clinical outcomes investigated were mortality, duration of PICU stay, duration of hospital stay, duration of mechanical ventilation, new acquired infections and incidence of hypoglycaemia (plasma glucose <40 mg/dl) during the first 7 days of admission. A complete list of investigated parameters is presented in the apendix.

The current study investigated the enteral intake in association with baseline patient characteristics and daily clinical and feeding characteristics, gastrointestinal symptoms, medication and clinical outcome. The randomisation of the primary study was only addressed as a covariate. For this secondary analysis, the subgroup of critically ill children with complete daily recorded gastrointestinal symptoms and EN intake during the first week was included. In order to account for differences in caloric goals across the centres, a general benchmark for the quantification of enteral intake was used for all patients, i.e. enteral intake from EN as % of predicted REE based on Schofield formula according to age and weight [16]. Mean daily EN as % of predicted REE (% EN/REE) was calculated for each patient for the duration of his or her stay.

Statistical analyses

Characteristics were described as numbers and percentages for categorical variables or as mean and standard deviation (SD, if normally distributed) or as median and interquartile range (IQR, if not normally distributed) for continuous variables. To account for the correlations in the repeated measurements of enteral intake for each child, a mixed-effects model has been used. Due to the fact that many patients had zero enteral nutrition intake, the specific model was specified into a two-part mixed model. This combines a mixed-effects logistic regression for the dichotomous outcome zero or positive enteral intake, and a linear mixed-effects model for the natural logarithm of only the positive EN intake measurements. For both models the random-effects structure was random intercepts.

For the univariable associations, the main effect of the follow-up time variable was included in the model together with clinical outcome variables. For the multivariable association, in the fixed effects of the linear mixed model we included the main effect of the follow-up time variable, as well as baseline patient characteristics (including PICU site and early PN randomisation), daily admission-level clinical characteristics, feeding characteristics, gastrointestinal symptoms and treatment with medication. A second model included all fixed effect baseline and daily clinical variables and the clinical outcome variable of interest. The duration of stay and duration of mechanical ventilation variables were penalised for mortality as a competitive risk. Data on EN intake and gastrointestinal symptoms needed to be

complete, however, multiple imputation has been used to impute missing covariate information using 30 imputed datasets.[22-24] Each imputed dataset has been separately analysed using the two-part mixed model, and the results were pooled using the formulas of multiple imputation. The fit of the model was assessed using scaled simulated residuals. No variable selection has been performed and all models. We hypothesised that patients admitted after gastrointestinal surgery had a different a priori feeding strategy, where EN would be withheld based on the discretion of the surgeons rather than EN intolerance or PICU related reasons. Therefore, sensitivity analyses were performed excluding this patient group (n=100).

The reported coefficients, the corresponding 95% confidence intervals and p-values are for the marginalised mean of EN intake. The marginalised mean is the sum of possible values of one variable to determine the contribution of another variable. Correction for multiple testing was performed using Holm's method.[25] The exponent of the coefficients is in the original scale of the main outcome, thus % EN compared to REE. Hence, the exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. For example, if the exponent of the coefficient for age is 0.98 it means that the average main outcome is decreased by 2% EN/REE for every unit increase of age. The reported 95% confidence intervals are for the exponentiated coefficients. These confidence intervals are not corrected for multiple testing. The mixed model analysis has been performed in R (version 3.6.2) using packages GLMMadaptive, mice, mitools, and DHARMa.

RESULTS

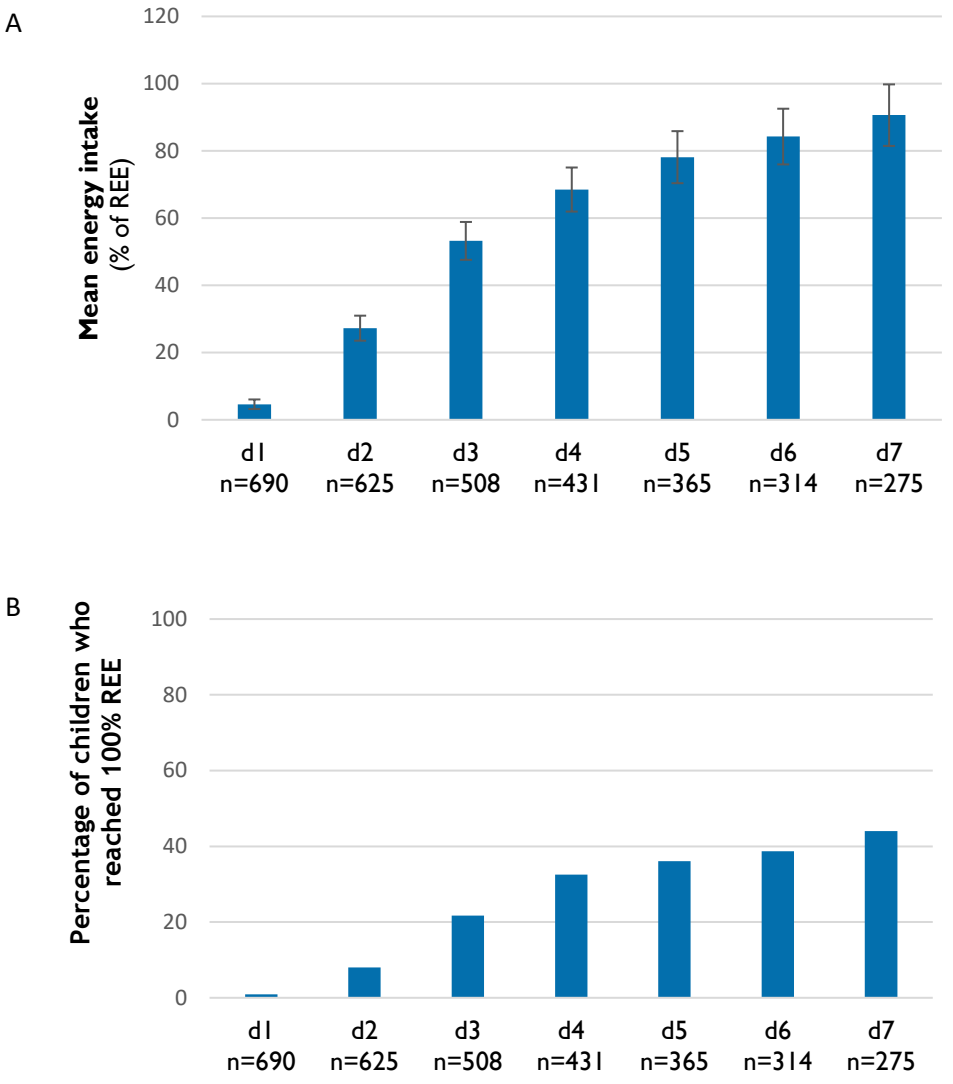
Of the total PEPaNIC patient population, 690 patients (58.1% male; 50.7% surgical diagnosis) had a complete recording of gastrointestinal symptoms and nutritional assessment during the first 7 days of admission or until discharge if discharge < 7 days and were included in the analyses. Table 1 presents the baseline patient characteristics. The median age was 1.2 (IQR: 0.1–6.5) year, mean PIM3 score was −2.9 (±1.9) and 76% of the patients had an emergency admission. Nutritional risk, assessed by STRONGkids, was high in 16.4% of patients and medium in 83.6%, whereas the median weight Z-score was −0.5 (IQR: −1.7 to 0.4), with a weight Z-score < -2 in 137 (19.8%) patients. A total of 50.7% was randomised to Early PN, with no differences between baseline patient characteristics (data not shown). Enteral intake and gastro-intestinal symptoms were collected on a total of 3208 admission days (median of 5 (IQR 2–7) days per patient). The presence of at least one gastrointestinal symptom occurred on 631 (19.7%) days, with vomiting or aspiration being the most recorded (7.9%) symptoms followed by diarrhoea (7.4%), large GRV (4.1%) and abdominal distention (2.8%).

Table 1. Baseline characteristics of the 690 critically ill children included in the present study

Characteristics upon PICU admission	**N=690**
Early PN randomisation	350 (50.7%)
Age, y, median (IQR),	1.2 (0.1 - 6.5)
Infant (age<1y)	339 (49.1%)
Male sex	401 (58.1%)
Weight or BMI Z-score, median (IQR)[d]	-0.7 (± 1.8)
Acute undernourished	59 (9.1%)
Severe acute undernourished	70 (10.8%)
Emergency admission	535 (77.5%)
Diagnostic group	
Surgical	
Gastrointestinal	100 (14.5%)
Cardiac	111 (16.1%)
Neurosurgery-Traumatic brain injury	54 (7.8%)
Other	85 (12.3%)
Medical	
Cardiac	45 (6.5%)
Neurologic	64 (9.3%)
Respiratory	161 (23.3%)
Other	70 (10.1%)
STRONGkids risk level[a]	
Medium	577 (83.6%)
High	113 (16.4%)
PeLOD score, first 24h in PICU, median (IQR)[b]	12 (2 - 21)
PIM3 score, mean (SD)[c]	-2.9 (1.9)
PRISM III (IQR)	8 (5 - 14)
Malignancy	44 (6.4%)
Confirmed syndrome or genetic abnormality	75 (10.9%)
Suspected syndrome or genetic abnormality	29 (4.2%)
Chronic disease	474 (68.7%)
Infection upon PICU admission	368 (53.3%)
Mechanical ventilatory support upon PICU admission	592 (85.8%)
Mechanical hemodynamic support on PICU admission	32 (4.6%)

Data are n (%), median (IQR) or mean (SD). [a] (STRONGkids scores range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk. [b] Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness. [c] Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality. [d] weight of BMI Z-score was defined as weight-for-age Z-score in children <1 year old and BMI-for-age Z-score in children ≥1 year old, acute under-nourished was defined as z-score between ≥ -3 and < −2, severely acute undernourished was defined as z- score less than −3 (<1 year) or body mass index-for-age z score less than −3 (if aged≥ 1 year). BMI, body mass index; : IQR, interquartile range; PeLOD, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3, paediatric index of mortality 3 score; PN, parenteral nutrition; PRISM Paediatric Risk of Mortality III; SD, standard deviation; STRONGkids, Screening Tool for Risk on Nutritional Status and Growth

Figure 1. Mean daily enteral energy intake as % of predicted resting energy expenditure of crtically ill children during the first week of PICU admission



A. Daily mean enteral energy intake (expressed as % of predicted resting energy expenditure (REE)) of critically ill children during first week of paediatric intensive care unit (PICU) admission. Bars represent the mean and the whiskers represent the 95% confidence interval (CI); B. Percentage of critically ill children who reached a daily mean enteral energy intake (expressed as % of predicted REE) of 100% during first week of PICU admission. Bars represent the percentage of children who reached 100% REE.

The mean daily EN as % of predicted REE provided during the first week of PICU admission is presented in Figure 1a. EN was provided in 503 (72.9%) patients with an overall median intake/day of 4.9 (IQR: 0.0–39.2) kcal/kg/d (Appendix). Reasons for not receiving EN were short admission duration ≤2 days (45%), gastrointestinal surgery (21%), gastrointestinal surgery and short admission stay (≤2 days) (17%), and other reasons (17%). In 314 (45.5%) patients EN was initiated within 48 h. The median daily enteral intake as % of predicted REE was 10.9% [IQR:0.0–84.0] and 28.3% [IQR 0.0–100.9] for the whole group (n=690) and the group of patients that had EN provided (n=503), respectively. A total of 139/425 (32.3%) and 120/275 (43.6%) patients achieved at least 100% of predicted REE via EN on day 4 and on day 7 respectively (Figure 1b). A total of 197/503 (39.2%) patients received enteral feeding via a post-pyloric tube. Mixed model analyses showed a mean EN/REE increase of 21.3% (95%CI 18.8; 23.8%; p<0.001) per day of admission for all patients.

Predictors for EN intake

Table 2 presents the multivariable associations between baseline patient characteristics and daily parameters with daily mean enteral energy intake as percentage of predicted REE of critically ill children during the first week of PICU admission. Mixed model analyses including all patients showed that 15 predictors were independently associated with the amount of EN intake. Early PN randomisation had no effect on the EN intake (p=0.418). After correction for multiple testing, 5 predictors remained significantly associated with EN intake. Mean enteral intake was 30.9% (95%CI -16.5; −47.0%) EN/REE lower with gastric feeding as compared with post-pyloric feeding (p<0.001), and 21.5% (95% CI -31.6; −9.9%) EN/REE lower in children when treated with inotropic agents as compared with no inotropic support (p<0.001). Patients admitted after gastrointestinal surgery and patients admitted to the centre Edmonton had 48.9% (95%CI -63.1; −29.3%, p<0.001) and 36.6% (95%CI -48.4; −22.2%, p<0.001) EN/REE lower intake respectively. Of the analysed daily recorded gastrointestinal symptoms, after correction for multiple testing, only large GRV was significantly associated with 64.4% lower enteral intake EN/REE (p<0.001). Sensitivity analyses, which excluded patients admitted after gastrointestinal surgery, did not result in different results (Appendix).

EN intake and outcomes

Of the 690 patients, 44 (6.4%) died during PICU admission and 90-day mortality was 52 (7.5%). Median duration of PICU stay was 5 (IQR 2–10) days, median duration of hospital stay was 13 (IQR 6–25) days and median duration of mechanical ventilation was 3 (IQR 2–7) days. Hypoglycaemia occurred in 23 (3.3%) patients during the first 7 days of PICU admission and 123 (17.8%) had a new acquired infection.

Table 2. Multivariable associations between baseline patient characteristics and daily parameters with daily mean enteral energy intake as percentage of predicted resting energy expenditure of critically ill children during first week of admission

	Coefficient[4]	% EN/REE	95% CI	p-value[5]
(Intercept)	2.961			<0.001
Baseline characteristics				
Randomisation to late vs early initiation of PN	0.043	+4.4%	-6.0; +16.0%	0.418
Day of admission	0.190	+21.0%	+18.2; +23.8%	<0.001*
Age in years	-0.018	-1.8%	-3.1; -0.7%	0.010
Female vs male sex	0.078	+8.1%	-2.6; +20.0%	0.145
Malnourishment[1] (as compared with normal)				
Acute malnourished	0.147	+15.8%	-2.4; +37.5%	0.093
Severe acute malnourished	0.165	+17.9%	-2.2; +40.6%	0.067
Urgent vs elective admission	-0.143	-13.3%	-28.8; +5.6%	0.156
Diagnostic category (as compared with cardiac surgery)				
Surgical - Neurosurgery	0.169	+18.4%	-12.8; +60.9%	0.279
Surgical - Gastrointestinal	-0.672	-48.9%	-63.1; -29.3%	<0.001*
Surgical - Other	-0.044	-4.3%	-22.5; +18.1%	0.680
Medical - Cardiac	0.069	+7.2%	-16.8; +38.1%	0.592
Medical - Neurologic	0.371	+45.0%	+10.3; +90.7%	0.008
Medical - Respiratory	0.328	+38.8%	+9.7; +75.7%	0.006
Medical - Other	0.114	+12.0%	-16.5; +50.3%	0.448
Centre Edmonton vs Rotterdam	-0.456	-36.6%	-48.4; -22.2%	<0.001*
STRONGkids score high risk vs medium risk	0.179	+19.6%	+2.7; +39.2%	0.021
PIM3 score (per point added)	-0.071	-6.8%	-10.9; -2.6%	0.002
PRISM score (per point added)	-0.000	+0.0%	-1.0; +1.0%	0.925
Malignancy vs no malignancy	-0.027	-2.7%	-24.3; +25.0%	0.831
Syndrome or genetic abnormality vs no syndrome	0.148	+15.9%	-2.2; +37.4%	0.088
Suspicion or genetic abnormality for syndrome vs no syndrome	-0.019	-1.9%	-21.6; +22.7%	0.865
Chronic disease vs no chronic disease	0.010	+1.0%	-11.9; +15.8%	0.883
Admitted with infection	-0.047	-4.6%	-17.4%; +10.2%	0.522

Admitted with mechanical ventilation support	0.222	+24.9%	+2.0%; +52.9%	0.032
Admitted with hemodynamic support	-0.185	-16.9%	-36.5%; +8.8%	0.178
Daily clinical characteristics				
PeLOD score (per point added)	-0.007	-0.7%	-1.2%; -0.3%	0.002
Maximum CRP in mg/L (per point added)	-0.000	+0.0%	-0.1%; +0.0%	0.150
Maximum WBC in 10^9/L (per point added)	-0.005	-0.5%	-1.0%; +0.0%	0.044
Maximum Lactate in mmol/L(per point added)	-0.001	-0.1%	-2.3%; +2.1%	0.909
Daily feeding characteristics				
Location Tube (as compared with nasogastric tube)				
post-pyloric tube	0.269	+30.9%	+16.5;+47.0%	<0.001*
No tube	-0.175	-16.1%	-35.6; +9.9%	0.202
Main type of feeding (as compared with no Standard formula)				
Human Milk	0.012	+01.2%	-12.3; +16.8%	0.866
Energy enriched formula	0.220	+24.6%	+7.7; +44.2%	0.003
Peptide formula	0.287	+33.2%	+5.5; +68.3%	0.016
Oral intake	-0.249	-22.0%	-37.7; -2.5%	0.029
No formula	-1.284	-72.3%	-84.9; -49.3%	<0.001*
Daily gastro-intestinal symptoms				
Large Gastric residual volume[2] (>50% of EN intake)	-1.032	-64.4%	-71.7; -55.2%	<0.001*
Presence of diarrhoea[3]	0.096	+10.1%	-8.3; +32.1%	0.302
Presence of vomit and/or aspiration	0.124	+13.2%	-10.2; +42.7%	0.293
Presence of abdominal distention	-0.314	-27.0%	-48.7; +3.9%	0.081
Presence of ≥ EN intolerance parameter	-0.053	-5.2%	0.784; +14.7%	0.584
Daily treatment with medication				
Treatment with anti-emetics	-0.119	-11.2%	-24.3; +4.2%	0.144
Treatment with oral laxation	0.175	+19.1%	+4.9; +35.3%	0.007
Treatment with acid suppression	-0.057	-5.5%	-15.4; +5.5%	0.313
Treatment with rectal enema	0.086	+8.9%	-7.2; +27.8%	0.294
Treatment with corticosteroids	-0.084	-8.0%	-17.9; +3.0%	0.147
Treatment with antibiotics	-0.114	-10.8%	-20.2; -0.3%	0.045

Treatment with benzodiazepines	-0.110	-10.4%	-19.6; -0.2%	0.045
Treatment with opiates	-0.097	-9.2%	-18.5; +1.2%	0.081
Treatment with vasopressors	-0.217	-19.5%	-30.6; -6.7%	0.004
Treatment with inotropic agents	-0.242	-21.5%	-31.6; -9.9%	<0.001*
Treatment with hypnotics and/or barbiturates	-0.005	-0.5%	-9.9; +9.8%	0.922
Treatment with Alpha-2 antagonist	-0.055	-5.3%	-18.2; +9.6%	0.465

[1]Children younger than 1 year: weight-for-age Z-score; children 1 year or older: body mass index–for-age Z-score; [2] Large gastric residual volume was defined as volume in ml more than 50% of prescribed EN feeding per 24 hours; [3]Diarrhoea was defined as four or more loose stools per 24 hours [4]The reported coefficients, and the corresponding 95% confidence intervals and p-values are for the marginalised mean of enteral nutrition intake. The exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. Hence, an exponent of the coefficients of 0.90 reflect an 10% lower mean enteral intake expressed as a % Of REE. [5.] *Statistically significant after correction for multiple comparisons using Holms method.

CRP, C-reactive protein; EN, enteral nutrition; GRV, gastric residual volume; PeLOD, Paediatric Logistic Organ Dysfunction; PIM, paediatric index of mortality; PN, parenteral nutrition; PRISM, Paediatric Risk of Mortality; REE, resting energy expenditure; WBC, white blood count

Table 3. Multivariable association between mean daily enteral energy intake as % of predicted REE and clinical outcomes during the first week of admission to the paediatric intensive care unit corrected adjusted for baseline and daily clinical parameters

	Coefficient[1]	% EN/REE	95% CI	p-value[2]
Clinical outcomes				
New acquired infection vs no infection	-0.031	-3.1%	-15.4; +11.1%	0.652
Hypoglycaemia <40mg/dl within the first 7 days of admission vs no hypoglycaemia	-0.494	-39.0%	-53.5; -19.9%	<0.001*
Duration of PICU stay (per day)	0.000	+0.0%	-0.2; +0.3%	0.687
Duration of hospital stay (per day)	-0.001	-0.1%	-0.2; +0.1%	0.331
Duration of mechanical ventilation (per day)	0.000	+0.0%	-0.2; +0.3%	0.729
First week non-survivor vs survivor	0.160	+17.3%	-23.4; +79.7%	0.462
PICU non-survivor vs survivor	0.218	+24.3%	-3.3; +59.9%	0.090
Hospital non-survivor vs survivor	0.159	+17.2%	-6.8; +47.4%	0.175
90 day non-survivor vs survivor	0.104	+11.0%	-12.7; +41.1%	0.395

[1]The reported coefficients, and the corresponding 95% confidence intervals and p-values are for the marginalised mean of enteral nutrition intake. The exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. Hence, an exponent of the coefficients of 0.90 reflect a 10% lower mean enteral intake expressed as a % of REE. [2] *Statistically significant after adjusting for multiple comparisons using Holms method. Appendix presents the complete list of included baseline and daily parameters for multivariate correction

PICU, paediatric intensive care unit. REE, Resting energy expenditure

Univariable associations between mean daily enteral intake as % of predicted REE during the first week and clinical outcomes showed that low EN intake was associated with new acquired infection ($p<0.001$), incidence of hypoglycaemia ($P<0.001$), duration of PICU stay ($p=0.017$), duration of hospital stay ($p<0.001$) and duration of mechanical ventilation ($p=0.024$). EN was not associated with mortality on any of the time-points (Appendix). However, after multivariable adjustment for confounders and multiple testing, the mixed model analyses did not show any significant associations between lower mean EN intake and duration of PICU or hospital stay, duration of mechanical ventilation or new acquired infection. Patients with an episode of hypoglycaemia during the first 7 days of admission had a 39% lower EN/REE intake as compared with children without hypoglycaemia ($p<0.001$) (Table 3). Sensitivity analyses, which excluded patients admitted after gastrointestinal surgery, did not result in different results (Appendix).

DISCUSSION

Our study reported possible predictors and outcomes associated with higher achievement of enteral nutrition during the first week of paediatric critical illness. Multivariable mixed model analyses showed that five clinical characteristics, i.e. admission after gastrointestinal surgery, centre, gastric tube feeding, receiving treatment with inotropic agents, and large GRV, were independently and negatively associated with lower enteral intake. Regarding outcomes, low EN during the first week was univariably associated with new acquired infection, hypoglycaemia, duration of PICU and hospital stay and duration of mechanical ventilation. However, after adjustment for confounders and multiple testing, these associations were no longer present, except for the risk of developing hypoglycaemia. Hence, these findings emphasise the necessity of adequate multivariable adjustment for confounders in observational nutritional support studies to avoid premature or even inaccurate conclusions.

Predictors

Whereas, five independent predictors for lower EN intake were recognised, the lack of relevance of higher EN achievement to clinical outcomes puts these predictors into perspective. Nonetheless, feeding provided via post-pyloric tube was associated with higher enteral intake as compared with gastric feeding. Current paediatric critical care guidelines advise gastric feeding as first choice and suggest to administer feeding via post-pyloric route on indication in children with signs of intolerance or high risk for aspiration.[10] However, despite the lack of studies investigating EN feeding route in relation to clinical outcomes, one small RCT involving 62 critically ill ventilated children found a 17% lower intake with gastric feeding,[26] whereas another small RCT involving 44 children found delayed EN initiation.[27] The associations found in our study might indicate that post-pyloric feeding could increase EN intake in patients who are a priori identified at risk for low enteral intake.

Furthermore, large GRV (defined as > 50% of delivered EN) was independently associated with lower mean enteral intake. In contradiction, abdominal distention, vomiting and/or aspiration and diarrhoea were not independently associated with mean enteral intake. Low EN is often a consequence of (perceived) feeding intolerance in critically ill children which is most often described by the presence of a combination of gastrointestinal symptoms, such as large GRV, diarrhoea, vomiting and abdominal distention.[8] No previous studies have explored the effect of individual parameters of feeding intolerance other than large GRV, such as abdominal distention, vomiting or diarrhoea on inadequate enteral intake. Studies on (routine) GRV measurements have shown inconsistent associations between GRV and enteral intake in critically ill children, possibly related to the small number of subjects within these studies].[28-30] GRV appears to influence bed-site decision making around initiating and withholding of EN and is the most commonly reported gastrointestinal symptom for (perceived) feeding intolerance .[31] The necessity of GRV measurements are complicated by the lack of standardization for large GRV to define intolerance as well as by differences in measurement technique that are also affected by post-pyloric versus gastric feeding policies and patients posture.[26,32] Furthermore, recent studies found no association between large GRV and clinical outcomes, and as a result, the current guidelines challenged the use of routine GRV as a sign for feeding intolerance.[9,33,34] Studies in critically ill adults report similar inconsistencies and the adult guidelines advise not to use GRV measurement for bed side decisions.[35] Nonetheless, large GRV is still reported as a major factor for not initiating or increasing EN in current studies and it is also the most important gastrointestinal symptom of influence in our population.[8,36]

Receiving vasopressors or inotropic agents was associated with a lower mean enteral intake, which is in agreement with previous observational studies.[37] However, a retrospective study investigating safety of EN while receiving vasoactive agents found no difference in the presence of gastrointestinal symptoms between children with and without EN.[38] The current recommendations state that EN is feasible in hemodynamically stable children and neonates with inotropic support. In our study we were not able to subdivide patients into stable on inotropic or vasopressor medication and patients with escalating support.

The gut serves multiple functions including absorption of nutrients, immunologic defence and microbiome to maintain health. Whether our reported independent predictors for low enteral intake reflect true effect on insufficient gut function as a result of critical gastrointestinal organ failure or merely perceived feeding intolerance based on the physicians judgment prescribing lower intake remains to be answered. Patients admitted after gastrointestinal surgery had a significantly lower mean intake, which is potentially influenced by preference of the physician/surgeon rather than feeding intolerance resulting in lower intake. Sensitivity analyses without this group resulted in similar results indicating the robustness of the predictors. Lastly, centre was also associated with the amount of EN

intake, with a higher EN intake in Rotterdam. This is most likely the result of differences in local enteral feeding protocols and thereby differences in caloric targets during the acute phase of illness.

Due to the large number of predictors included in the model, correction for multiple testing was required. Holms correction methods can be considered strict, and combined with the assumption that several daily and baseline characteristics might be correlated, it is more likely that our correction is too extensive rather than too little. As such, the predictors before multiple correction should not be discarded.[25] Before correction for multiple testing, a total of 15 predictors were identified with a potential effect on achieving EN intake, e.g. age, diagnosis, STRONGkids malnutrition risk score, white blood count marker and type of feeding (Table 2). Also, a worse mortality/illness severity score (PeLOD, PIM 3) was found to be associated with lower mean enteral intake. This is in line with previous studies suggesting that the degree of illness is related to the degree of gastrointestinal intolerance.[28,39] These factors may play a significant role in the clinicians judgement to prescribe or enhance EN and for interpreting each sign of (perceived) feeding intolerance, thus it is important that these associations should not be interpreted literally. Hypothesis generating, we would like to argue that these baseline and daily characteristics are predictors for low EN intake and should be taken into account as confounding factors in future research investigating relationships with clinical outcomes.

Outcomes

Our study presents the second largest observational study on achievement of enteral intake and clinical outcome. In contrast with published observational studies[1,5] our analyses were performed with a multivariable mixed model showing no association between enteral intake during the first week of paediatric critical illness and several clinical outcomes including mortality and PICU duration of stay. Current recommendations for early and high enteral intake are mostly based upon two large multicentre observational cohorts (paediatric international nutrition study (PINS) 1 and PINS 2) showing an association between enteral intake above two-third (as compared with below 1/3) of prescribed goal during the first 10 days of admission and an improved 60-day survival and PICU duration-of-stay.[1,5]

Methodological differences between the PIN studies and our study could explain the differences in results. Most importantly, the availability of extensive prospectively collected detailed daily characteristics and the large number of children enabled us to perform methodologically sound multivariable analyses adjusting for 40 baseline and daily clinical parameters with a potential mediating effect on clinical outcomes. Selecting only a small number of variables into the model based on the univariable coefficient quantities can provide misleading conclusions due to inappropriate adjustment of variables needed for control in the model.[40] Univariable analyses from our study showed indeed the frequently referenced association between higher achievement of EN and improved outcome.[1,5]

However, multivariable adjustment without pre-selection deemed imperative due to raised concerns on the potential influence of predictors on the amount of energy and protein intake as well as on clinical outcome. The PIN studies used pre-selection methods and included only a small number of confounders in their model. As such, EN intake could directly be related to outcome or indirectly reflect one or more underlying predictors, such as illness severity, resulting in worsened feeding intolerance and subsequently lower intake in the sickest children. Second, in both PIN studies data collection was not complete with illness severity scores reported to be missing in up to 31% of the participants.[1,5] Additionally, illness severity was found to be a significant confounder between the association of protein intake and 60-day mortality.[5] Hence, the influence of the severity of illness or other possible predictors cannot be ruled out in the observational PIN studies. A third important difference is the categorisation of essential continuous variables. For instance, the variable EN intake was categorised into three groups (energy/goal <33%, 33–67% and >67% or protein/goal <20%, 20–60% and >60%). Also, illness severity was categorised due to different scores used in different research centres in the PIN studies.

Inadequate enteral intake can be the consequence of (perceived) feeding intolerance during critical illness. Without interventional trials it is impossible to know if the perceived adverse impact on clinical outcome is caused by lower enteral intake or by the underlying confounders such as medication and severity of illness or bed site decisions resulting in lower enteral intake. A small retrospective study in fact found that overfeeding, defined as >110% of measured REE, was found to be unfavourable as compared with caloric restriction in 139 critically ill children.[41] Due to the differences in associations within the literature and our study, we believe further investigation is warranted, preferably with an RCT on timing and/or amount of EN where a trophic feeding strategy deserves to be taken into account.

Besides the lack of benefit of higher caloric goals achievement on most short-term outcomes, lower enteral intake remained associated with the risk for developing hypoglycaemia during the first seven days of PICU admission after multivariate correction. Although, the consequences of a short and transitory occurrence of hypoglycaemia are debatable, several studies involving neonates or critically ill children did not find a negative effect on long-term neurocognitive development.[42-44] The PEPaNIC RCT previously showed that lower artificial caloric and macronutrients intake during the first week of admission resulted in improved long-term physical and neurocognitive outcome.[45,46] Whether the amount of enteral caloric and macronutrients intake has long-term consequences was not investigated in these studies, therefore, long-term physical as well as neurocognitive follow-up of EN itself remains warranted.

Some limitations of the present study should be addressed. First, our study was limited to the first 7 days of admission and the effect of nutrition on outcome beyond this point could not be investigated. Second, due to differences in EN protocol and caloric goals between

centres we had to use a general benchmark for EN delivery.[19] The golden standard to assess energy expenditure and determine patients' caloric goal is via indirect calorimetry measurement in stable patients, however, the optimal method to determine energy expenditure during the acute phase remains debatable. Current guidelines recommend to consider performing indirect calorimetry beyond the acute phase, while using calculated REE with the use of the Schofield equation during the first 7 days of admission.[11,19] This calculated Schofield equation for weight was used in our study. Ideally, investigation of the amount of gastrointestinal failure should be monitored by means of assessing its function such as the ability to digest and absorb nutrients by recording patients' growth achievement or alterations in the gut microbiome. Our study was not designed to include additional makers for gastrointestinal dysfunction other than EN intake. Furthermore, it is important to consider that potential fluid restrictions placed on the individual patient, could have hampered the ability to achieve REE without signs of feeding intolerance present. Unfortunately, data on fluid restrictions were not available and could not be incorporated into the mixed model. Furthermore, many of our variables are based upon bed-site decision making, (e.g. location of feeding tube or type of feeding), and warrant further investigation with the use of RCTs to obtain a causal relationship with EN intake. Lastly, this study was limited in investigating only short-term outcomes. To validate our results and provide evidence on the burden of critical illness, future studies should incorporate functional outcomes (e.g. anthropometrics, muscle wasting, PICU acquired weakness), long-term neurocognitive development and quality of life post PICU admission.

CONCLUSIONS

Enteral intake was low in the majority of critically ill children and gastrointestinal surgery diagnosis, gastric feeding tube, treatment with inotropic agents and large GRV was independently and negatively associated with successfully achieving enteral nutrition using multivariable mixed models. After multivariable adjustment, there were no associations between achievement of enteral intake and clinical outcomes, suggesting that the impact on clinical outcome reported in previous studies might reflect insufficient adjustment for confounders. These data substantiate the requirement of sound multivariable adjustment in observational nutritional support research and the necessity for RCTs investigating optimal EN.

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APPENDIX

File S1. Prescription of parameters included in mixed model analyses.

Day of admission: Day 1 up to 7 days

Baseline characteristics

1. Randomisation to late or early initiation of PN
2. Age in years
3. Sex: female or male
4. Malnourishment:
    a. Acute undernourished was defined as weight-for-age z-score between -3 and −2 (aged <1 year) or body mass index-for-age z-score between -3 and −2 (if aged ≥ 1)
    b. Severely acute undernourished was defined as weight-for-age z-score less than −3 (<1 year) or body mass index-for-age z-score less than −3 (if aged≥ 1 year).
5. Emergency or elective admission
6. Diagnostic groups: categorised into 4 surgical (cardiac, neurologic, gastrointestinal and other) and 4 medical (cardiac, neurologic, respiratory and other) diagnoses
7. Centre: Leuven, Rotterdam or Edmonton
8. Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) score: range from 0 to 5, with a score of 0 indicating low risk of malnutrition, 1 to 3 indicating medium risk, and 4 to 5 indicating high risk
9. Paediatric Index of Mortality 3 (PIM3) score: higher scores indicate higher risk of mortality
10. Paediatric Risk of Mortality III (PRISM) score: higher scores indicate higher risk of mortality
11. Active malignancy upon admission
12. Syndrome or genetic abnormality upon admission: divided in confirmed or suspected abnormality
13. Chronic disease upon admission: cardiac, respiratory, renal, diabetes mellitus
14. Infection prior to admission
15. Mechanical ventilatory support upon PICU admission
16. Mechanical hemodynamic support on PICU admission

Daily clinical characteristics

17. Paediatric Logistic Organ Dysfunction (PeLOD) score: range from 0 to 71, higher scores indicate higher severity of illness
18. Maximum registered C-reactive protein (CRP) in mg/L
19. Maximum registered white blood count (WBC) in 10^9/L
20. Maximum registered lactate in mmol/L

Daily feeding characteristics

21. Location of feeding type: nasogastric tube, post-pyloric tube or no tube

22. Main type of feeding: Human milk, Standard formula, Protein and energy enriched formula, Peptide formula, oral intake or no intake

Daily gastro-intestinal symptoms

23. Large gastric residual volume (GRV): defined as ≥ 50% ml gastric residue of provided enteral feeding intake over 24 hours
24. Presence of diarrhoea: defined as ≥ 4 loose stools over 24 hours
25. Presence of vomiting and/or aspiration: classified into yes or no over 24 hours
26. Presence of abdominal distention: classified into yes or no over 24 hours
27. Presence of ≥ 1 EN intolerance parameter: combination of large GRV, diarrhoea, vomiting and/or aspiration and abdominal distention

Daily treatment with medication

28. Anti-emetics
29. Laxatives
30. Acid suppression
31. Rectal enema
32. Corticosteroids
33. Antibiotics
34. Benzodiazepines
35. Opiates
36. Vasopressors
37. Inotropic agents
38. Hypnotics and/or barbiturates
39. Alpha-2 antagonist

Clinical outcomes

1. New acquired infection
2. Hypoglycaemia <40mg/dl within the first 7 days of admission
3. Length of PICU stay (days)
4. Length of hospital stay (days)
5. Length of mechanical ventilatory support (days)
6. First week survival
7. PICU survival
8. Hospital survival
9. 90 day survival

Table S1. Overview of nutritional and fluid practices in the three research centres during the PEPaNIC RCT.

Practices	Leuven	Rotterdam	Edmonton
EN protocol present	Yes	Yes	Yes
Fluid allowance	100 ml/kg/d for the first 10 kg bodyweight, 50 ml/kg/d for the next 10 kg, and 20 ml/kg/d for the bodyweight > 20 kg	<3m: 150-180 ml/kg/d 3-6m: 150 ml/kg/d 6-9m: 140 ml/kg/d 9-12m: 120 ml/kg/d > 1y: 100 ml/kg/d for the first 10 kg bodyweight, 50 ml/kg/d for the next 10 kg, and 20 ml/kg/d for the bodyweight > 20 kg (This will be considered Total Fluid Intake, TFI)	100 ml/kg/d for the first 10 kg bodyweight, 50 ml/kg/d for the next 10 kg, and 20 ml/kg/d for the bodyweight > 20 kg (This will be considered Total Fluid Intake, TFI)
Fluid allowance in restricted patients	80-110 ml/kg/d	Post-op cardiac patients: day 1 50% TFI and day 2 75% Other patients around 75%, however Individually adjusted	75% TFI for intubated patients 50% TFI for post-op cardiac patients
Time to initiate EN	Within 24-48 hours of admission	Within 24 hours of admission	Within 24 hours of admission
Preferred feeding location	Gastric	Post-pyloric	Post-pyloric
Preferred feeding method	Infants: Slow bolus feed Children: Continuous over 10 hours, followed by 2 hours rest	Continuous	Continuous
Formula	Infants: Human milk or polymeric infant feeding Children: Polymeric age-based formula (+/- fibre)	Infants: Human milk or polymeric infant formula with fibre Children: Polymeric age-based formula with fibre	Infants: Human milk or semi-elemental infant formula Children: >12 months-10 years: Semi-elemental age-based formula

	Semi-elemental indicated by 'intolerance'	All children: Energy-protein enriched age-based formula (with fibre) if fluid restricted or mechanical ventilated Semi-elemental indicated by 'intolerance '	> 10 years: Semi-elemental energy-protein enriched age-based formula
Energy goals used	100 kcal/kg/d for the first 10 kg bodyweight, 50 kcal/kg/d for the next 10 kg, and 20 kcal/kg/d for the bodyweight > 20 kg	Predicted REE according to Schofield equation (200% in infants declining to 130% REE in adolescents)	Indirect calorimetry. Otherwise 65% of BMR when the patient was intubated, BMR when patient is extubated and TEE when the patient had been extubated and ambulatory. Goal is adjusted daily by dietician.
Indirect calorimetry measurement	No	Performed in ventilated patients on day 7 or 8	Used to guide energy goal from admission onwards
Feed advancement	Stepwise incline based on tolerance	Stepwise incline based on tolerance. Protocol allows for half EN on day 1 and full EN from day 2 onwards	Stepwise incline based on tolerance. Protocol allows for full energy goal from day 1.
Routine GRV measurement	Before starting the next planned feeding	Every 4 hours; amount GRV is subtracted from next feeding	No
Definition of feeding intolerance	Based on clinicians judgement and large GRV (>50% of bolus intake or previous 4 hours when continuously fed)	Based on clinicians judgement and large GRV (>50% of bolus intake or previous 4 hours when continuously fed)	Based on clinical judgement: nausea, vomiting, diarrhoea, bloody stool and/or abdominal distention.
GI reasons for stopping feeds	Signs of intestinal ischemia of discomfort and ≥ 2 times large GRV	Signs of intestinal ischemia of discomfort and ≥ 2 times large GRV	Vomiting, significant abdominal distention, bloody stool suspicion or NEC

BMR, basal metabolic rate; EN, enteral nutrition; GI, gastrointestinal; GRV, gastric residual volume; NEC, Necrotising enterocolitis; REE, resting energy expenditure; TEE, total energy expenditure; TFI: Total fluid intake

Table S2. Sensitivity analyses of the multivariate associations between baseline patient characteristics and daily parameters with daily mean daily enteral energy intake as percentage of predicted REE of critically ill children during first week of admission excluding children admitted after gastrointestinal surgery (N=590).

	Coefficient[4]	**% EN/REE**	**95% CI**	**p-value[5]**
(Intercept)	3.101			<0.001
Baseline characteristics				
Randomisation to late vs early initiation of PN	0.049	+5.0%	-5.6; +16.7%	0.368
Day of admission	0.193	+21.3%	+18.5; +24.2%	<0.001*
Age in years	-0.019	-1.9%	-3.2%: -0.6%	0.006
Female vs male sex	0.105	+11.1%	-0.4% +23.8	0.058
Malnourishment[1] (as compared with normal)				
Acute malnourished	0.133	+14.2%	-3.9; +35.6%	0.131
Severe acute malnourished	0.199	+22.0%	+1.6; +46.5%	0.033
Urgent vs elective admission	-0.174	-16.0%	-31.7; +3.4%	0.100
Diagnostic category (as compared with cardiac surgery)				
Surgical - Neurosurgery	0.192	+21.2%	-9.5; +62.3%	0.198
Surgical - Other	-0.014	-1.4%	-20.8; +22.9%	0.903
Medical - Cardiac	0.090	+9.5	-16.1; +42.8%	0.505
Medical - Neurologic	0.411	+50.8	+12.9; +101.4%	0.005
Medical - Respiratory	0.363	+43.7	+12.7; +83.4%	0.004
Medical - Other	0.154	+16.7	-11.7; +54.2%	0.279
Centre Edmonton vs Rotterdam	-0.405	-33.3%	-45.7; -18.0%	<0.001*
STRONGkids score high risk vs medium risk	0.162	+17.6	+0.8; +37.1%	0.040
PIM3 score (per point added)	-0.062	-6.1%	-10.4; -1.5%	0.010
PRISM score (per point added)	-0.000	+0.0	-1.1; +1.0%	0.931
Malignancy vs no malignancy	-0.042	-4.1%	-26.5; +25.1%	0.755
Syndrome vs no syndrome	0.152	+16.4	-1.5; +37.5%	0.074
Suspicion for syndrome vs no syndrome	-0.022	-2.1%	-22.0; +22.9%	0.852
Chronic disease vs no chronic disease	0.003	+0.3%	-13.3; +16.1%	0.967
Admitted with infection	-0.056	-5.5%	-18.1; +9.1%	0.442

Admitted with respiratory support	0.220	+24.6%	+0.7; +54.2%	0.042
Admitted with hemodynamic support	-0.212	-19.1%	-38.1; +5.6%	0.119
Daily clinical characteristics				
PeLOD score (per point added)	-0.007	-0.7%	-1.1; -0.2%	0.007
Maximum CRP (per point added)	-0.000	+0.0%	-0.1; +0.0%	0.100
Maximum WBC (per point added)	-0.005	-0.5%	-1.0; +0.0%	0.042
Maximum Lactate (per point added)	-0.001	-0.1%	-2.2; +2.0%	0.912
Daily feeding characteristics				
Location Tube (as compared with nasogastric tube)				
post-pyloric tube	0.268	+30.7%	+16.7; +46.4%	<0.001*
No tube	-0.198	-17.9%	-37.0; +7.0%	0.144
Main type of feeding (as compared with no Standard formula)				
Human Milk	0.021	+2.1	-12.1; +18.7%	0.784
Energy enriched formula	0.218	+24.4	+7.9; +43.5%	0.003
Peptide formula	0.248	+28.1	+0.8; +62.8%	0.043
Oral intake	-0.226	-20.2%	-36.3; +0.0%	0.050
No formula	-1.326	-73.5%	-85.7; -50.7%	<0.001*
Daily gastro-intestinal symptoms				
Large Gastric residual volume[2] (>50% of EN intake)	-0.998	-63.1%	-41.0; -53.1%	<0.001*
Presence of diarrhoea[3]	0.098	+10.3%	-8.3; +32.7%	0.297
Presence of vomit and/or aspiration	0.116	+12.3%	-10.8; +41.4%	0.324
Presence of abdominal distention	-0.398	-32.9%	-53.9; -2.3%	0.038
Presence of ≥ EN intolerance parameter	-0.069	-6.7%	-23.2; +13.5%	0.487
Daily treatment with medication				
Treatment with anti-emetics	-0.127	-11.9%	-24.7; +3.0%	0.113
Treatment with oral laxation	0.175	+19.2%	+5.3; +34.9%	0.006
Treatment with acid suppression	-0.036	-3.5%	-13.8; +7.9%	0.530
Treatment with rectal enema	0.072	+7.5%	-7.8; +25.3%	0.358
Treatment with corticosteroids	-0.095	-9.0%	-18.6; +1.6%	0.094
Treatment with antibiotics	-0.121	-11.4%	-20.6; -1.2%	0.030

Treatment with benzodiazepines	-0.104	-9.9%	-19.3; +0.7%	0.067
Treatment with opiates	-0.100	-9.5%	-18.6; +0.6%	0.066
Treatment with vasopressors	-0.214	-19.2%	-30.1; -6.7%	0.004
Treatment with inotropic agents	-0.258	-22.8%	-32.4; -11.8%	<0.001*
Treatment with hypnotics and/or barbiturates	-0.004	-0.4%	-9.5; +9.5%	0.928
Treatment with Alpha-2 antagonist	-0.050	-4.9%	-18.1; +10.4%	0.507

[1]Children younger than 1 year: weight-for-age z-score; children 1 year or older: body mass index–for-age z-score; [2] Large gastric residual volume was defined as volume in ml more than 50% of prescribed EN feeding per 24 hours; [3]Diarrhoea was defined as four or more loose stools per 24 hours [4]The reported coefficients, and the corresponding 95% confidence intervals and p-values are for the marginalised mean of enteral nutrition intake. The exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. Hence, an exponent of the coefficients of 0.90 reflect an 10% lower mean enteral intake expressed as a % Of REE. [5.] *Statistically significant after correction for multiple comparisons using Holms method.

CRP, C-reactive protein; EN, enteral nutrition; GRV, gastric residual volume; PeLOD, Paediatric Logistic Organ Dysfunction; PIM, paediatric index of mortality; PN, parenteral nutrition; PRISM, Paediatric Risk of Mortality; REE, resting energy expenditure; WBC, white blood count

Table S3. *Univariable* association between mean daily enteral energy intake as % of predicted REE during the first week of PICU admission and clinical outcomes

	Coefficient[1]	% EN/REE	95% CI	p-value
Clinical outcomes				
New acquired infection vs no infection	-0.370	-30.9%	-41.9; -17.9%	<0.001
Hypoglycaemia <40 mg/dl within the first 7 days of admission vs no hypoglycaemia	-0.906	-69.6%	-72.7; -40.3%	<0.001
Duration of PICU stay (per day)	-0.004	-0.4%	-0.7; -0.1%	0.020
Duration of hospital stay (per day)	-0.004	-0.4%	-0.6; -0.2%	<0.001
Duration of mechanical ventilation (per day)	-0.004	-0.4%	-0.8; +0.1%	0.029
First week non-survivor vs survivor	-0.171	-15.7%	-53.0; +51.1%	0.565
PICU non-survivor vs survivor	-0.066	-6.4%	-35.0; +34.7%	0.722
Hospital non-survivor vs survivor	-0.090	-8.7%	-34.4; +27.3%	0.593
90 day non-survivor vs survivor	-0.172	-15.8%	-39.6; +17.4%	0.311

[1]The reported coefficients, and the corresponding 95% confidence intervals and p-values are for the marginalised mean of enteral nutrition intake. The exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. Hence, an exponent of the coefficients of 0.90 reflect an 10% lower mean enteral intake expressed as a % of REE

PICU: paediatric intensive care unit. REE: Resting energy expenditure

Table S4. Sensitivity analyses of the *univariable* associations between mean daily enteral energy intake as % of predicted REE during the first week of PICU admission and clinical outcomes, excluding children admitted after gastrointestinal surgery (N=590).

	Coefficient[1]	% EN/REE	95% CI	p-value
Clinical outcomes				
New acquired infection vs no infection	-0.382	-31.8%	-42.4; -19.2%	<0.001
Hypoglycaemia <40 mg/dl within the first 7 days of admission vs no hypoglycaemia	-0.943	-61.0%	-73.7; -42.3%	<0.001
Time to live PICU discharge (days)	-0.003	-0.3%	-0.7; +0.1%	0.201
Time to live hospital discharge (days)	-0.003	-0.3%	-0.6; -0.1%	0.006
Time to live weaning form ventilation (days)	-0.004	-0.4%	-1.0; +0.3%	0.267
First week non-survivor vs survivor	-0.225	-20.1%	-55.2; +42.4%	0.446
Non-ICU survivor vs survivor	-0.102	-9.7%	-36.3; +28.2%	0.569
Non-hospital survivor vs survivor	-0.114	-10.8%	-34.8; +22.0%	0.474
90 day non-survivor vs survivor	-0.207	-18.7%	-40.8; +11.6%	0.201

[1]The reported coefficients, and the corresponding 95% confidence intervals and p-values are for the marginalised mean of enteral nutrition intake. The exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. Hence, an exponent of the coefficients of 0.90 reflect an 10% lower mean enteral intake expressed as a % of REE.

PICU, paediatric intensive care unit. REE, Resting energy expenditure

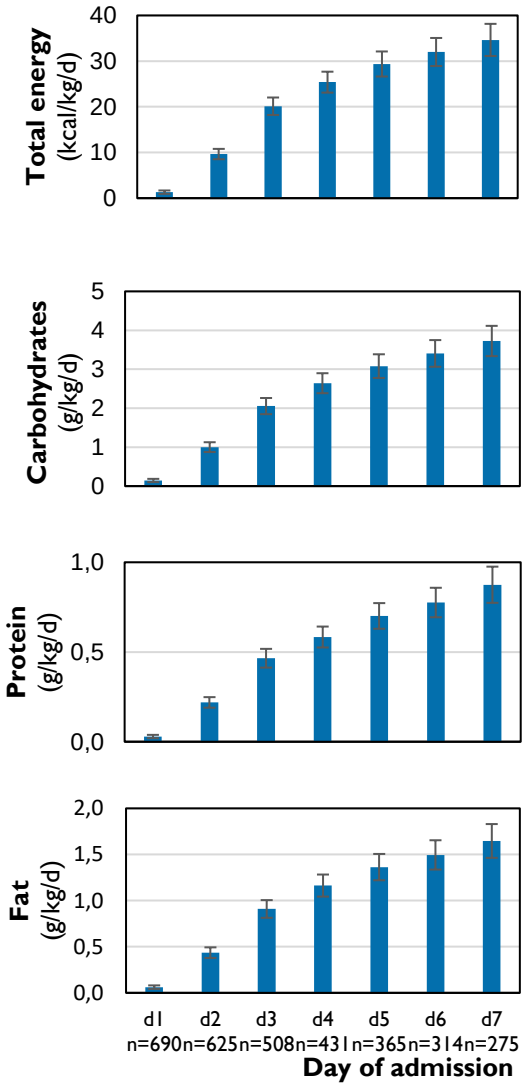
Table S5. Sensitivity analyses of the multivariable associations between mean daily enteral energy intake as % of predicted REE during the first week of PICU admission and clinical outcomes excluding children admitted after gastrointestinal surgery (N=590).

	Coefficient[1]	% EN/REE	95% CI	p-value[2]
Clinical outcomes				
New acquired infection vs no infection	-0.039	-3.8%	-16.3; +10.4%	0.581
Hypoglycaemia <40mg/dl within the first 7 days of admission vs no hypoglycaemia	-0.519	-40.5%	-55.1; -21.1%	<0.001*
Time to live PICU discharge (days)	0.002	+0.2%	-0.1; +0.5%	0.300
Time to live hospital discharge (days)	-0.000	+0.0%	-0.2; +0.1%	0.606
Time to live weaning form ventilation (days)	0.002	+0.2%	-0.2; +0.6%	0.260
First week non-survivor vs survivor	0.169	+18.4%	-23.5; +83.3%	0.448
Non-ICU survivor vs survivor	0.220	+24.6%	-3.7; +61.1%	0.094
Non-hospital survivor vs survivor	0.159	+17.3%	-6.2; +46.5%	0.161
90 day non-survivor vs survivor	0.100	+10.5%	-13.1; +40.6%	0.415

[1]The reported coefficients, and the corresponding 95% confidence intervals and p-values are for the marginalised mean of enteral nutrition intake. The exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. Hence, an exponent of the coefficients of 0.90 reflect a 10% lower mean enteral intake expressed as a % of REE. [2]*Statistically significant after correction for multiple comparisons using Holms method. Appendix presents the complete list of included baseline and daily parameters for multivariable adjustment.

PICU, paediatric intensive care unit. REE, Resting energy expenditure

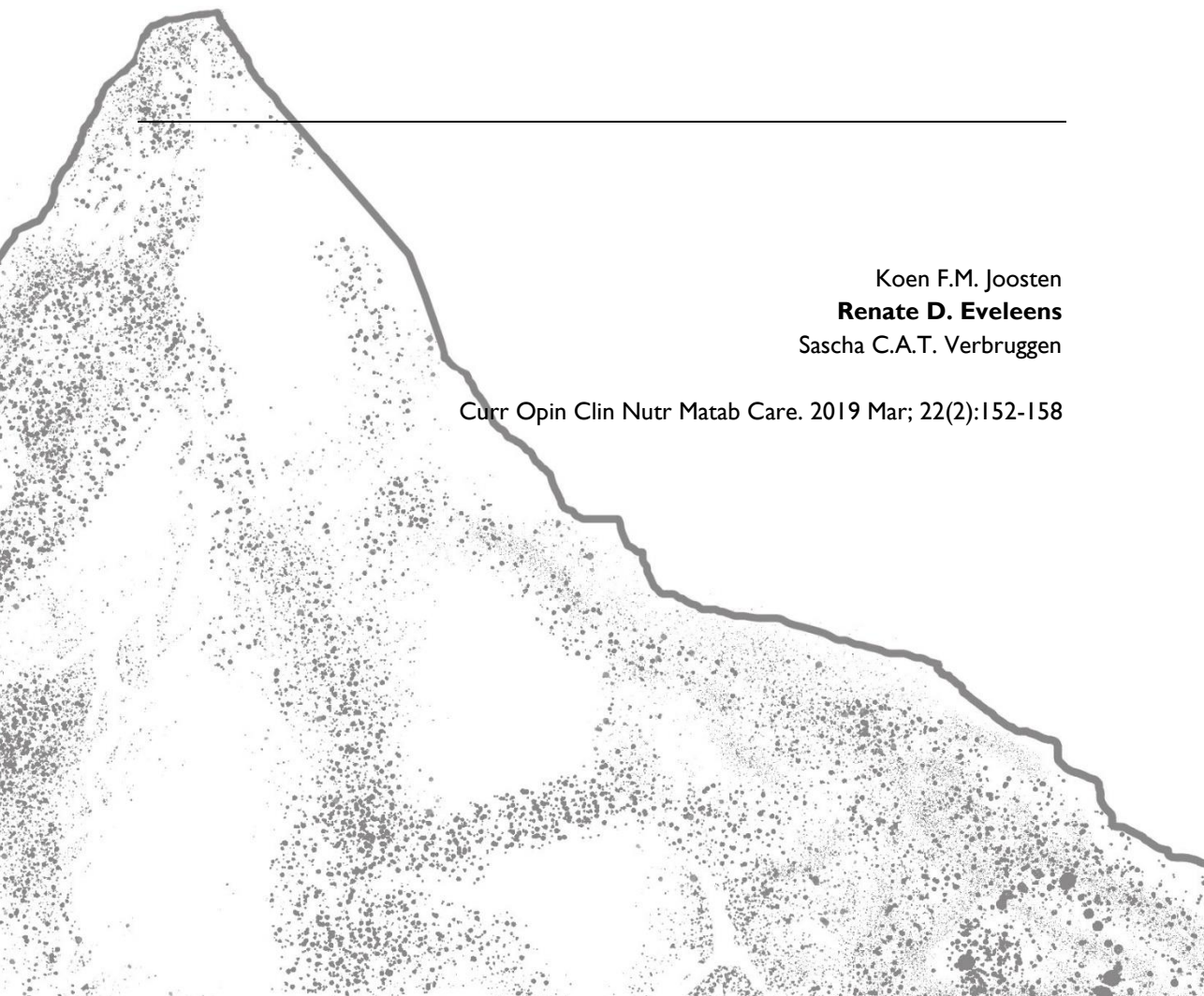
Figure S1. Daily mean enteral macronutrient doses during the first week of PICU admission



Daily amount of mean enteral energy in kcal/kg/day, and the daily amounts of mean enteral macronutrient substrates in g/kg/day are shown for the first 7 days in the paediatric intensive care unit (PICU). Bars represent the mean and the whiskers represent the 95% confidence interval (CI)

CHAPTER 6

NUTRITIONAL SUPPORT IN THE RECOVERY PHASE OF CRITICALLY ILL CHILDREN



Koen F.M. Joosten
Renate D. Eveleens
Sascha C.A.T. Verbruggen

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ABSTRACT

Purpose of review: The metabolic stress response of a critically ill child evolves over time and thus it seems reasonable that nutritional requirements change during their course of illness as well. This review proposes strategies and considerations for nutritional support during the recovery phase to gain optimal (catch-up) growth with preservation of lean body mass.

Recent findings: Critical illness impairs nutritional status, muscle mass and function, and neurocognition, but early and high intakes of artificial nutrition during the acute phase cannot resolve this. Although (parenteral) nutrient restriction during the acute phase appears to be beneficial, persistent nutrient restriction, when the metabolic stress response resolves, has short-term and long-term detrimental consequences. Requirements increase markedly during the recovery phase to enable recovery and catch-up growth. Such large amounts of intake demand for alternate approach, especially when intestinal problems constitute a barrier for full enteral feeding. As part of the nutritional recovery, mobilization and exercise are essential to achieve catch-up growth with an optimal body composition.

Summary: During the recovery phase of paediatric critical illness (catch-up) growth and muscle recovery require nutritional intakes at least two times the resting energy expenditure.

INTRODUCTION

Owing to scientific and clinical progress during the past two decades, most critically ill children nowadays survive the initial life-threatening event that required admission to the paediatric ICU (PICU).[1] However, although acute outcome has improved, many children who survived are often confronted with long-lasting physical, neurocognitive, and psychological problems.[2] Consequently, research focus is shifting from improving short-term vital outcomes to improving long-term morbidity and quality of life, years after PICU discharge. Although undernourishment during and after PICU stay are associated with worse outcome, nutritional support during critical illness has not been shown to improve short-term and long-term outcome.[3,4] Such nutritional interventions have traditionally been done during the acute phase of critical illness. Following this acute phase, critical illness generally evolves into a stable and recovery phase. Each of these three phases is characterised by a cascade of neuro-endocrine, immunologic, and metabolic responses that change over time.[5] The characterization of these phases is arbitrary and artificial, as no method currently exists to determine when and how patients evolve through these phases. In this review, the focus will be on nutritional interventions during the recovery phase critical illness and the potential long-term consequences.

Nutritional support during the acute phase

During the acute phase of critical illness, the metabolic stress response is characterised by severe catabolism. No evidence currently exists that the acute catabolic response can, or should, be countered with nutritional support. In fact, the Paediatric 'Early versus Late Parenteral Nutrition in the Paediatric Intensive Care Unit' (PEPaNIC) trial has shown that withholding supplemental parenteral nutrition during the first week in PICU, when enteral nutrition was insufficient, prevented infections and accelerated recovery with shorter stay in the PICU and the hospital.[6] These results corroborated with trials performed in the adult ICU which did not show any harm, and possibly even benefit, when they were fed with low nutritional macronutrient intakes during the acute phase.[7-11] In contrast to the concerns that withholding parenteral nutrition would be detrimental in critically ill children considered most vulnerable to low nutritional intakes because of low reserves, it proved also beneficial in term neonates and children already undernourished upon admission to PICU.[12,13] However, the optimum length of time how parenteral nutrition should be withheld is unknown.

A leading explanation for the counterintuitive benefits of lower nutritional intake during the acute phase might be the activation of autophagy.[11,14,15] Autophagy is an essential survival mechanism by which cells break down their own (damaged) components to recycle intracellular nutrients and generate energy during starvation, which is inactivated with nutritional intake.[16,17] When suppressed by forced mandatory overfeeding during the acute phase of critical illness, the risk of organ failure and cell death increases, resulting in worse

clinical outcome.[15,18] There are indications that during the recovery phase nutritional requirements rise markedly and even overshoot normal requirements of a healthy growing child.[19] No method currently exists to determine the exact point at which well-tolerated starvation during the acute phase ends and malnutrition-related complications begin in the recovery phase.

Consequences of prolonged undernutrition

Nutritional status

Undernourishment upon or during PICU admission are both associated with impaired outcome such as prolonged PICU stay, increased duration of mechanical ventilation, and even higher risk of mortality.[13,20-22] An observational study in critically ill children found significant cumulative nutritional deficits compared to recommended dietary allowance at 14 days after admission. These deficits were on average 20 and 12kcal/kg and 0.3 and 0.2 g/kg of protein per day for term neonates (n=91) and older children (n=67), respectively. These deficits were associated with declines in z-scores for weight and arm circumference from admission to discharge, which recovered within 6 months after discharge.[23] Additionally, lower enteral intake was associated with deterioration of the nutritional status.[24-26] In a study of 325 children who stayed at least 4 days in the PICU, 19% were acutely undernourished upon admission and in a subgroup of 223 with registered weight at discharge, this was still 26%.[27] However, this study was not designed to make an association between nutritional intake and outcome.[27] In a recent study, a longer length of PICU stay was associated with faltering growth (defined as deceleration of >-1 z-score within 3 months) during the first year after PICU admission.[28] There is a scarcity of data addressing the evolution of body composition during admission and at follow-up, and the effect of nutrition hereon.

Muscle wasting and weakness

The reported incidence of muscle weakness in critically ill children varies from 1.7 to 30%.[29-31] Furthermore, it was shown that muscle mass, as measured by thickness of the femoral quadriceps, decreased up to 13% during PICU stay.[32] Also, decrease in muscle mass was associated with increased length of mechanical ventilation and PICU stay.[33] Anabolic resistance of muscle during the acute phase of critical illness is now generally accepted. In fact, it has been recently shown that early supplementation of parenteral nutrition did not prevent muscle wasting and actually withholding parenteral nutrition during the first week of critical illness, through the activation of autophagy, improved muscle architecture and functioning.[11,14,34,35]

Cognitive development

Nutrition is a major factor affecting cognitive development and health of brain structure and function.[36-38] Indeed, proper building blocks need to be provided to the brain for creation and maintenance of connections to improve cognition and academic performance,[39]

particularly in the phase of rapid growth in the first 2 years of life [40]. But nutrition continuously plays an important role throughout childhood into adulthood.[36] There are some indications that even short nutritional interventions impact neurocognition and psychological health. Healthy adults undergoing a semi-starvation study developed neurocognitive and psychiatric problems only after a few weeks.[41,42] One patient who ended the study prematurely because of psychological problems recovered after only a few days of a normal diet.[42] Both undernutrition and overnutrition have been related with impaired cognitive health and poorer scholastic performance,[39] as well as behavioural problems.[40] Importantly, early effects of nutrition may not only immediately impact on structural and functional development of the brain, but may also affect other body functions in which the brain is involved, including endocrine and inflammatory signalling that regulates metabolic processes involved in growth and development.[40,43] In critically ill children, withholding parenteral nutrition for 1 week in the PICU improved certain domains of neurocognitive development at follow-up 2 years later, as compared with children who received parenteral nutrition early during critical illness.[38] In fact, in children who did not receive parenteral nutrition during the first week overall executive functioning, inhibition, meta-cognition, and externalising problems as reported by parents were not different any more than in healthy children.[38]

Figure 1. Energy requirements in different phases of critical illness; % of REE

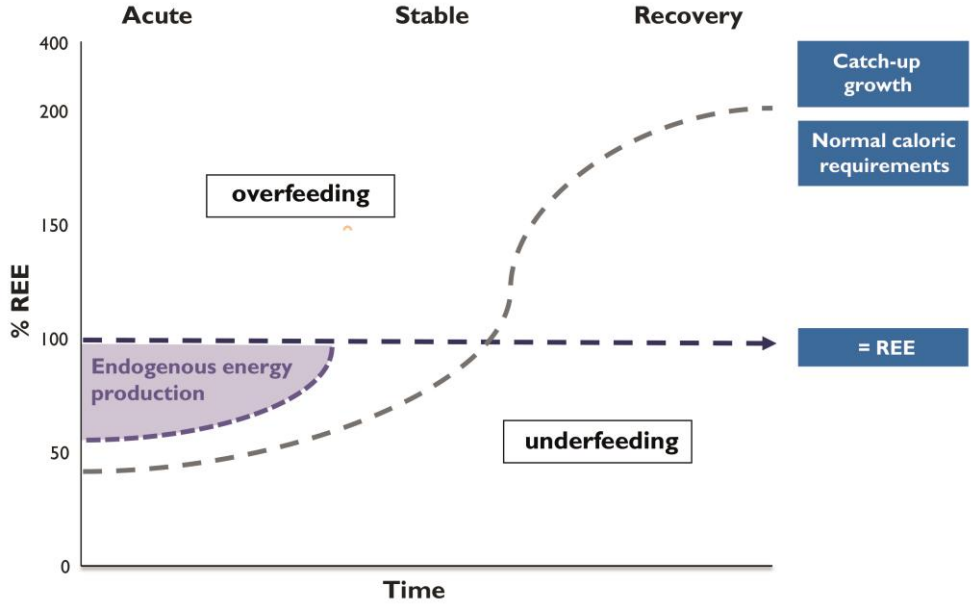

Table 1. Indications for targeted Indirect Calorimetry

- PICU stay > 1 week
- >10% weight change during PICU stay
- Inappropriate weight z-score change during stable or recovery phase
- Failure to consistently meet prescribed energy goals in stable or recovery phase
- Suspicion of hypermetabolism (burns, traumatic brain injury, systemic inflammatory response syndrome, dysautonomic storms, persistent fever)
- Suspicion to be hypometabolism (hypothermia, (medicational induced) coma)

PICU, Paediatric ICU

Nutritional support in recovery phase

During the acute phase, endogenous energy production can cover a substantial (up to 75%) part of energy requirements, irrespective of the exogenous energy provision.[44] In the recovery phase, resting energy expenditure (REE) values are the optimal guide for determining energy requirements. If possible, targeted indirect calorimetry is recommended in critically ill children with specific conditions (Table 1). However, in most clinical settings the lack of availability of indirect calorimetry means that prediction equations have to be used.[45] Reasonable values for REE can be derived from Schofield's prediction equation for REE using the actual weight of the patient.[46] In contrast to the acute phase, the recovery phase does necessitate to add stress and activity factors to REE to account for tissue repair, growth, and for catch-up growth and physical activity during mobilization. To further understand the concept of energy requirements in the recovery phase, we can learn from existing data of severely malnourished, sick children and malnourished adults who were previously healthy.[41,42] The WHO recommended, in children aged 6–59 months recovering from severe malnutrition in developing countries, to feed according to three evolving phases as well. In the first phase low protein-based milk formula should be provided, whereas in the second phase higher protein/energy content is necessary. Once children are ready to move into the third phase of rehabilitation to correct the emerged growth deficits energy intake up to 100–135 kcal/kg/day are required.[47] Also, in older children recovering from severe malnutrition because of anorexia nervosa supraphysiological energy intakes up to 3000–5000 kcal/day were needed for a weight gain of 0.5–1.0 kg/week.[48] Interestingly, in line with treatment of children with anorexia nervosa it has been shown in healthy adults (70 kg) that after significant weight loss (±25%), requirements reached 4000– 5000 kcal/day (approximately 60–70 kcal/kg/day = 2–3x REE) to fully regain weight after 6 months to 2years.[41,42]

Overall, in the recovery phase of critical illness, the body experiences a massive increase in metabolic needs with energy expenditure increasing as much as 2x REE, which increases even further up to 3–4x REE taking into account physical activity and catch-up growth. Figure 1 depicts the concept of energy requirements during the different phases of critical illness.

Table 2. Total energy requirement recorded in the recovery phase of specific disease states

Disease or disease state	Total energy requirement
Critically ill infants [49]	2 x REE
Severe malnutrition [47,48]	2-3 x REE
Congenital heart disease [50,51]	2-4 x REE
Burns [52-55]	2-2.5 x REE
Traumatic brain injury [56,57]	1.3-1.6 x REE

Nutritional support in specific diseases

Only few studies have investigated the energy requirements in the recovery phase in critically ill children, mostly with specific diagnoses (Table 2). In critically ill infants with a prolonged (>14 days) PICU stay normal weight gain was achieved by following a nutritional protocol with energy target set at 2x REE.[49] In infants recovering from surgical repair of a congenital heart disease, energy requirements were 2–3x REE (120–150 kcal/kg/ day) to obtain a weight gain of 20–30 g/day, which might increase to 4x REE (200kcal/kg/day) when a haemodynamically significant lesion remains after surgery.[50,51] Children with burns[52-55] and traumatic brain injury[56,57] develop a hypermetabolic state lasting from 1 week to 1 year after the injury, which increases energy requirements to 2.5x REE.

Protein requirements

The acute catabolic phase is characterised by extraordinary whole body protein breakdown and muscle loss (in adults up to 1kg per day). Beyond the acute phase, muscle wasting often persists because of disease-related factors, but also iatrogenic factors such as medication, immobilization, and undernourishment [58]. Increased length of stay in the PICU is associated with cumulative protein depletion [59]. In the recovery phase, protein requirements increase to replenish depleted stores but also to account for tissue repair and (catch-up) growth. American Society for Parenteral and Enteral Nutrition guidelines state that a minimum of 1.5 g/kg/day enteral protein, and in young children even 2.5–3.0 g/kg/day, is required to achieve a positive protein balance [60]. In the recovery phase, one has to account for the protein energy ratio of the prescribed formula. The WHO recommends 9–11.5% energy from protein for infants who are acutely malnourished and 11–15% for those with chronic malnutrition.[61] The protein energy content of most standard enteral formula is 10–11% and this will be sufficient to deliver an adequate amount of protein in the recovery phase.

Optimal feeding

Enteral nutrition also remains the preferred route to meet energy and nutrient requirements in the recovery phase. Due to markedly increasing requirements, this is even in the recovery phase still challenging because of multiple barriers such as delayed initiation, fluid restriction, and interruptions as a result of perceived feeding intolerance and prolonged fasting around procedures.[5] Independent of the need to provide high amounts of intake, a stepwise approach to deliver nutritional support can be considered (Table 3).[27,49] This

approach entails protein-energy dense and/or hydrolysed formulas. Ultimately, when enteral nutrition remains insufficient after the first week of critical illness, parenteral nutrition allows for substantial amounts of nutrient intake. However, almost 50%of children fully dependent of parenteral nutrition for a prolonged period are stunted.[62-64] This is at least partially explained by maximum amount of macronutrient feasible to provide with parenteral nutrition, not allowing more than 2x REE, and the fact that caloric-dense lipids often have to be decreased because of intestinal failure-associated liver disease.[65] Table 4 shows the energy recommendations in recovery phase of critical illness if (supplemental) parenteral nutrition is prescribed according the current Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline.[19] One has to take into account that these are recommendations only for parenteral nutrition. When enteral nutrition is given, energy requirements are generally 10–20% higher compared with the parenteral route because splanchnic metabolism contributes significantly to whole body energy and protein turnover, and because some nutrients are excreted in the stool.

Table 3. Stepwise approach for nutritional therapy in the PICU

	Nutritional therapy	Consideration
Step 1	Infants: standard polymeric formula/breastmilk Children: standard polymeric formula	May result in nutritional deficits as a result of the lower energy and protein content of these formulas/breastmilk
Step 2	Infants and children: polymeric protein:energy enriched formula	Higher energy and protein content may overcome nutritional deficits especially in fluid restricted patients
Step 3	Infants and children: (semi)-elemental protein:energy enriched formula	Absorption, tolerance and utilization of proteins and fats may be altered and (semi)-elemental feeds are considered as an alternative
Step 4	If insufficient EN (<80%) or no EN possible >1 week after admission: start PN	Especially in children with intestinal failure; appropriate growth and normal body composition difficult to achieve and risk for associated liver disease

Table 4. Recommendations for energy intake with (supplemental) PN in recovery phase of critical illness

Age group	**Kcal/kg/day**
0-1 yr	75-85
1-7 yr	65-75
7-12 yr	55-65
12-18 yr	30-55

Assessing the effects of high nutritional intake during the recovery phase

The success of nutritional support during the recovery phase of paediatric critical illness will often be reflected by catch-up growth. However, catch-up growth may have some long-term consequences, such as the development of obesity, metabolic syndrome, and related problems. Most of these associations have been described when catch-up growth developed in (very) low birth-weight neonates and after (semi)starvation during infancy.[66,67] Whether catch-up growth after a period of growth restriction during critical illness has similar risks has not been investigated. However, adult healthy volunteers exposed to 6 months of undernutrition also showed a disproportionate gain in fat relative to lean body mass during their weight recovery.[68] Therefore, the success of nutritional support should also take into account lean body mass, muscle mass and function, and functional status.[69,70] Mobilization of patients might be an additive treatment. Although the role of (early) mobilization in maintaining lean body mass and improving muscle function in paediatric critical illness is unclear, there are some clear theoretical benefits.[71] Physical activity and exercise are essential in allowing muscle protein anabolism and should be part of the nutritional recovery after critical illness.

CONCLUSIONS

Understanding that after the acute and stable phase of critical illness the recovery phase demands markedly higher nutritional intakes. Nutritional requirements increase because of increased activity and additional requirements for tissue repair and (catch-up) growth. In specific group of patients, a hypermetabolic state may persist up to a year after the initial insult. Restoration of the lean body mass and functional rehabilitation should be the hallmark of the recovery phase.

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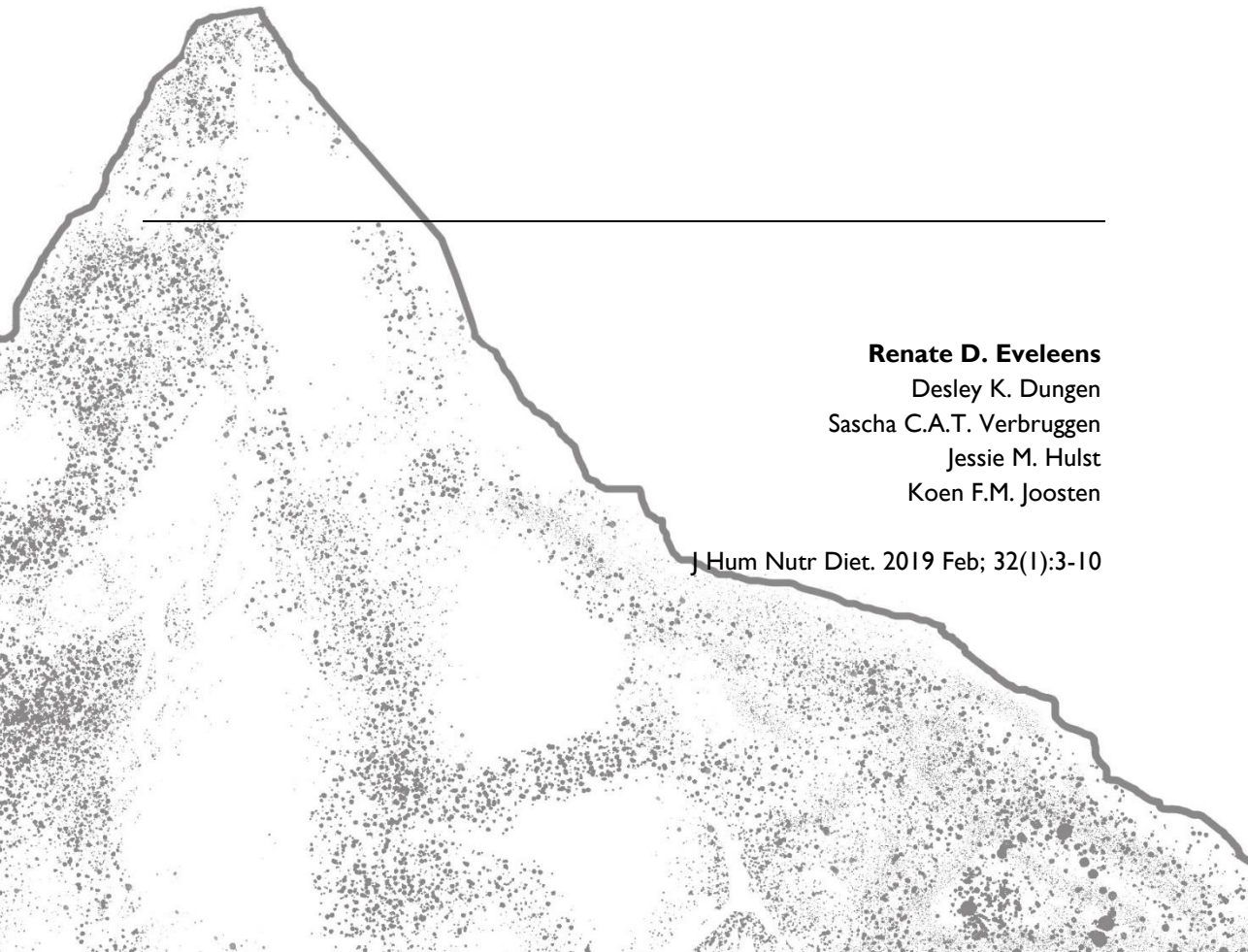
CHAPTER 7

WEIGHT IMPROVEMENT WITH THE USE OF PROTEIN AND ENERGY ENRICHED NUTRITONAL FORMULA IN INFANTS WITH A PROLONGED PICU STAY



Renate D. Eveleens
Desley K. Dungen
Sascha C.A.T. Verbruggen
Jessie M. Hulst
Koen F.M. Joosten

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ABSTRACT

Background: Reaching an optimal nutritional intake is challenging in critically ill infants. One possible way to minimise nutritional deficits is the use of protein and energy-enriched (PE) - formulas. We aimed to describe weight achievement and gastrointestinal symptoms in infants admitted to the paediatric intensive care unit (PICU) while receiving PE-formula for a prolonged period.

Methods: Records from infants admitted to a multidisciplinary PICU and using PE-formula were analysed retrospectively. Infants were eligible if they received PE-formula daily for at least 2 weeks. Weight achievement was determined as the difference between weight-for-age (WFA) Z-scores at the start and end of PE-formula use. Gastrointestinal symptoms, including gastric residual volume, constipation and vomiting, were evaluated as tolerance parameters.

Results: Seventy infants with a median [interquartile range (IQR)] age of 76 (30–182) days were eligible. The PICU duration was 50 (35–83) days during which they received PE-formula for 30 (21–54) days. Predominant admission diagnoses were post-cardiac surgery, respiratory and cardiac diagnosis. A significant mean (SD) WFA Z-score increase of 0.48 (1.10) ($P<0.001$) and a median (IQR) weight gain of 5.80 (3.28–9.04) g kg^{-1} day^{-1} was observed. Multivariate regression showed that a lower WFA Z-score at start was associated with a higher WFA Z-score increase during PE-formula use (b -0.35 (95% confidence interval = -0.50 to -0.19); $P<0.001$). The maximum 24-h gastric residual volume was 8.1 mL (IQR = 2.2–14.3) for each 1 kg in bodyweight. Three (4%) infants were treated for diarrhoea and three infants were treated for vomiting.

Conclusions: The majority of infants with a prolonged PICU stay showed weight improvement when using PE-formula. PE-formula was well tolerated because gastrointestinal symptoms only occurred in few infants

INTRODUCTION

Critically ill children are at risk of developing malnutrition during a stay in a paediatric intensive care unit (PICU). Studies in Dutch populations have shown that 14% to 32% of critically ill infants already suffer from acute or chronic malnourishment upon admission to the PICU.[1,2] Development of malnutrition during PICU stay is associated with increased mortality, length of mechanical ventilation and length of stay.[3,4] Infants are particularly vulnerable to malnutrition because of their limited body reserves and their higher nutrient requirements for growth and development.[4-6] Also, a prolonged PICU stay is associated with lower weight-for-age (WFA) Z-scores during and after admission in critically ill infants.[2] Therefore, providing optimal nutritional support is especially important in critically ill infants admitted for a prolonged time to the PICU.[6,7]

This optimal nutritional support should account for the different phases (acute, stable and recovery) of critical illness.[8] During the acute phase, there is a considerable risk of overfeeding and nutrient restriction might be beneficial in the early acute catabolic phase.[9] During the stable and recovery phase, there will be a shift from catabolism to anabolism and nutritional support should focus on increasing protein and energy intake to enable recovery, growth and catch-up growth.[8]

The preferred route to meet energy and nutrient requirements is via enteral nutrition (EN). This is challenged by multiple barriers such as delayed initiation, fluid restriction, interruptions as a result of perceived feeding intolerance and prolonged fasting around procedures.[6] The use of standard infant formulas may result in nutritional deficits as a result of the lower energy and protein content of these formulas. Previously, it has been shown in a small group of infants that protein balances were positive in the first days after admission with the use of protein and energy-enriched (PE)-formula compared to standard formula.[10] However, no data are available on the prolonged use of PE-formula on recovery and growth. The present study aimed to describe the feasibility of PE-formula in infants with a prolonged PICU admission by means of assessing gastrointestinal tolerance parameters and weight achievement.

METHODS

Patients and setting

This retrospective database study was conducted at a multidisciplinary tertiary PICU. All medical records of infants admitted from January 2007 until June 2017 using a PE-formula (Infatrini®; Nutricia, Zoetemeer, The Netherlands) were reviewed concerning demographic variables, daily nutritional intake and duration of PE-formula and gastrointestinal symptoms.

Inclusion criteria were: (i) age between 37 post-menstrual weeks and 12 months; (ii) a prolonged PICU stay defined as a PICU stay of ≥14 days; (iii) a minimum of 14 days enteral feeding with PE-formula; and (iv) at least 80% of energy intake from PE-formula on days with PE-formula use (energy intake provided by PE-formula divided by the total energy intake; enteral and parenteral). Exclusion criteria were: (i) oral intake other than human milk or formula; (ii) interruptions from PE-formula of more than 5 days or of more than 20% of the total duration of PE-formula use; and (iii) less than two weight measurements reported or weight measurements less than 14 days apart during the period of PE-formula. The study protocol was approved by the institutional review board of the Erasmus Medical Centre, Rotterdam, The Netherlands (MEC-2017-316). The committee waived informed consent as a result of the retrospective design.

Nutritional intake

The type of enteral feeding was mainly chosen on discretion of the clinician using a nutritional protocol in which fluid restriction was taken into account. Human milk was the first choice and preferred in all critically ill infants. In general, a PE-formula (100 kcal per 100 mL; 2.6 g protein per 100 mL) was started if human milk was not available in mechanically ventilated children >3.5 kg and below the age of 12 months and in non-ventilated children on the discretion of the clinician. The preferred route was via a post-pyloric tube. EN was started as soon as possible after admission, preferably the day after admission. PE-formula was generally switched to standard formula after weaning from ventilation or when the weight goal was achieved. If EN was tolerated, feeding was increased until an energy target of twice the individual calculated resting energy expenditure (using the Schofield equation for weight) was achieved in all critically ill infants.[11]

Anthropometric measurements

Weight measurements were performed according to local protocol at the start and end of PE-formula use. Z-scores for WFA were calculated using Dutch reference standards (*GROWTH ANALYSER RCT, version 4.0; https://growthanalyser.org*).[12] Changes in nutritional status were determined as the difference between WFA Z-scores at start and end of PE-formula use. The age of the infants was corrected for prematurity for all measurements. A WFA Z-score < -2 was used to indicate acute malnutrition.[13] Birth weight Z-scores were compared with WFA Z-scores at start and end of PE-formula use. Birth weight Z-scores were converted using the Fenton growth charts for preterm infants.[14] As a result of the different standard values for expected growth, growth velocity in g kg^{-1} day^{-1} was calculated separately for infants between the ages of 0–3 months, 3–6 months and 6–12 months.[15]

Gastrointestinal symptoms and tolerance

There is no validated definition for feeding intolerance; therefore, gastrointestinal symptoms that are frequently used to describe feeding intolerance were used to determine tolerance to PE-formula. Parameters of enteral feeding tolerance were recorded each day during PE-formula use and consisted of gastric residual volume (GRV) (mL kg^{-1} day^{-1}; yes/no), vomiting (frequency) and defaecation (frequency), as well as treatment for vomiting, diarrhoea and constipation. Constipation was defined as 4 or more days without stools. According to protocol, GRV was checked every 4 h via a nasogastric tube. Gastric retention was defined as GRV exceeding more than 50% of the volume received in the previous 4 h when infants were continuously fed or of the previous bolus feeding volume when intermittently fed. When PE-formula was interrupted by the clinician because of signs of gastrointestinal symptoms, these were also recorded.

Statistical analysis

Data are reported as the number (%), mean (SD or SEM) if normally distributed or as the median [interquartile range (IQR)] if not normally distributed. A paired-sample t-test was used to evaluate the mean difference in WFA Z-scores between start and stop of PE-formula. These measurements were also compared with the WFA Z-scores at birth. Stepwise multivariate linear regression analysis was used to identify which baseline and admission variables were associated with alterations in WFA Z-score during PE-formula use. Investigated variables were gender, birth weight Z-score, prematurely born infants, age and weight Z-score at start of PE-formula, diagnosis, reason to start PE-formula, post-pyloric feeding and caloric intake compared to the target. Variables were included in the model if the association with the outcome had a significance of $P \leq 0.1$. Multicollinearity was assessed by the variance inflation factor (VIF) calculated through a linear regression between all included predictor variables. VIF was calculated by $1/(1 - r^2)$, using the total r^2 from the regression. Multicollinearity assumption is met if VIF is below 2.5. The constant, unstandardised beta values with their corresponding standard errors, 95% confidence intervals (CIs) and P-values were reported for multivariate linear regression model. All statistical analyses were performed using SPSS, version 24 (*IBM Corp., Armonk, NY, USA)*. $P<0.05$ (two-tailed) was considered statistically significant.

RESULTS

Patients

In total, 470 infants received PE-formula during PICU admission within the inclusion period of whom 70 infants were eligible for inclusion in the analysis. Reasons for exclusion were receiving PE-formula <14 days or <14 days between weight measurements (n=335); <37 post-menstrual weeks or >1 year at start (n=28); caloric intake received via PE-formula less

than 80% of total caloric intake (n=33); and an interruption of more than 20% of feeding duration (n=8).

Of infants eligible for analyses, the median (IQR) PICU length of stay was 49.7 (34.9–83.1) days in which they received PE-formula for 29.2 (20.9–54.3) days. Predominant diagnostic groups were post-cardiac surgery (34%), respiratory diseases (19%), cardiac diseases (11%) and neurological conditions (6%) (Table 1).

Nutritional intake

The median (IQR) time between admission to the PICU and start of PE-formula was 8 (1–24) days. Reasons to start PE-formula were 30 (43%) infants in accordance with the protocol for ventilated infants; 30 (43%) infants because of insufficient growth; three (4%) infants because of fluid restriction; five (7%) infants who had already started before admission; and four (6%) infants where the reason to start was not documented in the medical files. The reasons to stop PE-formula were discharge from PICU (n=32); reaching weight goal (n=12); signs of enteral feeding intolerance (n=8); and switching to standard formula after weaning from ventilation (n=3). In two (3%) infants, PE-formula was stopped because the infant died during admission and the remaining 13 (19%) infants had no documented or other reason to stop (Figure 1).

The mean (SD) energy intake from PE-formula was 104.6 (19.4) kcal kg^{-1} day^{-1}, which was 100.9% (21.5%) of the energy target. Forty (57%) infants received the amount of energy which was set as target. The mean (SD) protein intake from PE-formula was 2.72 (0.50) g kg^{-1} day^{-1}.

Weight achievement

The mean (SD) WFA Z-score at start of PE-formula was -1.93 (1.68); 3 (47%) infants had a WFA Z-score < -2. The changes in WFA Z-scores from birth to start of PE-formula and from start to stop of PE-formula are shown in Figure 2. A significant (P<0.001) increase in mean (SD) WFA Z-score of 0.48 (1.10) was noted during PE-formula use and, at the end of PE-formula, the number of infants with a WFA < -2 had decreased to 23 infants (33%). Overall, the median (IQR) increase in body weight during PE-formula use was 5.80 (3.28–9.04) g kg^{-1} day^{-1} and 7.54 (4.70–10.47), 4.49 (1.48–5.82) and 3.88 (2.92–6.18) g kg^{-1} day^{-1} in infants between the age 0–3 months (n=40), 3–6 months (n=13) and 6–12 months (n=17) respectively. Multivariate regression showed that a lower WFA Z-score at start was associated with a higher increase in WFA Z-score during PE-formula use (r^2 = 0.26; b -0.35; 95% CI = -0.50 to -0.19; P<0.001). Other predictive baseline variables (e.g. WFA Z-score at birth, respiratory diagnosis, corrected age at start and reason to start) were not associated with changes in WFA Z-score during PE-formula use.

Gastrointestinal symptoms and tolerance

Overall, five (7%) infants had constipation, whereas another 19 (27%) infants were treated for constipation at least once during PICU stay without fulfilling the criteria for constipation. In total, 47 (67%) infants vomited at least once during the period on PE-formula. Three infants (4%) were treated for vomiting with oral rehydration solution during the use of PE-formula. GRV was measured in 43 (61%) infants receiving EN via gastric or combined (gastric and post-pyloric) route and in 22 (31%) infants receiving EN via a post-pyloric route. The median (IQR) daily GRV of infants receiving EN via gastric or combined route was 0.81 (0.13–2.08) mL kg^{-1} per 24 h. The feeding was provided via boluses (n=10), continuous (n=5) or both continuous and boluses (n=28) in these 43 infants. Gastric retention occurred in two (5%) of the 43 infants via gastric of combined route, as well as in one (5%) infant receiving EN via a post-pyloric route. Parameters of gastrointestinal tolerance are summarised in Table 2.

PE-formula was stopped in eight (11%) infants as a result of signs of enteral feeding intolerance, which comprised vomiting (n=4), gastric retention (n=2) and signs of discomfort (n=2) (Figure 1). Infants received PE-formula for a median (IQR) of 24.5 (15.9–55.0) days before PE-formula was stopped and switched to standard infant formula or an extensively hydrolysed (whey-based) protein and energy-enriched formula.

DISCUSSION

The present retrospective study describes weight gain and parameters of enteral feeding tolerance in critically ill infants with a prolonged PICU stay and beyond the acute phase when using PE-formula. In the majority of the infants, an improvement of WFA Z-score was achieved and, overall, PE-formula was well tolerated. Before starting PE-formula, 47% of the critically ill infants were identified as acutely malnourished, emphasising the importance of adequate nutritional support in this patient group. Previous studies have reported difficulties with respect to achieving energy targets, with enteral intakes ranging from 12% to 38% of the prescribed targets.[1,16-18] In the present study, using PE-formula, 57% of the infants were able to reach the energy target based on twice the individual calculated resting energy expenditure.[11]

Table 1. Patient and admission characteristics

Patient characteristics		**Total group (n=70)**	
Gender male	n (%)	36	(51)
Birth weight (gr) *(N=62)*	mean (±SD)	2448	(±855)
Birth weight z-score *(N=59)*	mean (±SD)	-0.64	(±1.21)
Gestational age (days) (N=63)	median [IQR]	260	[242 - 270]
Age at start (d)[b]	median [IQR]	76.2	[30.0 - 181.8]
Weight at start (gr)	median [IQR]	3943	[3289 - 5803]
WFA Z-score at start	mean (±SD)	-1.93	(1.68)
HFA Z-score at start *(N=14)*	median [IQR]	-1.44	[-2.44 to -0.75]
Admission duration (d)	median [IQR]	49.7	[34.9 - 83.1]
Nutritional intake			
Post-pyloric feeding	n (%)	45	(64)
Feeding strategy	n (%)		
Continuous		27	(39)
Portion		10	(14)
Both[c]		33	(47)
Duration admission to start PE-formula (d)	median [IQR]	8	[1 - 24]
Duration PE-formula (d)	median [IQR]	29.2	[20.9 - 54.3]
Percentage of PE-formula[d]	median [IQR]	98.9	[93.8 - 100]
Diagnostic groups			
Reason for admission	n (%)		
Respiratory insufficiency		30	(43)
Cardiac surgery		15	(21)
Cardiac insufficiency		10	(14)
GI surgery		4	(6)
Surgery other		2	(3)
Sepsis/Infection		1	(1)
Neurology		1	(1)
Other		7	(10)
Primary diagnosis	n (%)		
Cardiac surgery		24	(34)
Respiratory[e]		13	(19)
Cardiac		8	(11)
Neurology[f]		4	(6)
GI surgery		3	(4)
Surgery other		1	(1)
Infection / sepsis		1	(1)
Other		16	(23)

[a]Data are presented either as number of subjects(%), median[IQR] or mean(±SD) ; [b]Age at start was corrected for prematurity in case gestational age was below 37 weeks; [c]Patient received continuous drip and portion feeding during the period of PE-formula; [d]Percentage of energy intake from PE-formula divided by total energy intake (PE-formula, EN and PN) [e]Includes pneumonia, respiratory syncytial virus bronchiolitis and bronchopulmonary dysplasia; [f] Includes neurosurgery, neurotrauma and epilepsy. GI, gastrointestinal; EN, enteral nutrition; PN, parenteral nutrition; PE- formula, protein and energy-enriched formula

Table 2. Gastrointestinal symptoms in infants using PE-formula

Parameter		N (%) or Median [IQR]
Defaecation	Frequency per day	0.93 [0.85-1.00]
N=70	Number of patients with constipation[a]	5 (7%)
	Number of patients treated for constipation	24 (34%)
	Number of patients treated for diarrhoea	1 (1%)
Vomiting	Number of patients with vomiting	47 (67%)
N=70	Number of patients treated for vomiting	3 (3%)
Retention[bc]	*Infants with gastric EN (N=43)[d]*	
N=65	Number of patients with retention	2 (5%)
	Average retention in 24 hours in ml kg^{-1}	0.81 [0.13-2.08]
	Maximum retention in 24 hours in ml kg^{-1}	8.11 [2.18-14.32]
	Infants with post-pyloric EN (N=22)[e]	
	Number of patients with retention	1 (5%)
	Average retention in 24 hours in ml kg^{-1}	2.11 [0.75-4.29]
	Maximum retention in 24 hours in ml kg^{-1}	11.70 [6.64-19.62]

[a] Constipation was defined as 4 or more days without defecation; [b] In 65 infants both gastric residual volume and weight were recorded; [c] Only days with measurement were included in the analyses; [d] Infants receiving EN through gastric route, including infants receiving EN through both gastric and post-pyloric route; [e] Infants receiving EN through post-pyloric route.
PE- formula, protein and energy-enriched formula

Figure 1. Reasons to start and stop PE-formula in 70 infants

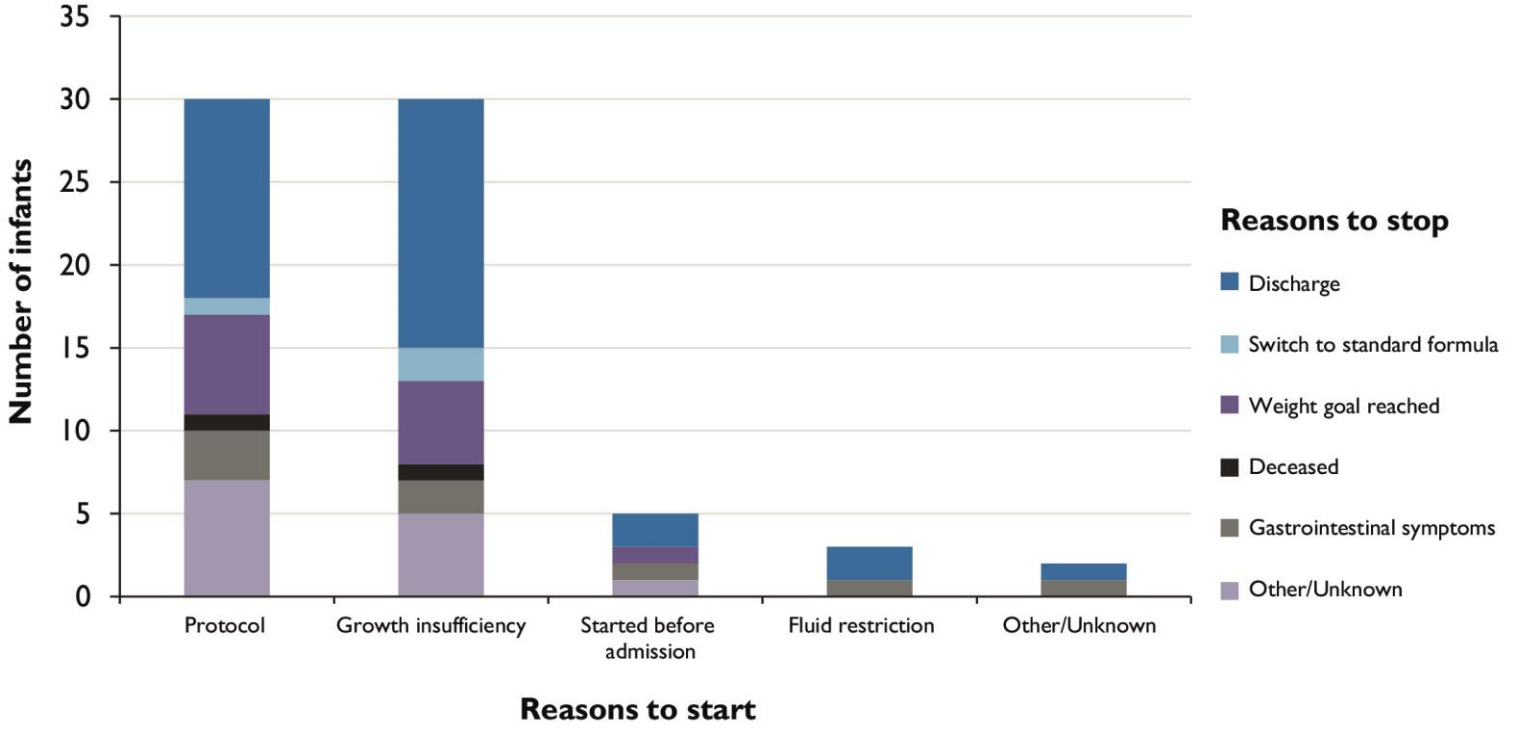
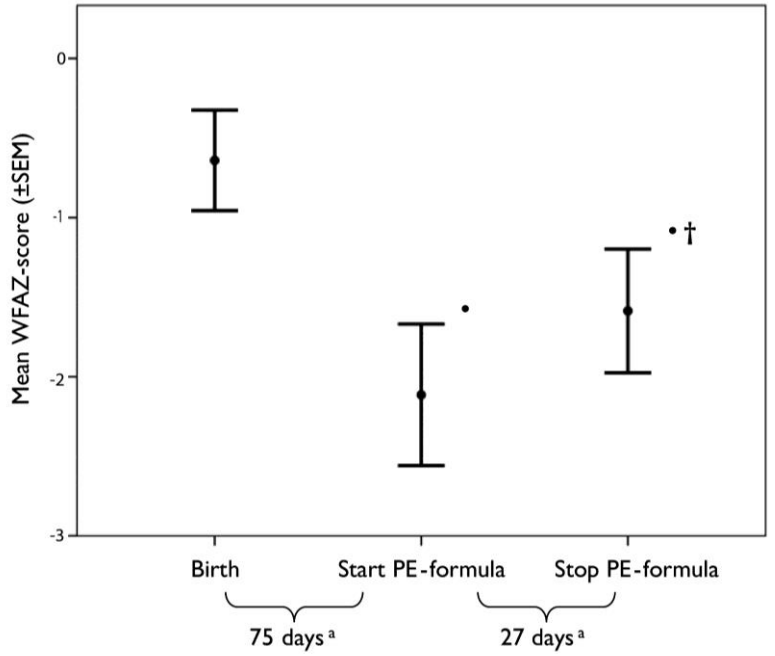


Figure 2. Weight-For-Age Z-scores over time (N=70)



Start moment of PE-formula and stop moment of PE-formula in 70 infants with minimum duration of PE-formula of two weeks; [a] Median duration between two time points; • Value is significantly different when compared to WFA Z-score at birth p<0.001; † Value is significantly different when compared to WFA Z-score at start of PE-formula p<0.001.PE- formula, protein and energy-enriched formula; WFA, weight-for-age. WFA Z-scores at birth (N=59).

Previous studies focusing on the effects of PE-formula compared to standard formula were performed in infants with viral bronchiolitis, infants after cardiac surgery and mechanically ventilated children aged 1 month to 16 years.[10,19,20] In these studies, PE-formulas were well tolerated and a higher energy and protein intake and a positive nitrogen balance were achieved compared to standard formula. In all of these studies, no data were reported about the follow-up of these children and specifically not about growth.

So far, only a limited number of studies have investigated weight achievement when using PE-formulas in non-critically ill children.[21,22] In a study investigating infants with faltering growth receiving either a nutrient dense formula or an energy supplemented formula, the nutrient dense formula showed a trend toward better improvement in length compared to the energy supplemented formula after 6 weeks.[21] Also, infants with complex medical conditions receiving extensively hydrolysed PE-formula for 28 days showed a significant increase in WFA Z-scores.[22] To our knowledge, the present study is the first to examine the course of weight in critically ill infants using PE-formula for a longer period of time. In our study, weight gain was achieved in 93% of the infants, whereas, in 71% of the infants, an increase in WFA Z-score was observed. Moreover, it appeared that infants who had a lower WFA Z-score at start of the PE-formula benefited the most. However, catch-up growth during the recovery phase of critical illness and the implications for short-term and long-term outcome have never been reported. Previously, our research group showed a decrease in WFA Z-score during PICU stay in critically ill infants and children that was related to cumulative negative energy and protein balances.[2] In this previous study, no PE-formula were used. Overall, median weight velocity was 5.80 g kg^{-1} day^{-1}. Also, and as might be expected, weight velocity in infants aged 0 – 6 months was higher than in infants aged 6 – 12 months. Compared with the normal weight velocity data for healthy infants, weight achievement in the present study was similar for the three age groups: 0 – 3 months, 3 – 6 months and 6 – 12 month.[15] Weight gain was achieved by following the nutritional protocol with energy target set at twice the resting energy expenditure (calculated with the Schofield equation for weight).[11] Although indirect calorimetry is currently the golden standard for determining the individual energy requirement during critical illness in the acute phase and to detect over- or underfeeding[23,24] in the stable and recovery phase of (critical) illness, an increase in the amount of energy to enable weight gain is recommended in those infants who have a prolonged stay in the PICU.[8] Moreover, it is suggested to increase the protein-energy ratio to enable adequate (catch-up) growth, especially in (critically) children with acute malnutrition.[25-27]

Intolerance to EN is frequently reported in critical illness but, surprisingly, no uniform definition exists. To report tolerance to PE-formula, we decided to describe gastrointestinal symptoms that are frequently used in relation to EN intolerance in critically ill children, such as large GRV, vomiting, diarrhoea or constipation.[28-30] In the present study, PE-formula was

well tolerated because signs of intolerance only occurred in few of the infants. This is in accordance with previous findings in which early administration of PE-formula in critically ill infants with viral bronchiolitis was also well-tolerated.[10] GRV is one of the most routinely used parameters in the PICU despite a lack of evidence to support this parameter and current guidelines challenge the use of GRV as a marker for feeding intolerance.[6,31] There is also no consensus for a standardised threshold for large GRV; however, the threshold of more than 50% of the feeding volume of the previous 4 h has been used in some studies and is the standard of care in our PICU.[32,33] In the present study, gastric retention occurred in two infants receiving their feeding via a gastric route or a combined route and in one infant receiving EN via a post-pyloric route. We reported GRV separately for the two feeding routes because there is some evidence advising against the routine advancement of post-pyloric tubes. In these infants, large GRV might not indicate feeding intolerance or correlate with delayed gastric emptying. However, gastric aspiration might be useful for detecting tube dislocation when gastric retention does not solely consist of gastric secretion.[34,35] The prevalence of constipation was 7%, which is much lower than previously reported in a study of critically ill children (prevalence of 46.7%).[36] Of note, we did find a large number of infants (62%) who vomited at least once when on PE-formula. In this age group, some regurgitation could be physiological as a result of immaturity. We were not able to differentiate between physiological and non-physiological vomiting. In 11% of infants, the PE-formula was stopped because of signs of enteral feeding intolerance, with vomiting being the most reported reason. This percentage is relatively low compared to the prevalence of enteral nutrition discontinuation as a result of the feeding intolerance reported in literature (prevalence ranging from 7% to 29%).[37-40]

The lack of a comparison group receiving (fortified) human milk or standard infant formula and the retrospective design are major limitations of the present study. It is therefore not known whether the same growth would have been achieved with human milk or standard formula. However, in clinical practice, it is known that achieving adequate nutritional goals is very difficult because these children frequently have fluid restriction, in addition to any consideration of the lower protein-energy ratios of these types of feeding. Other factors, such as intravenous fluid administration and the presence of oedema, might influence body weight and therefore the measured weight may not accurately display the alterations in lean body mass. Unfortunately, we were unable to account for these influencing factors, such as the presence of oedema, because no information was reported in the records. However, by using a long interval between measurements, in conjunction with our experience with respect to children often being oedematous at the start of admission to the PICU, we consider that the influence of possible fluid imbalances on our results was limited. Additional anthropometric measurements to assess the nutritional status, such as length and mid-upper arm circumference, could not be evaluated in this retrospective study. Infants with chromosomal or syndromic disorders were not excluded and specific growth charts were

not taken into account. The final limitation is a possible selection bias in the description of enteral gastrointestinal parameters. Only infants with a prolonged PE-formula use were considered to be eligible in our analysis of the weight course. Consequently, infants in the present study already tolerated PE-formula for at least 2 weeks.

CONCLUSIONS

The majority of critically ill infants receiving protein and energy-enriched formula for a prolonged period gained weight and had an increase in WFA Z-score during PICU admission. Furthermore, signs of gastrointestinal intolerance were sparse during PE-formula use.

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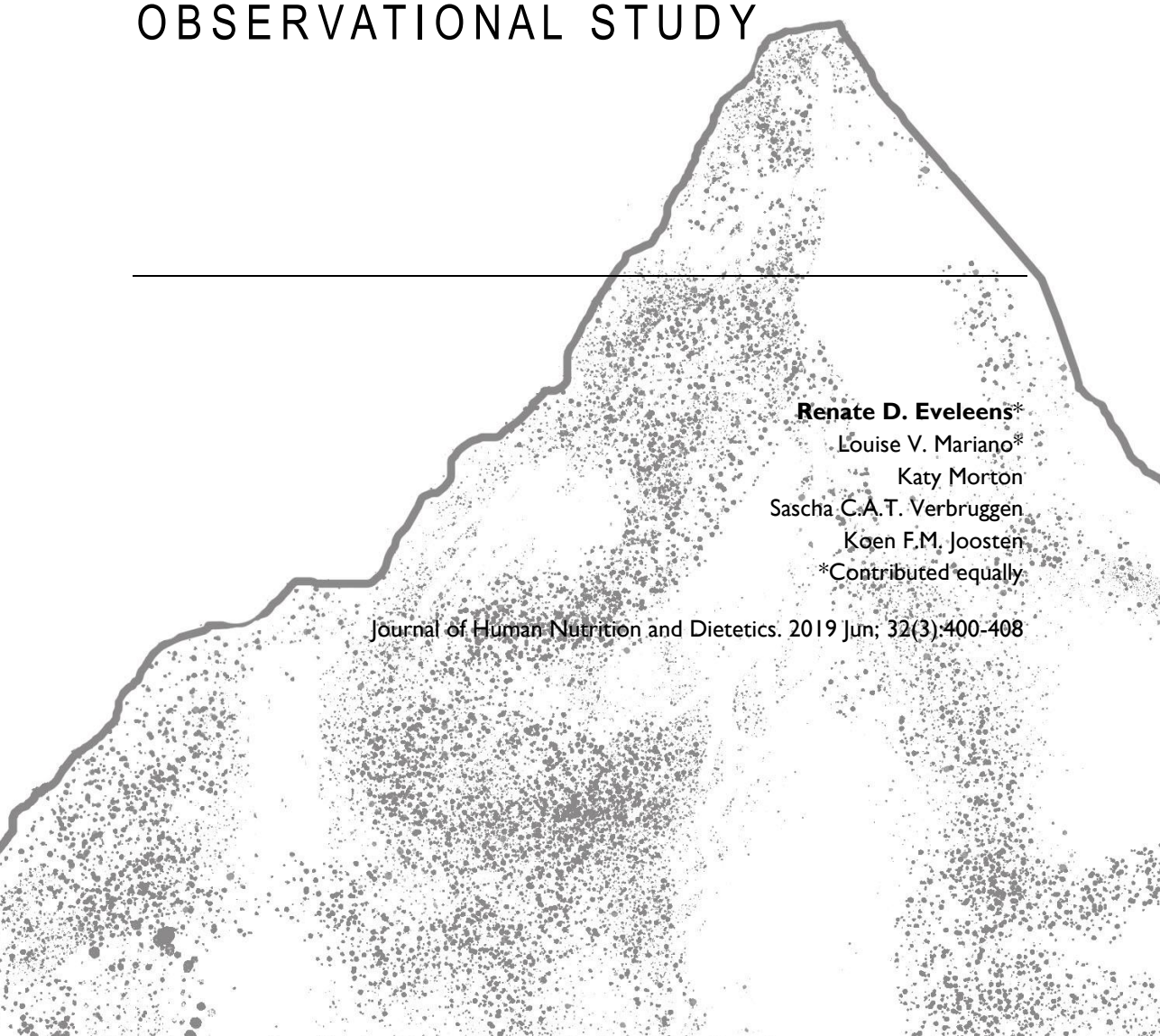
CHAPTER 8

PEPTIDE NUTRIENT - ENERGY DENSE ENTERAL FEEDING IN CRITICALLY ILL INFANTS: AN OBSERVATIONAL STUDY



Renate D. Eveleens*
Louise V. Mariano*
Katy Morton
Sascha C.A.T. Verbruggen
Koen F.M. Joosten
*Contributed equally

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ABSTRACT

Background: Enteral feeding is challenging in critically ill infants. Target intakes are often not achieved as a result of fluid restriction, procedural interruptions and perceived enteral feeding intolerance. In those infants perceived to have poor feeding tolerance, the use of a peptide nutrient-energy dense enteral feed (PEF) may improve nutritional intake and minimise feeding interruptions as a result of gastrointestinal symptoms. The aim of this observational study was to characterise the use of a PEF amongst critically ill infants in two paediatric intensive care units (PICUs).

Methods: Records from critically ill infants aged <12 months admitted to two PICUs were retrospectively reviewed with a PICU length of stay (LOS) ≥ 7 days. Achievement of nutritional targets for the duration of PEF was reviewed. Gastrointestinal symptoms, including gastric residual volume, constipation and vomiting, were evaluated as tolerance parameters.

Results: In total, 53 infants were included, with a median age on admission of 2.6 months. Median admission weight was 3.9 kg in PICU-1 and 4.7 kg in PICU-2. Median (interquatile range) energy intake in PICU-1 and PICU-2 was 68 (47-92) and 90 (63-124) kcal kg-1, respectively, and median (interquatile range) protein intake 1.7 (1.1-2.4) g kg-1 and 2.5 (1.6-3.2) g kg-1, respectively. Feeding was withheld because of feeding intolerance in one infant (4%) on two occasions in PICU-1 for 2.5 h and in two infants (7%) on two occasions in PICU-2 for 19.5 h. Gastric residual mean (SD) volumes were 3.5 (5.4) mL kg-1 in PICU-1 and 16.9 (15.6) mL kg-1 in PICU-2.

Conclusions: Peptide nutrient-energy dense feeding in infants admitted to the PICU is feasible, well tolerated and nutritional targets are met. However, with this study design, it is not possible to draw any conclusions regarding the benefit of PEF over standard PE feed in critically ill children and future work is required to clarify this further.

INTRODUCTION

Feeding a critically ill child appropriately is difficult. There is often a discrepancy in what is prescribed and what is delivered and the cumulative deficits of protein and energy are associated with impaired outcome.[1] Optimal nutritional support evolves with the acute, stable and recovery phase of critical illness. During the acute phase, energy intake to a maximum of the resting energy expenditure is recommended with increasing amounts of nutrition perceived to be required during stable and recovery phases.[2] However, target intakes are often not achieved as a result of fluid restriction, procedural interruptions and perceived enteral feeding intolerance. [3,4] In those infants perceived to have poor feeding tolerance, the use of a peptide nutrient-energy dense enteral feed (PEF) may be tolerated better and improve nutritional intake.[5] Limited research to date has focused on the optimal nutrition composition of nutrients during the time course of critical illness in children.[6-8]

Traditionally polymeric enteral feeds are used as first line;[8-9] however, the metabolic utilisation and assimilation of proteins, carbohydrates, fats and other nutrients during critical illness may be affected by hypoxaemia, dysbiosis and impoverishment of the microbiome.[10-12] As such absorption, tolerance and utilisation of protein[13], fats and energy may be altered.[14-15]

Peptide feeds are usually considered as a second line when tolerance to complex feeds cannot be established,[5,8,16] such as with ongoing diarrhoea, vomiting and abdominal distention resulting in feeding interruptions.[8,17] Nutrient-energy dense whey based protein feeds have been successfully used in critically ill infants during the first week of admission, resulting in significantly higher de novo arginine synthesis and higher nutritional intakes compared to standard infant feeds alone.[18,19] The aim of this retrospective observational study was to describe the use of a peptide nutrient-energy dense enteral feed amongst critically ill infants with a paediatric intensive care unit (PICU) length of stay ≥7 days, in two different PICUs, considering feasibility, tolerance and nutritional targets.

METHODS

Subjects and setting

A retrospective observational study was completed in two PICUs to investigate the feasibility and tolerance of a ready to use PEF (100 kcal and 2.6 g protein per 100 mL; Infatrini Peptisorb®; Nutricia, zoetermeer, The Netherlands), amongst critically ill infants <12 months of age in infants with a PICU length of stay (LOS) ≥ 7 days. In PICU-1, the standard of care is to provide a PEF onadmission to all critically ill infants and, in PICU-2,

PEF is provided to infants with gastrointestinal symptoms or perceived feeding intolerance. The units were comparable in size and number of patients admitted per year. PICU-1 and PICU-2 are both tertiary paediatric intensive care units and based in Southampton, UK (PICU-1) and Rotterdam, The Netherlands (PICU-2), respectively (Table 1).

As a result of the different feeding practices, data collection time periods varied. Retrospective data were collected for a 2-year period from (2016–2018) in PICU-1 and a 5-year period (2013–2018) in PICU-2 to identify all infants with a PICU LOS ≥ 7 days up to 21 days who received PEF. Inclusion criteria were: children aged 0– 12 months and critically ill infants with a PICU stay ≥7 days. Exclusion criteria were premature infants ≤37 weeks gestational age at the time of admission (corrected age) and infants who had not received PEF or whose PICU LOS was ≤7 days. The University Hospital Southampton NHS Foundation Trust (UK) retrospective study was registered as a service evaluation within the NHS Trust (reference SEV03) and Erasmus University Medical Centre (The Netherlands) was the study protocol was approved by the institutional review board (MEC-2017-316).

Fluid and nutrition management

In PICU-1 and PICU-2, nutritional targets are based on the calculated resting energy requirements (REE) using Schofield equation for weight[20] (Table 1). In PICU-1, energy target during the acute phase was calculated as 100% of REE and, in the stable and recovery phase, as 140% and 160% of REE, respectively. In PICU-2, PEF energy target was set at 200% of REE for the stable and recovery phases.[20-22]

Anthropometric measurements

Anthropometric measurements were performed and recorded in accordance with local Standardised Operating Procedures and World Health Organisation (WHO) guidelines,[23] weight was corrected for prematurity in those infants born ≤37 weeks. Infants ≤12 months of age were weighed naked and weight was measured to the nearest 0.001 kg using a digital scale.

A dataset from each of the centres was downloaded into EXCEL (Microsoft Corp., Redmond, WA, USA). Z-scores were calculated using ANTHRO, version 3.3.3.[24] WHO growth reference interpretation of cut-offs for malnutrition was used. Malnutrition was defined as a weight for age ≤ -2 Z-scores of the mean of the WHO child growth standards.[23] For ex-preterm infants, weight Z-scores were corrected using the Fenton growth charts for preterm infants.[25]

Gastrointestinal symptoms

Gastrointestinal symptoms were recorded each day from the start of PEF and included: gastric residual volume (GRV) (mL kg^{-1} day^{-1}), vomiting (frequency) and constipation defined

as ≥4 days without stools. Medication for diarrhoea was also recorded in PICU-2. Furthermore, it was recorded when PEF was interrupted by the clinician because of signs of gastrointestinal symptoms.

Statistical analysis

Statistical analyses were performed in SPSS, version 24 (IBM Corp., Armonk; NY, USA). The results are expressed as the mean (SD) or the median with the interquartile range (IQR), and with the percentage and number for binary or categorical data.

RESULTS

Demographics of infant populations

In total, 53 children met the study inclusion criteria of a PICU length of stay ≥7 days and receiving PEF. The median duration of mechanical ventilation was 168 h in PICU-1 and 143 h in PICU-2. Mean (SD) length of stay was 9.9 (3.4) days in PICU-1 and 13 (2.9) days in PICU2. Predominant diagnostic groups were post-cardiac surgery, respiratory diseases and sepsis (Table 2).

Nutrition support: energy intake

The median (IQR) time between admission and start of PEF was 1 (1–1) days in PICU-1 and 14 (1–30) days in PICU-2. Reasons to start PEF in PICU-1 were standard nutrition protocol (100%) and, in PICU-2, growth insufficiency (14%) started PEF prior to admission (18%), fluid restriction (3%) or clinician led decision (61%). The reason to stop PEF in PICU-1 was discharge from the unit (89%) or death (11%) and, in PICU-2, was discharge from the unit (50%), change to standard infant formula (7%), weight goal achieved (11%), resolved gastrointestinal symptoms (7%) or death (11%). Nutritional intake increased following the commencement of PEF in both centres (Table 3).

Gastrointestinal symptoms

The preferred route of feeding in PICU-1 was via a nasogastric route and PICU-2 via a post-pyloric enteral tube. One infant admitted in PICU-2 fulfilled the criteria for constipation and required treatment. In PICU-1, vomiting occurred in 11 infants (40%) with a median (IQR) frequency of 2 (1–5) vomits per day. GRV was measured in 22 (88%) infants, with mean (SD) GRV of 3.5 (5.4) mL kg^{-1} day^{-1}. Feeding was withheld for perceived feeding intolerance (e.g. nonspecific gastrointestinal symptoms) in one infant (4%) on two occasions for 2.5 h. In PICU-2, vomiting occurred in 23 infants (82%) with a median (IQR) frequency of0.3 (0.0–1.2) vomits per day. GRV was measured in 28 (100%) infants, with mean (SD) GRV of 4.7 (5.6) mL kg^{-1} day^{-1} and a maximum GRV over a 24-h period of 16.1 (15.8) mL kg^{-1} day^{-1}.In PICU-2 GRV was further specified into the two feeding routes. Gastric fed infants had a

mean (SD) GRV of 3.5 (2.9) mL kg^{-1} day^{-1} and post-pyloric fed infants a GRV of 5.4 (6.9) mL kg^{-1} day^{-1}. Feeding was withheld for perceived feeding intolerance in two infants (7%) on two occasions for 19.5 h. In PICU-2, medication for the management of diarrhoea was prescribed to four infants (14%) on a median (IQR) of7 (3–14) occasions.

Feeding interruptions: procedures

In both centres, the most common non-feeding related interruptions were as a result of airway procedures, surgery or clinical deterioration e.g. escalation of inotropic support (Table 3).

Change in weight for age Z-score during peptide nutrient-energy dense enteral feeding

Mean (SD) weight for age Z-score on admission was -2.0 (2.2) in PICU-1 and -0.8 (2.5) in PICU-2. There was a positive change in weight for age Z-score during PICU stay amongst infants who were weighed during the observational study period (n=17).

DISCUSSION

The results of the present observational study suggest that the use of peptide nutrient-energy dense formula in critically ill infants in two centres with differing populations and feeding practices is feasible, without any major complications being found. Expert consensus recommend polymeric enteral feeds and the use of protocols to guide in the detection and management of feed intolerance,[21,16] suggesting that peptide feeds be provided where there is failure to establish enteral feeding or in for those children who will not tolerate whole cow's milk protein.[16,26,27] The use of a PEF may further improve nutritional intake and minimise feeding interruptions as a result of gastrointestinal symptoms.

In this observational study, there were two different approaches to enteral feeding. In PICU-1, the approach was to gastrically feed infants proving PEF from admission with the aim of ameliorating episodes of perceived feeding intolerance. In PICU-2, infants were post-pylorically fed, providing PEF only when there was perceived feeding intolerance.[26,28] The predominant diagnostic group in this observational study was post-cardiac surgery in infants with congenital heart disease (CHD) on vasoactive inotropes. Infants with CHD are a notably challenging group to adequately nourish during the peri-operative period because they are often malnourished prior to surgery with poorer post-operative resilience[29-31] and as a result of post-operative fluid restriction post-operatively[32,33] and the use of inotropes with the concern of risk of inadequate bowel perfusion.[34]

Concerning the amount of energy provided, 135% and 213% of REE was achieved in PICU-1 and PICU-2, respectively, indicating that, with the use of PEF, it was possible to meet recommended nutritional requirement amongst infants in the different phases of disease (PICU1, acute phase, PICU-2, stable and recovery phase). Previously, Gentles et al.[35] reported that only 54% of infants with CHD achieved REE during a PICU admission (median length of stay 5 days). More recently, Zhang et al.[36] compared nutritional intake of post-surgical infants with CHD who were randomised to receive standard infant formula or a polymeric protein-energy dense (PE) energy intake. Those who received PE formula had an higher average energy intake during the 7-day intervention period, suggesting that nutrient dense formula may better enable nutritional targets to be achieved {Zhang, 2018}. In other studies considering a mixed PICU population, energy goals are reported to be achieved in 36%–76% of critically ill children up to day 10 of admission.[1,37-40] A recent study evaluated the use of use of a PE formula in critically ill infants with a LOS ≥14 days and reported that 57% of infants achieved energy targets calculated as twice the REE.[41]

Inadequate intake and gastrointestinal symptoms are the most commonly used descriptors to describe feeding intolerance.[42-44] Despite the lack of evidence to support the use of GRV as a surrogate for delayed gastric emptying,[26,44,45] large GRV has been used as the most common reason for feeding interruptions.[6,40,46] Both centres in the present study had similar criteria GRV as a surrogate marker of gastric emptying. GRV was measured in 88%–100% of infants, with mean (SD) GRV low measured volumes [3.5 (5.4) to 4.7 (5.6) mL kg^{-1} day^{-1}]. It is debatable if routine assessment of GRV measurements should be used in infants receiving enteral nutrition via post-pyloric route, the standard route in PICU-2.[47,48] Therefore, GRV was reported separate for the post-pyloric [5.4 (6.9) mL kg^{-1} day^{-1}] and gastric route [3.5 (2.9) mL kg^{-1} day^{-1}] in PICU-2. In this study, enteral feeds were withheld for perceived feeding intolerance in 4% and 7% of infants in PICU-1 and PICU-2, respectively, which is lower than reported in other studies (11–19%).[3,49] Therefore, our results suggest the use of a PEF for infants was suitable without increased GRV's or feeding interruptions as a result of perceived feed intolerance compared to previous studies.

Vomiting occurs common in critically ill children and is taken as a sign of feeding intolerance[50] or iatrogenic withdrawal from sedation.[51] Feeding is often withheld following episodes of vomiting because concerns of increased risk of aspiration.[6] Both PICUs used morphine and midazolam as analgesic and sedation agents, although it was not possible to determine the causality of vomiting (e.g. feeding intolerance, or withdrawal from sedation arising from prolonged use).

Malnutrition is associated with prolonged PICU-LOS, increased morbidity and mortality,[29,31,52-54] with a reported incidence of up to 24% in European centres.[55-57] In the

present study, the incidence of moderate acute and persistent malnutrition was similar in both units with 16%–18%. The use of PE formula in critically ill children has been associated with improved weight for age Z-score during PICU stay.[36-41] Although only 17 of the 53 infants had serial weight measures completed during the observational period, in those in whom it was completed, there was a positive change in weight for age Z-score. Similar findings have been described with the use of PEF amongst non-critically ill infants with complex disease and growth faltering.[27]

Our understanding of gastrointestinal function during critical illness is limited and although it is assumed a child's gastrointestinal tract is completely functional and capable of normal digestion and absorption during acute illness, this may not be the case.[6,58] Gastric emptying is complex and influenced by the type of food and form; for example, liquid over solid and feed composition,[59] disease pathology and mode of feed delivery,[61,61] and feed osmolality.[62] Both extensively hydrolysed protein and medium chain triglyceride rich infant feeds have been shown to empty from the stomach faster than respectively diets with whole protein and long chain fats.[63,64] In a single-centre prospective cohort study in ill critically ill children (n=291), factors were analysed that were associated with peptide-based formula prescription. These factors were malnourishment, fasting >48 h as a result of feed intolerance and use of a-adrenergic drugs.[5] In the present study in PICU-2, the reasons to start PEF were growth insufficiency, starting PEF prior to admission, fluid restriction or a decision by the clinician based on clinical judgement.

There are a number of limitations to the present study, particularly with regard to the retrospective nature of the cohort, limited study numbers and the lack of a comparison group (e.g. standard infant or PE formula) and, as such, it is not known whether a similar nutritional intake would have been achieved or whether the incidence of gastrointestinal symptoms would have been any different. Also, the time periods for each cohort were different because of variances in unit practice and thus feeding strategies. As there is a paucity of comparative or prospective data within a randomised controlled study it is not possible to draw any causal relationships. However, from the results presented, the use of peptide-nutrient energy dense feeds in critically ill infants with a prolonged PICU-LOS appeared to be well tolerated and resulted in few interruptions as a result of feed intolerance, enabling recommended nutritional requirements to be met during critical illness. Further larger multicentre studies will be required to investigate the relationship of PEF in this setting and the impact on short-term and long-term outcomes.[65]

CONCLUSIONS

Peptide feeding in two different centres with different population and feeding indications is feasible without any major complications found. Infants met nutritional targets and there were minimal feeding interruptions arising from feeding intolerance. There may be a role for the use of peptide nutrient-energy dense feed in critically ill infants who are difficult to feed as a result of feeding intolerance and gastrointestinal symptoms. However, with this study design, it is not possible to draw any conclusions regarding the benefit of PEF over standard PE feed in critically ill children and future work is required to clarify this further.

Table 1. Description of standard practices in study units

	PICU 1	PICU 2
Unit size	16 PICU beds Admit 0 – 17 years	24 PICU beds Admit 0 – 17 years
Fluid allowance	12 – 24 hrs post admission 2 – 3 ml/kg/hr (48-72ml/kg/day) and 4ml/kg/hr (96ml/kg/day) on consecutive days; once extubated 5 – 6ml/kg/hr; restricted after (cardiac) surgery	Depending on age fluid 5 – 7.5 ml/kg/hr (120 – 180) ml/kg/day); restricted after (cardiac) surgery
Registered nurse: patient ratio	1:1	1:2
Written feeding policy	Yes	Yes
Dedicated dietetic support	Yes	Yes
Estimated energy estimation	Schofield equation (adjusted age, sex, weight)	Schofield equation (adjusted age, sex, weight)
Energy goals (sedated ventilated children)	Aim to achieve energy goal by day 5	Aim to achieve energy goal by day 3
Gastric residual volume measured	Yes – every 4 hours	
Response to GRV	If GRV > 4 hours or > 200ml, replace ½ of the GRV and stop feed for 2 hours. When GRV > 50% persists, feeding is halved	If GRV > 50% of feeding volume in 4 hours, replace GRV and subtract from next feeding. When GRV > 50% persists, feeding is halved
Feeding methods used	Continuous feeds over 20 hours with 4 hour break; 6am – 10m	Continuous feeds over 24 hours
Target feed start time	Within 6 hours	Within 24 hours
Feed advancement rate	0.5 – 1ml/kg/hr depending on fluid allowance	Non cardiac diagnosis: 2ml/kg/hr Cardiac diagnosis: 0.6 – 2 ml/kg/hr depending on fluid allowance
Post-pyloric tubes	Not first line, only if ongoing feed intolerance or high risk patients e.g. traumatic brain injury	Standard practise
Standard feed type	Peptide nutrient-energy dense enteral feed (PEF)/ human milk	Nutrient-dense polymeric feed/ human milk

Table 1. Description of standard practices in study units

	PICU 1	PICU 2
Characteristics of nutrient-dense peptide feed	100% extensively hydrolysed whey protein (short chain peptides/ free amino acids), lactose free, maltodextrin, 50% medium chain triglycerides (MCT), 50% long chain triglycerides (LCT), 100kcal and 2.6g protein per 100ml	
Guidance on stopping EN	6 hours prior to extubation, for transport depending on procedure	
Guidance on withholding feeds	Mechanical bowel obstruction, suspected necrotising enterocolitis, significant gastrointestinal bleed, bowel ischaemia, significant abdominal distention; feeding intolerance (e.g. large GRV, vomiting)	
Usual sedation and analgesia for > 1 day ventilation	Morphine and midazolam	

GRV, gastric residual volume, EETs, endotracheal tubes, RDA, recommended dietary allowance, NGT, naso-gastric tube

Table 2. Patient demographics and feeding characteristics

	PICU 1 (N=25)	**PICU 2 (N=28)**
Gender: Male – No. (%)	17 (43%)	13 (46%)
Number of episodes of care (days)	254	513
Diagnosis – No. (%)		
Sepsis/other	4 (16%)	2 (7%)
Respiratory disease	4 (16%)	7 (25%)
Congenital anomalies		3 (11%)
Congenital heart disease	17 (68%)	16 (57%)
RACHS-1 score - median (IQR)	3 (0 – 3)	3 (2 - 4)
Age (months) - median (IQR)	2.6 (0.03 - 6.0)	2.6 (0.4 - 3.6)
Weight (kg) - median (IQR)	3.9 (3.5 - 4.7)	4.7 (3.3 - 5.7)
Weight for age z score - mean (SD)	--2.0 (±2.2)	-0.8 (±2.5)
≤-2 – No. (%)	10 (40%)	4 (14%)
PICU days - median (IQR)	9 (7 – 12)	13.5 (9 – 16)
Mechanical ventilation hours - median (IQR)	168 (138 – 252)	143 (0 – 383)
PIM2 score - median (IQR)	4.4 (1.2 – 8.9)	Not recorded
Inotropes days - No. (%)	132/254 (52%)	130/513 (25%)
Mortality - No. (%)	3 (12%)	5 (18%)

PIM, paediatric index of mortality, RACHS, Risk adjustment for congenital heart surgery

Table 3. Comparison of feeding characteristics

	PICU-1 (N=25)	PICU-2 (N=28)
Day of admission where PEF feeding is started - median (IQR)	1 (1 - 1)	14 (1 - 30)
Kcal/kg intake - median (IQR)	68 (47 – 92)	90 (63 – 124)
Protein g/kg intake day - median (IQR)	1.7 (1.1 – 2.4)	2.5 (1.6 – 3.2)
Enteral Nutrition		
Day 1 – 5 of PEF		
Energy kcal/kg - median (IQR)	32 (6 - 57)	94 (37 - 114)
% REE	61% (10% – 112%)	152% (74% – 229%)
Protein g/kg - median (IQR)	0.9 (0.2 – 1.5)	2.0 (1.0 – 3.0)
Day 6 – 10 of PEF		
Energy kcal/kg - median (IQR)	59 (42 - 84)	104 (70 - 138)
%REE	118% (85% – 168%)	209% (141% – 276%)
Protein g/kg - median (IQR)	1.6 (1.1 – 2.2)	2.7 (1.8 – 3.6)
Day 11 – 21 of PEF		
Energy kcal/kg - median (IQR)	68 (49 - 92)	107 (77- 131)
%REE	135% (98% – 184%)	213 (155 – 262)
Protein g/kg - median (IQR)	1.8 (1.2 – 2.4)	2.8 (2.0 – 3.4)
Gastric fed - No. (%)	24 (96%)	10 (36%)
Post-pyloric tube - No. (%)	1 (4%)	18 (64%)
GRV ml/kg/d (total) – mean (SD)	3.5 (± 5.4)	4.7 (± 5.6)
Gastric fed[a]		3.5 (± 2.9)
Post-pyloric fed		5.4 (± 6.9)
Vomiting per day - No. (%)	2 [IQR 1-5]	0.3 [IQR 0.0-1.2]
Constipation- No. of infants (%)	0 (0%)	1 (3,6%)
Feeding interruption hours - Median (IQR)	0 (0 – 5)	0 (0 – 0)
Interruption reasons % of episodes - No. (%)	2 (4%)	1 (5%)
Extubation/ airway procedure	2 (4%)	1.1 (6%)
Ileus/ Abdominal distention	3.2 (8%)	1.1 (6%)
Surgery	4.4 (11%)	0.6 (3%)
Other/ deteriorating illness		
WAZ scores reported at - Median (IQR)		
day 1 – 5	-1.6 (-3.0 - 0.1) (N=25)	-0.6 (-2.2 - 0.9) (N=28)
day 6 – 10	-1.2 (-2.5 - -0.6) (N=14)	0.2 (-1.8 - 1.6) (N=10)
day >11	-1.2 (-2.4 - 0.0) (N=10)	0.3 (-1.1 - 1.3) (N=7)
WAZ change during PICU stay	1.2 (0.7 - 1.6) (N=10)	0.4 (-0.2 - 1.8) (N=7)

[a] Infants receiving enteral nutrition via a gastric route, including infants receiving enteral nutrition via both a gastric and a post-pyloric route. GRV, gastric residual volume, PEF, nutrient and energy dense peptide enteral feed, REE, resting energy expenditure, WAZ, weight for age Z-score

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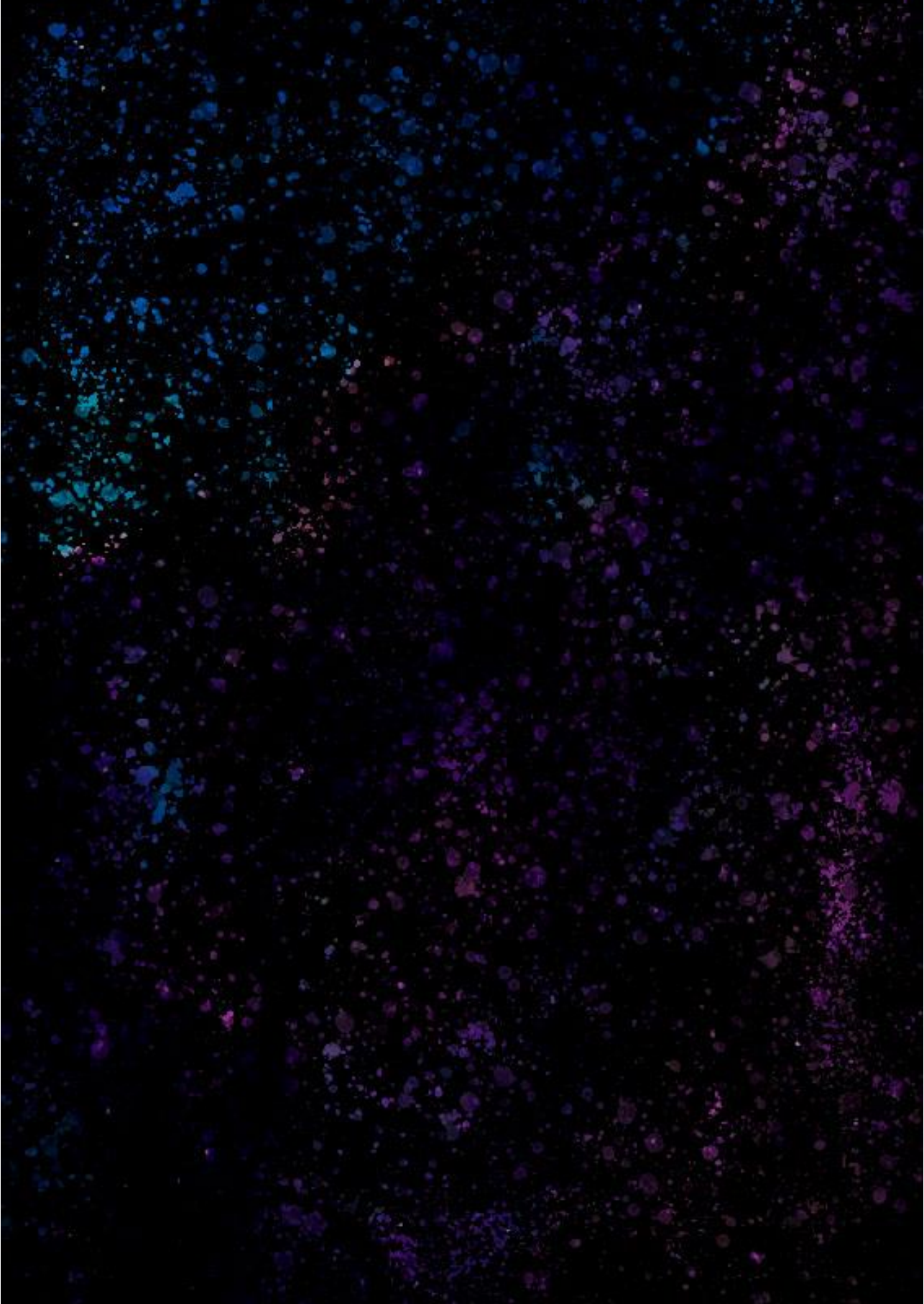
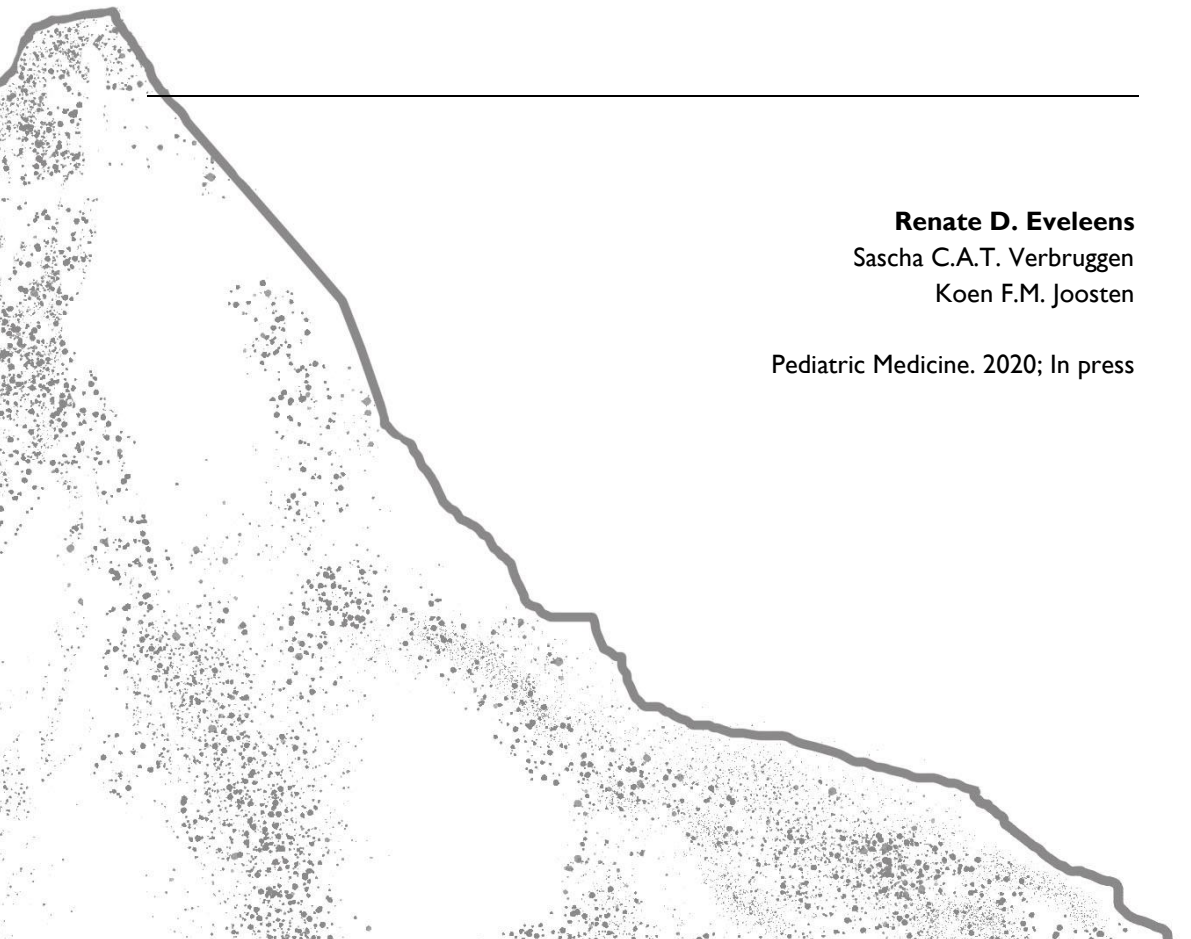


PART III

CHAPTER 9

THE ROLE OF PARENTERAL NUTRITION IN PAEDIATRIC CRITICAL CARE; AND ITS CONSEQUENCES ON RECOVERY



Renate D. Eveleens
Sascha C.A.T. Verbruggen
Koen F.M. Joosten

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ABSTRACT

The goal of nutritional support during critical illness is to provide the appropriate amount of nutrition accounting for the acute, stable and recovery phase in order to accelerate recovery and to improve short-term and long-term outcome. Although the preferred route to provide nutritional support during paediatric critical illness is via enteral route, reaching target intakes is often difficult due to (perceived) feeding intolerance, fluid restriction, and interruptions around procedures. Because undernourishment in these children has been associated with impaired outcome, parenteral nutrition (PN) has therefore been viewed as an optimal alternative for reaching early and high nutritional targets. However, PN recommendations regarding timing, dose and composition varied widely and were based on studies using intermediate or surrogate endpoints and observational studies. It was not until the paediatric early versus late PN in critically ill children (PEPaNIC) randomised controlled trial (RCT) that the advice to reach high and early macronutrient goals via PN was challenged. The PEPaNIC study showed that omitting supplemental PN during the first week of PICU admission as compared with early initiation of PN (<24 hours) reduced new acquired infections and accelerated recovery. The provision of amino acids in particular was negatively associated with short-term outcomes, probably explained by the suppression of the activation of autophagy. Autophagy is an evolutionary conserved intracellular degradation process and it is crucial for maintaining cellular integrity and function, which becomes even more important during acute stress. Results of the long-term PEPaNIC follow up study showed that withholding early PN did not negatively affect anthropometrics and health status but improved neurocognitive and psychosocial development two and four years later. Current guidelines therefore advise to consider withholding parenteral macronutrients for the first week of PICU admission, while providing micronutrients. Although parenteral restriction during the first week of critical illness has been found beneficial, further research beyond the acute phase is warranted to determine the best role of PN in terms of optimal timing, dose and composition in order to improve short-term recovery and long-term developmental outcomes.

INTRODUCTION

Providing optimal nutrition is essential for normal growth, health and development of children. Nutrition is known to both cure and cause diseases, and with this viewpoint in mind, the role of parenteral nutrition (PN) has developed substantially over de last decade. During critical illness the child is subjected to hormonal and metabolic changes, commonly referred to as acute stress response, which temporarily inhibits the normal developmental process in order to survive. Furthermore, the gut is subjected to many adverse influences such as ischemia, altered blood flow, lack of enteral nutrition (EN)and medication. As such, the goal of nutritional support is to provide the appropriate amount of feeding during the different phases of disease in order to accelerate recovery and to have beneficial effects on short-term and long-term outcome. Nutritional requirements of critically ill children depends on many factors, including nutritional status on admission, the underlying and actual diagnosis. Furthermore, the awareness of the changes in amino acid, lipid, carbohydrate and micronutrient metabolism during the different phase of the acute stress response is essential in determining the dynamic metabolic and nutritional support, and thereby counteract malnourishment and overfeeding (Table 1).

Nutritional support

The preferred route to provide nutritional support during paediatric critical illness is via enteral route.[2-5] Enteral nutrition or even trophic feeding is supposed to have a positive influence on reduction of oxidative stress and maintaining the immune response and gastrointestinal mucosal integrity limiting bacterial translocation via the gut. However, the clinical impact of these positive modulations of EN is unknown. Due to many reasons, such as (perceived) feeding intolerance, fluid restriction, fasting around (bedside) procedures, target caloric and protein goals are often not achieved via enteral route and discrepancies between the amounts prescribed and delivered ranges up to 60%.[6-11]

Observational studies have found that malnourishment and underfeeding due to macronutrient deficits are associated with delayed wound healing, reduced immune response, malabsorption, bacterial overgrowth and increased morbidity and mortality.[8,9,12,13] Overfeeding in its turn may lead to intestinal failure associated liver disease (IFALD), hyperglycaemia and increased respiratory burden due to the increase in CO_2 production present by lipogenesis from carbohydrates.[14,15] Besides short-term consequences, both underfeeding and overfeeding have been associated with impaired growth, cognitive functioning and emotional and behavioural problems in non-critically ill children.[16,17] Thus far, the long-term consequences of underfeeding and overfeeding in critically ill children have not been established.

Due to the inability to achieve caloric and protein goals via EN, parenteral nutrition is often initiated in critically ill children. A world-wide survey investigating PN practises in the paediatric intensive care units (PICUs) showed a wide variety between macronutrient and

caloric targets, as well as estimation of energy requirements during critical illness and timing of initiation, amount and composition of PN.[18,19] What should be considered as optimal PN during critical illness is controversial due to the majority of findings that are being derived from observational studies and the inability to provide a causal relationship between nutrition and short-term or long-term recovery and outcomes. To understand the optimal role of PN during paediatric critical illness, the following two fundamental questions should be answered:

1) What is the optimal timing of parenteral nutrition?
2) What is the optimal dose and composition of parenteral nutrition?

Timing of parenteral nutrition

Acute phase

The paediatric early versus late parenteral nutrition in critically ill children (PEPaNIC) RCT, published in 2016 was the first randomised controlled trial (RCT) that aimed to determine optimal timing in critically ill children.[20] This large multicentre RCT involving 1440 critically ill children showed that withholding supplemental PN for seven days (Late PN), as compared with initiating PN within 24 hours after admission (Early PN), improved short-term outcome such as new acquired infections and length of stay.[20] EN was provided in both groups when possible and tolerated within 24 hours and PN was supplemented up to total caloric need following the randomisation groups. When more than 80% of total caloric need was reached enterally, supplemental PN was stopped. Weight deterioration during PICU admission was not affected by the intervention, however, a decrease in weight-for-age z-score itself was associated with worse clinical outcomes in both groups.[21] Furthermore, secondary analyses of the PEPaNIC RCT showed that even term neonates and undernourished children upon admissions benefited from this intervention.[22,23] The results of the PEPaNIC RCT had a great impact on international guidelines which currently advise to consider (supplemental) PN beyond day 7 of critical illness while providing micronutrients.[2-5] So far, it is still the only RCT focussing on optimal initiation of PN in critically ill children in the first week of admission in the PICU.

Stable and recovery phase

Although restriction of PN during the acute phase of illness, continuing this course beyond the acute phase seems detrimental for short-term and long-term outcome. Currently, it is not known at which point in time safe parenteral restriction ends and the potential detrimental effects of macronutrient starvation starts.

During the stable and recovery phases, PN should focus on allowing normal or even catch up growth and successful provision is usually monitored through anthropometric measurements, muscle strength and function) and tissue repair (e.g. wound healing). Nutritional needs can rise above normal requirements for healthy children,[24] however, it is unclear how fast optimal feeding goals can be achieved. A stepwise caloric enhancement is

recommended while providing EN, however the guidelines do not provide recommendations for stepwise enhancement of PN.[4]

Autophagy

The leading explanation behind the counter-intuitive finding of the PEPaNIC RCT is the consequence of early and high nutritional intake to suppress the fasting response, which induces ketosis and activates autophagy.[25-28] Autophagy is an evolutionary conserved intracellular degradation process and it is crucial for maintaining cellular integrity and function. This becomes even more important during acute stress, as children suffer from extensive cell and organ damage, leading to organ failure and muscle weakness. Animal studies showed that impaired autophagic control caused by early PN let to liver and skeletal muscle deficiency.[27] This process was confirmed by a study in adults establishing that early PN did not prevent muscle wasting and even increased adipose tissue deposition in the muscle.[25] These studies open perspectives for therapies that activate autophagy during critical illness. Although still controversial, possible endeavours can lie within pharmacological agents inducing autophagy. For instance an animal experiment found that stimulation of autophagy in the kidney with rapamycin correlated with protection of renal function.[29]

Intermittent PN

PN can be provided continuously over 24 hours as well as intermittently, meaning a period of withholding PN. Several intermittent techniques have been described, including cyclic feeding with a period of fasting (10-12 hours) throughout the night or day. A cyclic regime in non-critically ill children with long-term PN, i.e. children with short bowel syndrome or intestinal failure, has been used for many years and was shown not to change intestinal microbiome[30] and decreased the risk of IFALD and cholestasis.[31] Furthermore, a reduction of serum bilirubin levels and livers enzymes was seen, which was associated with a reduction in both hyperinsulinaemia and fat deposition in the liver.[32,33] Metabolic studies showed that lipid oxidation was higher and dextrose use was lower during cyclic PN.[34,35] Overall, cyclic PN was well tolerated without a higher risk for hypo- or hyperglycaemia, however, using a tapering technique can be considered in younger children as abrupt discontinuation had may cause hypoglycaemia.[36] Based on this evidence cyclic PN is currently recommended in stable patients during and after hospital admission.[37]

Also, there is currently no evidence for continuous versus cyclic PN in critically ill children. Cyclic feeding has some additional hypothetical benefits in critical ill children compared to continuous provision of nutrients, e.g. fasting induces activation of autophagy, preservation of the circadian rhythm and even enhanced protein synthesis.[28,38] This strategy remains controversial, however, the findings in the non-critically ill paediatric population underpin the rationale for a cyclic feeding strategy opposed of continuous feeding which is standard of care in most PICUs and opens perspectives for intervention studies in critically ill children

to define an optimal fasting periods to allow autophagy and potentially improve clinical outcomes.

Parenteral micronutrients

Micronutrients, consisting of vitamins, trace elements and electrolytes, are considered to have an important role in body metabolism, immune response and tissue function, and are therefore essential during critical illness. While the current guidelines on parenteral nutrition in critically ill children recommended to consider withholding PN for the first week of admission, they advise to maintain supplementation of micronutrients during this time window.[2-5] In addition, the ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommend to provide micronutrients daily because this prohibits adverse reactions from transient high levels, except from vitamin K which can be provided weekly without harmful side effects.[39-41]

Dose of parenteral macronutrients

Energy

The actual energy requirement of the child will depend on many factors including medication, need for mechanical ventilation, temperature, (lack of) physical activity and on the phase of the disease. During the acute phase, endogenous energy production accounts for a substantial proportion of energy requirement (up to 75%) irrespective of the energy provision via exogenous source.[42] Therefore, the energy requirement from EN or PN can be much lower than the calculated or measured resting energy expenditure (REE) (Figure 1). During the recovery phase the focus shifts from acute interventions to optimising activity, tissue repair and physical and neurocognitive development. There is an increasing demand in energy during this phase to allow normal development of the child and even to catch up.[2,4,43]

Amino Acids

Amino acid dose requirement is lower via PN than EN due to the bypass of the utilization by the gastro-intestinal tract. A secondary analyses from the PEPaNIC study showed that during the acute phase higher doses of parenteral administered amino acids was negatively associated with PICU length of stay, new acquired infections and duration of mechanical ventilation.[44] Even low doses of parenteral amino acids during the acute phase were found to be harmful, whereby a maximal risk of harm was reached with a median daily dose of 1.15 g/kg for children < 10 kg, 0.83 g/kg for children between 10–20 kg, and 0.75 g/kg for children > 20 kg. Therefore, the current guidelines suggest to withhold amino acids via PN during the first week of illness.[45]

After the acute phase muscle wasting often continues due to immobilization and undernourishment. Therefore, the ESPGHAN/ESPEN/ESPR/CPNN guidelines advise from day eight onwards to provide a minimum amino acid intake of 1.0 mg/kg/min in stable term infants and 0.7 mg/kg/min in children from 1 month – 18 years to avoid a negative nitrogen

balance while the maximum amino acid intake should not exceed 2.1 mg/kg/min in neonates, 1.7 mg/kg/min in infants and children up to 3 years and 1.4 mg/kg/min in older children).[45]

Specific amino acids

Amino acids are classified into essential (cannot be synthesised from other elements), semi-essential and non-essential (can be synthesise from other elements). There is little evidence regarding specific amino acids administration during critical illness. Moreover, the available evidence focusses primarily on (pre)term neonates. Although, trials in adults providing glutamine, a semi-essential amino acid, as a single nutrient or in combination with other nutritional supplements did find a reduction in sepsis and mortality[46] and was found safe in 19 infants after surgical interventions,[47] there seems to be no evidence for glutamine in PN in infants and young children as this failed to show a beneficial effect on outcome and is currently not advised in PN in children up to 2 years.[48-50] The semi-essential amino acid arginine has, among others, a role the endogenous nitric oxide synthesis. A small study in critically ill septic children aged 6-16 years found arginine to increase arginine oxidation for the production of nitric oxide without an effect on arginine synthesis.[51] Nonetheless, due to the overall lack of evidence the SCCM/ESICM guidelines advised against the use of glutamine, arginine, supplementation in children with septic shock or sepsis-associated organ dysfunction.

Carbohydrates

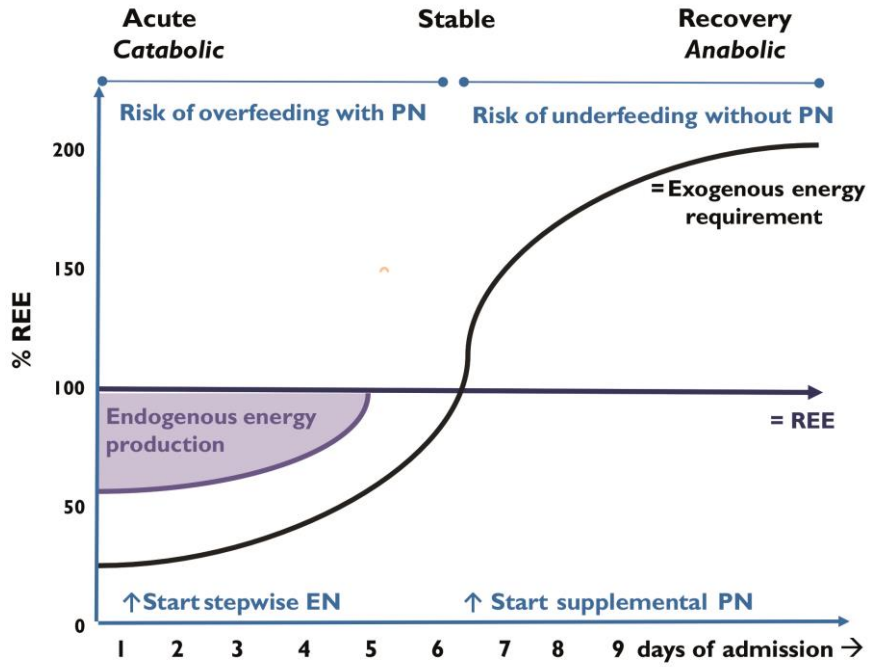
Carbohydrates or glucose are one of the main and preferred energy sources during health and during critical illness. Glucose levels are among others influenced by the route carbohydrates are provided and administration of glucose outside of the main feeding sources, such as medication. Plasma glucose levels are a balance between glucose utilization and exogenous glucose intake and endogenous glucose production (glycogenolysis and gluconeogenesis). During critical illness glucose metabolism is affected due to insulin resistance and β-cell dysfunction, which increases the risk of developing hyperglycaemia. Due to the restricted glucose utilisation in the acute phase lower doses are advised during this acute phase compared to the acute and stable phase. Recommended doses per phase and weight are presented for children from 28 days to 18 years in Table 2.[52] For term neonates it is recommended to start with 2.5-5 mg/kg/min gradually increasing towards 5-10 mg/kg/min. Additionally, during stable and recovery phase the concomitant provision of protein and lipids should be incorporated in the amount of glucose provision. It is important to maintain normal plasma levels of glucose as hyperglycaemia and hypoglycaemia are both associated with impaired outcomes and carbohydrate tolerance should be controlled through glycemic monitoring (<8 mmol/L in critically ill; <10 mmol/L sepsis or traumatic brain injury).[5,52]

Table 1. Definitions of the three phases of the stress response in critically ill children[1] including the nutritional considerations per phase

	Definition	Nutritional considerations
Acute phase Catabolic	First phase after event, characterised by requirement of (escalating) vital organ support. Phase when the patient requires vital organ support (sedation, mechanical ventilation, vasopressors, fluid resuscitation)	1) Energy acquired via endogenous production. Intake requirement lower than REE. 2) Start of enteral nutrition and accepting low and slowly inclining intakes up to 1 times REE, while monitoring patients EN tolerance. 3) Withhold PN during the acute phase (fist 7 days) to allow autophagy and improve clinical outcomes. 4) Be aware of hypo- and hyperglycaemia
Stable phase Catabolic – anabolic	Stabilisation or weaning of vital organ support, while the different aspects of the stress response are not (completely) resolved. The patient is stable on, or can be weaned, from this vital support	1) Stepwise inclining EN intakes, while monitoring patients EN tolerance. 2) Provide PN from day 8 onwards 3) Be aware of hyperglycaemia and IFALD
Recovery phase Anabolic	Clinical mobilisation with normalisation of neuro-endocrine, immunologic and metabolic alterations, characterised by a patient who is mobilising	1) Higher caloric and protein requirements with EN and/or additional PN might be necessary to account for increasing physical activity, tissue repair, and long-term development.

EN: enteral nutrition; IFALD: intestinal failure associated liver disease; PN: parenteral nutrition; REE: resting energy requirement

Figure 1. Dynamic energy need during the different phases of critical illness
EN: Enteral Nutrition; REE: resting energy expenditure; PN: Parenteral Nutrition



Lipids

Parenteral lipid provision should be a fundamental part of PN in critically ill children during stable and recovery phase. Normally, lipid intake accounts for 25-50% of the non-protein caloric intake in parenterally fed patients, however, critical illness can result in acceleration of the lipid metabolism. Providing lipid emulsions is essential because this allows a high energy supply without administering high doses of carbohydrates as an iso-osmolar solution in a low volume. The supply of fatty acids, with a minimum of linoleic acid intake of 0.1 g/kg/day, is essential to prevent essential fatty acid deficiencies.[53] The provided dosage of lipids should not exceed the capacity for lipid clearance and should be lowered in case of hyperlipidaemia (serum triglyceride level is >265 mg/dl (>3.0 mmol/L) in infants >400 mg/dl (>4.5 mmol/L) in children. It is currently advised not to exceed a lipid intake of 4g/kg/day and 3 g/kg/day via PN in infants and children respectively.

Dose of parenteral micronutrients

Comparable to the macronutrients, the micronutrient needs may also differ during the course of paediatric critical illness. During the catabolic acute phase energy expenditure is altered and protein breakdown is increased. The demand for trace elements and water-soluble vitamins, which serve as coenzymes in these metabolic pathways, will rise.

Simultaneously, the cell breakdown results in release of intracellular elements ensuring the availability of many elements. During anabolic phase the micronutrient need rises to allow normal of even catch-up development and patients presenting with deficiencies are more likely during the anabolic phase after a prolonged catabolic phase.[54,55] Increased losses e.g. zinc deficiency as a result of diarrhoea, potassium with vomiting, may also interfere with maintaining optimal levels.

When depletions passed the subclinical phase, it may manifest in encephalopathy, muscle weakness, neuropathy, wound healing and affect cardiac and other organ functions and as a final stage result in death.[54] Critical illness and inflammation are known to have an effect on the plasma levels of micronutrients and associations with deficiencies have been made with continuous renal replacement therapy and cardiac surgery. Low micronutrient levels are reported for thiamine, riboflavin, folate, vitamin B6, vitamin B12, vitamin A, b-carotene, zinc, selenium, iron and chromium, were high or unchanged levels were found for vitamin E, vitamin B6, copper and manganese.[4] The clinical interpretation of blood plasma levels can be misleading during critical illness and might not reflect true intracellular deficiencies.[56] Furthermore, the actual relevance of micronutrient deficiencies or redistribution in critically ill children remains uncertain, nonetheless reported prevalence's are high and associations have been made with adverse outcome.[4,57-59]

Supplementation

Adult studies in critically ill patients confirm the association between micronutrient deficiency and stress response, however, recent randomised controlled trials and meta-analyses failed to find a causality between single or combination of supplemented micronutrients (i.e. selenium, copper, zinc, thiamine and vitamins vitamin B12, D, C & E) and clinical outcomes including mortality, length of stay and time to recover from sepsis.[60-69] Several recent studies have invested in the combination of vitamin C, thiamine and hydrocortisone as a potential therapy to accelerate recovery.[68,70-74] An observational study in paediatric septic patients who received vitamin C, thiamine in addition to hydrocortisone showed improved short-term outcomes compared to hydrocortisone alone.[70] Though, the benefit of this supplementation therapy was not confirmed by a RCT performed in adults.[68]

Because there is currently no evidence for the optimal micronutrient doses accounting for paediatric critical illness,[4] the recommendations provided in the guidelines for parenteral micronutrients are based upon dietary intake recommendations for healthy children and do not account for the phase of illness, potential increased demands or altered losses (Table 3).[4,57-59,75]

Some comments can be made for specific micronutrients:

Sodium

Critically ill children are at risk to develop hyponatremia. A meta-analysis showed that isotonic maintenance fluids with sodium concentrations similar to blood plasma reduce the

risk of developing hyponatraemia when compared with hypotonic intravenous fluids.[76] The evidence suggest to use isotonic fluids for at least the first 24 hours of critical illness or post-operative care, while using the Holliday and Segar formula to calculate the amount of maintenance fluid required.[77-79] In patients with excessive sodium losses sodium chloride solutions can be switched to sodium lactate or sodium acetate to decrease the chloride intake and thereby the risk of metabolic acidosis associated hyperchloraemia.[79]

Iron

Due to the risk of overload via PN iron is preferably provided enterally and in children receiving short-term PN (<3 weeks) iron supplementation is not recommended.[40]

Calcium, phosphorus, magnesium, potassium and Vitamin B1 (Thiamine)

Adequate threshold of calcium, phosphorus and magnesium are required for normal growth and bone mineralization. The risk of developing hypophosphatemia, hypomagnesemia, hypocalcaemia, and hypokalaemia is associated with the provision of nutrients. Especially high nutrient incline after a period of malnutrition placed critically ill children at risk of developing these depletions, commonly referred to as the refeeding syndrome. This syndrome is further characterised by hyperglycaemia and fluid retention causing oedema and can be managed by parenteral trace mineral supplementation and/or caloric feeding restriction.[80] Vitamin B1 serve as a co-factor in the substrate oxidation and depletions are known to affect the neuro and cardiovascular system causing diseased as Beriberi, Wernicke's and Korsakoff syndrome. During critical illness depletions in this micronutrient may occur after introduction of feeding after a period of malnutrition.[81]

Zinc

Zinc serves as a cofactor for over 300 body enzymes including DNA synthesis and RNA transcription and deficiency is characterised by impaired immune function, glucose homeostasis wound healing and growth retardation. Zinc supplementation during critical illness is the only element investigated in critical ill children with two RCTs. The first trial showed in 24 critically ill children that by providing 500 mcg/kg/d plasma levels could be restored to the near 50th percentile.[82] While the second RCT providing whey protein, zinc, glutamine, selenium and metoclopramide versus whey protein in 298 critically ill children and found no differences on the immune status of these children. Additionally, this trial was terminated for futility before half the children were enrolled.[83]

Selenium

Selenium is an essential antioxidant and serves as a cofactor for glutathione peroxidase, an enzyme that is linked to resolving oxidative tissue damage. It is also involved in iodothyronine deiodinase and thioredoxin and thereby having a role in the thyroid metabolism which is affected in the acute phase of critical illness.[84] Selenium deficiency has been associated with e.g. muscle weakness, immune disorders and carcinogenesis in adults, while selenium toxicity have been reported in association with gastrointestinal disturbance,

skin lesions, liver dysfunction and paralysis.[85] The only RCT performed in critically ill children is the previously described RCT which included selenium as one of the added nutrients which showed no favourable outcomes of supplementation of selenium together with whey protein, zinc, glutamine and metoclopramide [83]. Systematic reviews in preterm neonates and adults showed that supplementation of selenium resulted in decreased mortality and duration of ICU stay, however supplemented amounts and methods varied substitutional and no dose recommendations were extracted.[65,86]

Vitamin B12, vitamin C and vitamin D

The anti-inflammatory Vitamin B12 supports macronutrient metabolism and DNA synthesis in health and deficiencies may results in anaemia and neurodegenerative demyelination. The absorption of this vitamin can be affected by gastrointestinal surgery, feeding via post-pyloric tube and using proton pump inhibitors, all common in the PICU.[87] Measured plasma levels are unreliable which hinders detecting deficiencies and clinical trials regarding optimal supplementation are non-existent. The isolated provision of Vitamin C has been investigated and high doses up to 66mg/kg/hour may lead to reduced duration of mechanical ventilation and vasopressor support in critically ill adults, without reporting adverse effects. However, no effect was seen of this antioxidant on mortality in a systematic review combining the 5 RCTs.[88] Vitamin D has been a topic of interest for many years in critical illness due to its important role in calcium and bone homeostasis, cardiovascular system and inflammation.[89] A recent systematic review including 52 studies in critically ill children found a deficiency prevalence of 55% which was indeed associated with mortality.[90] Again, when the 6 available RCTs evaluating Vitamin D supplementation either enteral of parenteral in critically ill adults were combined in a systematic review, no benefit regarding recovery or mortality was found.

Besides acknowledging the potential modulatory effect of micronutrients on the acute stress response, the risk of intoxication caused by over supplementing should not be dismissed. It is an uncommon reported phenomenon during critical illness, nonetheless, safe upper intake levels most be verified to find the balance between both deficiency and toxicity.[91] The limited available paediatric research restrains the guidance for lower and upper levels in the different phases of illness, therefore it might be a practical solution to aim for future research on the micronutrients who require more routine measurements in instable patients. Currently, daily or weekly laboratory measurements are advised for electrolytes (sodium, potassium, chloride, calcium, phosphorus and magnesium), trace minerals (iron, selenium, zinc and copper) and vitamin B12.[92]

Long-term consequences of Parenteral Nutrition

Children requiring long-term PN

Children requiring long-term PN are shorter and have an affected body composition and a higher fat mass compared to healthy subjects.[93] Therefore, the success of PN support should be measured by body composition measurements which includes knowledge on lean body

mass and fat mass and accompanied with muscle mass function and functional status.[94,95] Furthermore. IFALD, cholestasis, metabolic syndrome and catheter-related bloodstream infections are commonly described long-term consequences of PN therapy in children requiring PN due to short bowel syndrome or low birth-weight infants.[93,96-98] The pathogenesis is multifactorial, and association have been made with imbalances in amino acids composition, duration of PN and providing PN continuous (non-cyclical).[99]

In addition, the occurrence of cholestasis or IFALD is highly associated with intravenous lipid emulsions (ILEs) composition. Although there is no evidence suggesting an effect of different ILEs during short-term PN use on cholestasis or bilirubin levels, during long-term PN multicomponent ILEs (with fish oil) may contribute to a decrease in bilirubin levels and cholestasis.[100] Furthermore, composite ILEs are found to be superior to pure soybean ILEs as they have less inflammatory properties, are immune modulating, have higher antioxidant content and prevent against cholestasis and IFALD,[101,102] however no study have assessed the pro- and anti-inflammatory effects of these different ILEs in critically ill children. Therefore, for PN lasting longer than a few days, pure soybean ILEs should not be used and composite ILEs with or without fish oil are the first choice treatment.[53] Provision of pure soybean oil ILEs can be considered in short-term PN with the knowledge that this may provide a less balanced nutrition than composite ILEs.Long-term neurocognitive development of children requiring long-term PN was investigated in 13 studies. The reported prevalence for normal neurocognitive development varied substantial and ranged between 29-100%, with 80-90% of the children in mainstream schools.[97] There was no evidence favouring specific timing (cyclic or continuous) or other variables related to PN such as duration for its long-term consequences on neurocognitive development.

Critically ill children

Due to the advances in medical therapy and thereby increasing PICU survivorship, it becomes more and more important to consider long-term developmental outcomes of PN. Overall, studies investigating PICU survivors find lower scores for neurocognitive functioning as compared with a healthy population or normative scores. Additionally, health-related quality of life, physical and mental health status can also be affected after PICU admission.[103] Additional to the evaluation of body composition and commonly described PN complications, the effect of PN therapy on organ function and short-term and long-term consequences should be monitored when critically ill children are concerned.[104]

Table 2. Advised parenteral glucose dose during acute, stable and recovery phase according to the ESGPHAN/ESPEN/ESPR/CSPEN guideline per age or weight class[52]

	28d-10 kg	**11-30 kg**	**31-45 kg**	**>45 kg**
Acute phase	2-4 mg/kg/min	1.5-2.5 mg/kg/min	1-1.5 mg/kg/min	0.5-1 mg/kg/min
Stable phase	4-6 mg/kg/min	2-4 mg/kg/min	1.5-3 mg/kg/min	1-2 mg/kg/min
Recovery phase	6-10 mg/kg/min	3-6 mg/kg/min	3-4 mg/kg/min	2-3 mg/kg/min

The PEPaNIC RCT was the first interventional study to investigate long-term developmental effects of a PN intervention. Two years after admission, PICU survivors had worse outcomes on anthropometrics, health status, and neurocognitive development as compared with matched healthy control children. Furthermore, the omission of PN during the acute phase of critical illness caused no harm and even resulted in better scores for visuomotor integration, and parent-reported executive functioning, in particular inhibitory control.[105] Due to the large number of young infants in this trial and the plasticity of the developing brain, a longer assessment period was warranted to investigate the effect on all long-term physical, neurocognitive, and psychosocial developmental domains. The four year post-randomisation follow up study affirmed that omitting supplemental PN during the first week of critical illness caused no harm and even resulted in less parent-reported emotional and behavioural problems.[103] These emotional and behavioural problems can arise from poor executive functioning, such as poor inhibitory control which was already affected at the two year post PICU time point.[106,107] These clinical findings were supported by differences in telomere length and DNA methylation between children who received early-PN and late-PN, which substantiates plausible molecular basis of detrimental long-term consequences of high and early provision of parenteral macronutrients.[108,109] However, further research is needed to unravel the underlying mechanisms of the long-term harm caused by high and early parenteral nutrition.

To be able to provide optimal parenteral nutrition beneficial for short-term and long-term outcomes, the timing, amount, composition and concomitant provision of enteral nutrition should be integrated into a comprehensive approach incorporating all these features. First, the optimal timing should be defined for the individual patient which is now based on the PEPaNIC RCT on day 7, followed by a steady stepwise incline towards energy and protein targets to avoid refeeding syndrome.

CONCLUSIONS

Enteral intake is often insufficient in critically ill children which might result in a need for parenteral nutrition. Understanding the course of metabolic needs during the acute stress response is essential before providing parenteral nutrition. Based upon the findings of the landmark PEPaNIC RCT, the current recommendations changed to withhold parenteral nutrition during the first week of admission while continue to provide micronutrients.[2-5] Although this parenteral macronutrient restriction during the acute phase has been found beneficial for critically ill children regarding physical and neurocognitive short-term and long-term consequences, further research is required to obtain the optimal timing, dose and composition of parenteral nutrition during stable and recovery phase as well as the determination of the role of parenteral micronutrients. Furthermore, cyclic feeding or pharmacologic interventions allowing autophagy are controversies to overcome.

Table 3. Advised parenteral micronutrient dose according to the ESGPHAN/ESPEN/ESPR/CSPEN guideline per age class[39-41,79]

Nutrient	Term – 6 m	6 – 12 m	> 12 m
Sodium	Day 1: 0-2 mmol/kg/d Day 2-4: 1-3 mmol/kg/d > d7: 2-3 mmol/kg/d	2-3 mmol/kg/d	1-3 mmol/kg/d
Potassium	Day 1-3: 0-3 mmol/kg/d Dag 4-7: 2-3 mmol/kg/d > d7: 1.5-3 mmol/kg/d	1-3 mmol/kg/d	1-3 mmol/kg/d
Calcium	0.8-1.5 mmol/kg/d	0.5 mmol/kg/d	0.25-0.4 mmol/kg/d
Magnesium	0.1-0.2 mmol/kg/d	0.15 mmol/kg/d	0.1 mmol/kg/d
Phosphate	0.7-1.3 mmol/kg/d	0.5 mmol/kg/d	0.2-0.7 mmol/kg/d
Chloride	Day 1: 0-3 mmol/kg/d Day 2-4: 2-5 mmol/kg/d > d7: 2-3 mmol/kg/d	2-4 mmol/kg/d	2-4 mmol/kg/d
Iron	Not recommended in short-term PN	Not recommended in short-term PN	Not recommended in short-term PN
Zinc	250 µg/kg/d (term - 3 months) 100 µg/kg/d (3-6 months)	100 µg/kg/d (max 5mg/d)	50 µg/kg/d (max 5mg/d)
Copper	20 µg/kg/d (max 0.5 mg/d)	20 µg/kg/d (max 0.5 mg/d)	20 µg/kg/d (max 0.5 mg/d)
Iodine	At least 1 µg/kg/d	At least 1 µg/kg/d	At least 1 µg/kg/d
Selenium	2-3 µg/kg/d (max 100 µg/kg/d)	2-3 µg/kg/d (max 100µ/d)	2-3 µg/kg/d (max 100µ/d)
Manganese	Max 1 µg/kg/d	Max 1 µg/kg/d	Max 1 µg/kg/d
Molybdenum	0.25 µg/kg/d (max 5.0 µg/d)	0.25 µg/kg/d (max 5.0 µg/d)	0.25 µg/kg/d (max 5.0 µg/d)
Chromium	Not advised in PN	Not advised in PN	Not advised in PN
Vitamin A	150-300 µg/kg/d	150-300 µg/kg/d	150 µg/d
Vitamin D	400 IU/d (or 40-150 IU/kg/d)	40-150 IU/kg/d	400-600 IU/d
Vitamin E	2.8-3.5 IU/kg/d	2.8-3.5 IU/kg/d	11 IU/d
Vitamin K	10 µg/kg/d	10 ug/kg/d	200 µg/d
Vitamin C	15-25 mg/kg/d	15-25 mg/kg/d	80 mg/d
Thiamine	0.35-0.5 mg/kg/d	0.35-0.5 mg/kg/d	1.2 mg/d
Riboflavin	0.15-0.2 mg/kg/d	0.15-0.2 mg/kg/d	1.4 mg/d
Pyridoxine	0.15-0.2 mg/kg/d	0.15-0.2 mg/kg/d	1.0 mg/d
Niacin	4-6.8 mg/kg/d	4-6.8 mg/kg/d	17 mg/d
Vitamin B12	0.3 µg/kg/d	0.3 µg/kg/d	1 µg/d
Pantothenic acid	2.5 mg/kg/d	2.5 mg/kg/d	5 mg/d
Biotin	5-8 µg/kg/d	5-8 µg/kg/d	20 µg/d
Folic acid	56 µg/kg/d	56 µg/kg/d	140 µg/d

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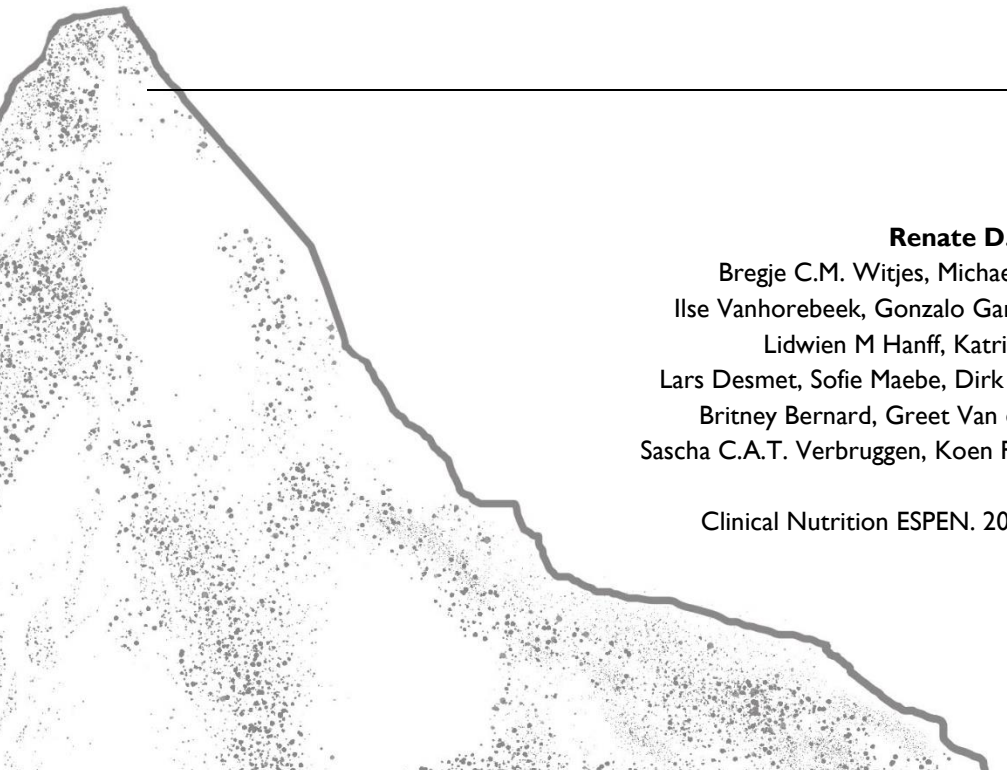
CHAPTER 10

SUPPLEMENTATION OF VITAMINS, TRACE ELEMENTS AND ELECTOLYTES IN THE PEPANIC RANDOMISED CONTROLLED TRIAL: COMPOSITION AND PREPARATION OF THE PRESCRIPTION



Renate D. Eveleens,
Bregje C.M. Witjes, Michael P. Casaer,
Ilse Vanhorebeek, Gonzalo Garcia Guerra,
Lidwien M Hanff, Katrien Cosaert,
Lars Desmet, Sofie Maebe, Dirk Vlasselaers,
Britney Bernard, Greet Van den Berghe,
Sascha C.A.T. Verbruggen, Koen F.M. Joosten

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ABSTRACT

Background & aims: Following the results of the paediatric early versus late parenteral nutrition in critical illness (PEPaNIC) multicentre, randomised, controlled trial (RCT), the new ESPGHAN/ESPEN/ESPR/CSPEN and ESPNIC guidelines recommend to consider withholding parenteral *macro*nutrients for 1 week, while providing micronutrients, in critically ill children if enteral nutrition is insufficient. Critically ill children are suspected to be vulnerable to micronutrient deficiencies due to inadequate enteral nutrition, increased body's demands and excessive losses. Hitherto, micronutrient requirements in PICU are estimated based on recommended daily intakes for healthy children and expert opinion. We aimed to provide an overview of the current practice of micronutrient administration and practical considerations in the three participating centres of the PEPaNIC study, and compare these therapies with the recommendations in the new ESPGHAN/ESPEN/ESPR/CSPEN guidelines.

Methods: We describe the current composition and preparation of the prescribed parenteral micronutrients (consisting of vitamins, trace elements and electrolytes) in the three centres (Leuven, Rotterdam and Edmonton) that participated in the PEPaNIC RCT, and compare this per micronutrient with the ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommendations.

Results: The three centres use a different micronutrient supplementation protocol during the first week of critical illness in children, with substantial differences regarding the amounts administered. Leuven administers commercial vitamins, trace elements and electrolytes in separate infusions both in 4 hours. Rotterdam provides commercial vitamins and trace elements simultaneously via 8-hour infusion and electrolytes continuously over 24 hours. Lastly, Edmonton administers commercial vitamins and institutionally prepared trace elements solutions in 1 hour and electrolytes on demand. Comparison with the ESPGHAN/ESPEN/ESPR/CSPEN guidelines yields in differences between the recommendations and the administered amounts, which are most substantial for vitamins.

Conclusion: The practice of intravenous micronutrient administration differed substantially between the three PEPaNIC centres and in comparison with the current guideline recommendations. This deviation is at least partially explained by the inability to provide all recommended amounts with the currently available commercial products and by the lack of strong evidence supporting these recommendations.

INTRODUCTION

Micronutrients play an important role in metabolism, immune response and maintenance of tissue function.[1,2] Critically ill patients are suspected to be vulnerable to micronutrient deficiencies due to inadequate enteral nutrition, increased body's demands and excessive losses.[3] The relevance of micronutrient deficiencies in critically ill children remains unclear, although reported prevalence's are high and associations with adverse outcome were found.[4-6] It seems justifiable to provide micronutrients, i.e. vitamins, trace elements and electrolytes, early and adequately during critical illness. However, due to a lack of evidence, current recommendations are based upon expert opinion and dietary reference nutrient intake for healthy children.

The provision of parenteral *macro*nutrients during critical illness have been investigated in the landmark Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) Randomised Controlled Trial (RCT). In this RCT, critically ill children (term neonates – 17 years) were randomly assigned to withholding *macro*nutrient provision via parenteral nutrition (PN) during the first week (Late-PN) or to initiation of PN within 24 hours (Early-PN) to reach caloric goals when enteral nutrition (EN) was insufficient.[7,8] The major finding was that the later start of parenteral nutrition (i.e. the intervention arm), resulted in a better clinical outcome.[8,9] However, parenteral micronutrients, including vitamins, trace elements and electrolytes, during this first week of critical illness were provided in both randomization groups within 24 hours when EN was insufficient, so that between group differences in outcome would be solely attributable to differences in macronutrient intake.

The findings of the PEPaNIC RCT had a subsequent impact on the recently published ESPGHAN/ESPEN/ESPR/CSPEN and ESPNIC guidelines on parenteral nutrition in critically ill children, which now recommend to consider withholding parenteral *macro*nutrients, meaning withholding amino acids and lipids provision, and substantial lower carbohydrate intake, during the first week of paediatric critical illness while continuing micronutrient provision.[10,11] In addition, the recent guidelines adapted part of the micronutrient recommendations compared to the previous guidelines which were valid during the PEPaNIC RCT. After publication of the recent guidelines and the PEPaNIC RCT, many practical difficulties on how to supplement parenteral micronutrients without simultaneously providing *macro*nutrients persisted. Therefore, the primary aim of this study was to report the current protocols on composition and preparation of the prescribed parenteral micronutrients in the three centres that participated in the PEPaNIC RCT. Secondly, we performed a comparison between the three local parenteral micronutrient protocols and the recommendations according to the new ESPGHAN/ESPEN/ESPR/CSPEN guidelines regarding timing and amount of administration of micronutrients.

METHODS

Protocols for nutrition in critically ill children were obtained from the three centres. One researcher (RDE) compared micronutrient doses and the technical organisation of their administration between centres and compared these with existing recommendations. For this study micronutrients were defined as both electrolytes as well as vitamins and trace elements. Parenteral *macro*nutrient supplementation is currently withheld during the first week of critical illness in the three participating PICU sites, while providing parenteral micronutrients via standard protocols (University Hospitals Leuven, Leuven, Belgium – Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands – Stollery Children's Hospital, Edmonton, Canada). Each centre individually developed a micronutrient protocol to accommodate the micronutrient supplementation. In the present study, we first report the three protocols for the composition and preparation of the different micronutrient prescriptions, consisting of vitamins, trace elements and electrolytes, as they are currently used per research centre during the first PICU-week if EN is less than 80% of target intake. If the enteral intake exceeds 80% of target intake intravenous micronutrient supplementation is stopped in all three centres. Secondly, these protocols are compared with the new ESPGHAN/ESPEN/ESPR/CSPEN guidelines.[10]

RESULTS

Leuven

The protocol aims at approaching the ESPGHAN/ESPEN/ESPR/CSPEN recommended intake through pragmatic administration of commercially available micronutrient preparations.[10] Vitamins and trace elements are given daily in separate infusions and shielded from daylight. Vitamins are administered over a 4 hour period and diluted in a glucose infusion (Dextrose 5% or 10%), followed by trace elements which are administered via a similar 4 hour infusion. Different doses are used for term infants up to 10 kg, for children >10 kg and <30kg and for children >30kg. Vitamin K is administered weekly. The composition of the two infusions is described in Table 1 for the different weight categories.

Electrolytes are administered via a nurse driven protocol to prevent and/or supplement depletion (e.g. potassium chloride and potassium phosphate). The maintenance fluids provide NaCl 0.9% at roughly 2ml/kg/h (~ 7.2 mmol/kg/day) (Appendix). Potassium phosphate (10 – 40 mg/kg/d ~0.32 mmol/kg/d) is administered distributed over a maximum of three 4-hours administrations per day to avoid simultaneous infusion and potential reaction with copper. Nurses titrate potassium to a target of 3.5 to 4.5 mmol/L, using infusions of 1mmol/kg over 1 hour. Magnesium sulphate (60 mg/kg/d ~ 0.24 mmol/kg/d) is divided over a maximum of three administrations daily as well and adjusted so that magnesium thresholds between 0.63 – 1.05 mmol/L are obtained.

Rotterdam

The provision of micronutrients is based upon the new ESPGHAN/ESPEN/ESPR/CSPEN recommendations.[10] Micronutrients are administered daily via two infusions shielded from direct daylight. The first mixture contains trace elements and vitamins and is administered over an 8-hour infusion period. For this infusion, three commercially available products containing different vitamins and trace elements are mixed in a sodium chloride 0.9% bag and prescribed according to two different weight categories (term neonate – 12 kg and >12 kg) (Table 2). These commercial available products were tested stable during 24 hours at 20-25°C both single and in combination when diluted in sodium chloride 0.9% by their pharmaceutical company. The second mixture contains glucose and electrolytes (sodium, potassium, calcium, magnesium and phosphate) and is administered continuously over 24 hours/day. The electrolyte mixture differs according to two different weight categories (< 5 kg and > 5kg). For preparing the electrolyte solution standard commercially available glucose and sodium chloride bags are used (glucose 5% - NaCl 0.45% < 5 kg or glucose 2.5% / NaCl 0.45% >5 kg) (Appendix).

Edmonton

The provision of micronutrients is based upon the current American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommendations.[12-15] Vitamins and trace elements are prescribed in two different doses for infants up to 12 months and for children >12 months. Vitamins are provided via commercially available products and trace elements are prepared in the local hospital pharmacy (Table 3). The institutionally prepared trace element solution contains zinc, selenium, copper and iodine and is administered daily in a period of 30-60 minutes. The preparation and stability of the trace element solutions have been reported previously.[16] Chromium and manganese are not provided in the solution, as they both exist as contaminants in other parenteral nutrition elements including electrolytes, and thereby meeting the amounts that are required. The trace element solutions were found physio-chemically stable up to 7 days when the needs for appropriate storage conditions were met.[16]

The amount of maintenance fluid NaCl 0.9% is provided according to Holliday et al.[17] and adjusted to diagnosis and clinical status (Apendix). The following amount of electrolytes are recommended for infants and children <50 kg: potassium 2-4 mmol/kg, magnesium 0.15-0.25 mmol/kg, phosphorus 0.5-2 mmol/kg and calcium 0.25-2 mmol/kg. Electrolytes administered are prescribed on demand based on the patient's condition and titrated based on laboratory values. The administration of calcium is limited by solubility and phosphate precipitation. Potassium chloride is added as 20 - 40 mmol/100ml to the maintenance fluid, or when severely depleted an extra potassium chloride 1 mmol/ml infusion is provided starting at 0.1mmol/kg/hr. In addition, in post-cardiac surgery patients magnesium sulphate is supplemented with a bolus of 0.10-0.20 mmol/kg per dose every 12 hours to aim for higher magnesium levels.

Comparison with ESPGHAN/ESPEN/ESPR/CSPEN guidelines

Comparison between prescribed micronutrient doses and the current ESPGHAN/ESPEN/ESPR/CSPEN guidelines are provided in Tables 4-5.[10]

Leuven

For vitamins, the provision is defined as one fixed volume (1 or 2 ml per day) for each weight group (<10 kg and >10 kg). The ESPGHAN/ESPEN/ESPR/CSPEN recommendations, however, are defined in doses per kilograms per day in the children up to 12 months. Therefore, the prescribed amount – as compared to recommendations - could be low, high or adequate in range depending on the actual weight of the child. A relatively high provision of sodium, chloride, phosphate and magnesium was found in all age groups. Overall, the prescription of vitamins is considered to be below the recommended doses in younger children (<10 kg). In the older children (>10 kg) vitamin supplementation is in the range of the guidelines. However, vitamin A is provided above and vitamin D below recommendations. Trace elements zinc and copper are relatively low in young infants, while in older children zinc and molybdenum are provided above recommendations and the provision of copper is relatively low. Iron and chromium are provided in all children, which is not recommended in short-term PN by the current ESPGHAN/ESPEN/ESPR/CSPEN guidelines.

Rotterdam

When comparing the current practice in Rotterdam to the ESPGHAN/ESPEN/ESPR/CSPEN guidelines, a relatively high provision of sodium and chloride is found in all age groups. The highest deviation is found for sodium, providing an amount of 11.1 mmol/kg/d in neonates. ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommend sodium amounts provided via PN of 1-3 mmol/kg/d in older non-critically ill children and 3-5 mmol/kg/d in neonates.[18] In addition, the provision of water-soluble vitamins is above recommend doses in most age groups. In neonates, trace elements were in line with the guidelines, whereas in the older children provision of copper is relatively low. In the older children (>12 kg) the trace element mixture contained iron and chromium which is not recommended in short-term PN.

Edmonton

The micronutrient doses administered in Edmonton are based upon the ASPEN guidelines and literature.[12-15] Nevertheless, when comparing the amounts provided with the new ESPGHAN/ESPEN/ESPR/CSPEN guidelines, most trace elements and vitamins are within the recommended range for children above 12 months. In the younger children the provision of most vitamins is difficult to compare due to the provision in different weight classes in doses/day and recommendations provided in doses/kg/day. In general, the provision of vitamin K is high and the provision of most water-soluble vitamins can be considered low. In compliance with the ESPGHAN/ESPEN/ESPR/CSPEN guidelines, iron and chromium are not administered during the first week of illness.

Table 1. Current micronutrient provision in critically ill children in Leuven, Belgium

Weight class	Electrolyte Infusion	Vitamin infusion	Trace element infusion
< 10 kg	Glucose 5% -NaCl 0.9% (ratio: 60/40) 50 ml/m²/hour (~2ml/kg/h)	Cernevit® 1 ml/d Vitamine K 2 mg (1-2 times per week)	Addaven® 0.25 ml/kg (max 10 ml/d)
> 10 kg	Glucose 5% -NaCl 0.9% (ratio: 60/40) 50 ml/m²/hour (~2ml/kg/h)	Cernevit® 2.5 ml/d Vitamine K 5 mg (1-2 times per week)	Addaven® 0.25 ml/kg (max 10 ml/d)
> 30 kg	Glucose 5% -NaCl 0.9% (ratio: 60/40) 50 ml/m²/hour (~2ml/kg/h)	Cernevit® 5 ml/d Vitamine K 10 mg (1-2 times per week)	Addaven® 0.25 ml/kg (max 10 ml/d)
Composition of the commercial products are provided in Appendix			

Table 2. Current micronutrient provision in critically ill children in Rotterdam, the Netherlands

Weight class	**Electrolyte Infusion**	**Vitamin and trace element infusion**
< 5 kg	Glucose 5% - NaCl 0,45% 113 ml, KCl 15% (2 mmol/ml) 0,8 ml, Ca-gluconate 10% (0,23 mmol/ml) 4 ml, Mg-sulphate 10% (0,4 mmol/ml) 0,50 ml, Glycophos (1 mmol P/ml, 2 mmol Na/ml) 1,2 ml 120 ml/kg/d as continuous infusion	Soluvit® 1,5 ml/kg, Vitintra Infant® 2,5 ml/kg (max 10ml), Peditrace® 1 ml/kg, NaCl 0.9% 37 ml
5 – 12 kg	Glucose 2,5% - NaCl 0,45% 69 ml, KCl 15% (2 mmol/ml) 0,6 ml, Ca-gluconate 10% (0,23 mmol/ml) 1,5 ml, Mg-sulphate 10% (0,4 mmol/ml) 0,25 ml, Glycophos (1 mmol P/ml, 2 mmol Na/ml) 0,5 ml 72 ml/kg/d as continuous infusion	Soluvit® 1,5 ml/kg (max 8ml), Vitintra Infant® 10ml, Peditrace® 1 ml/kg (max 10ml), NaCl 0.9% 37 ml
12 – 30 kg	Glucose 2,5% - NaCl 0,45% 69 ml, KCl 15% (2 mmol/ml) 0,6 ml, Ca-gluconate 10% (0,23 mmol/ml) 1,5 ml, Mg-sulphate 10% (0,4 mmol/ml) 0,25 ml, Glycophos (1 mmol P/ml, 2 mmol Na/ml) 0,5 ml 72 ml/kg/d as continuous infusion	Soluvit® 8 ml, Vitintra Infant® 10 ml, Supliven® 0,25 ml/kg (max 10 ml), NaCl 0.9% 50 ml
> 30 kg	Glucose 2,5% - NaCl 0,45% 69 ml, KCl 15% (2 mmol/ml) 0,6 ml, Ca-gluconate 10% (0,23 mmol/ml) 1,5 ml, Mg-sulphate 10% (0,4 mmol/ml) 0,25 ml, Glycophos (1 mmol P/ml, 2 mmol Na/ml) 0,5 ml 48 ml/kg/d as continuous infusion (max 2L/d)	Soluvit® 8 ml, Vitintra Infant® 10 ml, Supliven® 0,25 ml/kg (max 10 ml), NaCl 0.9% 50 ml
Composition of the commercial products are provided in Appendix		

Table 3. Current micronutrient provision in critically ill children in Edmonton, Canada

Age	Electrolyte Infusion	Vitamin infusion	Trace element infusion
< 12 months	Glucose 5% -NaCl 0.9% Rate according to Holliday et al.[17]	MULTI-12/K1® 2ml/kg/d (max 5ml/d)	Zinc sulfate; 500 µg/ml, copper sulfate; 40 µg/ml, selenious acid; 4 µg/ml, sodium iodide; 2 µg/ml in sterile water 0.5 ml/kg/d (max 10ml/d)
> 12 months	Glucose 5% -NaCl 0.9% Rate according to Holliday et al.[17]	MULTI-12/K1® 5ml/d	Zinc sulfate; 500 µg/ml, copper sulfate; 40 µg/ml, selenious acid; 4 µg/ml, sodium iodide; 2 µg/ml in sterile water 0.25 ml/kg/d (max 10ml/d)
Composition of the commercial products are provided in Appendix			

Table 4. Comparison of the standard provision of micronutrients in infants < 5 kg and infants between 5-10 kg of the three PEPaNIC RCT centres and the ESPGHAN guidelines.

	< 5 kg				Infants 5-10 kg*			
Nutrient	**Leuven**	**Rotterdam**	**Edmonton**	**ESPGHAN guidelines**	**Leuven**	**Rotterdam**	**Edmonton**	**ESPGHAN guidelines**
Sodium	7.2 mmol/kg/d	11.1 mmol/kg/d	15.4 mmol/kg/d	d1: 0-2 mmol/kg/d d2-4: 1-3 mmol/kg/d > d7: 2-3 mmol/kg/d	7.2 mmol/kg/d	6.3 mmol/kg/d	15.4 mmol/kg/d	2-3 mmol/kg/d
Potassium	0.73-2.92 mmol/kg/d	1.6 mmol/kg/d	2-4 mmol/kg	d1-3: 0-3 mmol/kg/d d4-7: 2-3 mmol/kg/d > d7: 1.5-3 mmol/kg/d	0.73-2.92 mmol/kg/d	1.2 mmol/kg/d	2-4 mmol/kg	1-3 mmol/kg/d
Calcium	-	0.92 mmol/kg/d	0.25-2 mmol/kg/d	0.8-1.5 mmol/kg/d	-	0.35 mmol/kg/d	0.25-2 mmol/kg/d	0.5 mmol/kg/d
Magnesium	0.24 mmol/kg/d	0.20 mmol/kg/d	0.15-0.25 mmol/kg/d	0.1-0.2 mmol/kg/d	0.24 mmol/kg/d	0.1 mmol/kg/d	0.15-0.25 mmol/kg/d	0.15 mmol/kg/d
Phosphate	0.73-2.92 mmol/kg/d	1.2 mmol/kg/d	0.5-2 mmol/kg/d	0.7-1.3 mmol/kg/d	0.73-2.92 mmol/kg/d	0.5 mmol/kg/d	0.5-2 mmol/kg/d	0.5 mmol/kg/d
Chloride	7.2 mmol/kg/d -	12.7 mmol/kg/d	17.4-19.4 mmol/kg/d	d1: 0-3 mmol/kg/d d2-4: 2-5 mmol/kg/d > d7: 2-3 mmol/kg/d	7.2 mmol/kg/d -	7.5 mmol/kg/d	17.4-19.4 mmol/kg/d	2-4 mmol/kg/d
Iron	27.5 µg/kg/d	-	-	Not advised in short-term PN	27.5 µg/kg/d	-	-	Not advised in short-term PN
Zinc	126 µg/kg/d	250 µg/kg/d	250 µg/kg/d	250 µg/kg/d (term neonate until 3 months)	126 µg/kg/d	250 µg/kg/d	250 µg/kg/d	100 µg/kg/d (max 5mg/d)

				100 µg/kg/d (3-12 months)				
Copper	9.5 µg/kg/d	20 µg/kg/d	20 µg/kg/d	20 µg/kg/d	9.5 µg/kg/d	20 µg/kg/d	20 µg/kg/d	20 µg/kg/d (max 0.5 mg/d)
Iodine	3.3 µg/kg/d	1.0 µg/kg/d	1.0 µg/kg/d	At least 1 µg/kg/d	3.3 µg/kg/d	1.0 µg/kg/d	1.0 µg/kg/d	At least 1 µg/kg/d
Selenium	2.0 µg/kg/d	2.0 µg/kg/d	2.0 µg/kg/d	2-3 µg/kg/d (max 100 µg/kg/d)	2.0 µg/kg/d	2.0 µg/kg/d	2.0 µg/kg/d	2-3 µg/kg/d (max 100µ/d)
Manganese	1.4 µg/kg/d	1.0 µg/kg/d	-	Max 1 µg/kg/d	1.4 µg/kg/d	1.0 µg/kg/d	-	Max 1 µg/kg/d
Molybdenum	0.48 µg/kg/d	-	-	0.25 µg/kg/d (max 5.0 µg/d)	0.48 µg/kg/d	-	-	0.25 µg/kg/d (max 5.0 µg/d)
Chromium	0.25 µg/kg/d	-	-	Not advised in PN	0.25 µg/kg/d	-	-	Not recommended in PN
Fluor	23.8 µg/kg/d	57 µg/kg/d	-		23.8 µg/kg/d	57 µg/kg/d	-	
Vitamin A	700 µg/d	173 µg/kg/d	690 µg/d	150-300 µg/kg/d	700 µg/d	690 µg/d	690 µg/d	150-300 µg/kg/d
Vitamin D	44 IU/d	100 IU/kg/d	400 IU/d	400 IU/d (or 40-150 IU/kg/d)	44 IU/d	400 IU/d	400 IU/d	40-150 IU/kg/d
Vitamin E	2.24 IU/d	1.8 IU/kg/d	7 IU/d	2.8-3.5 IU/kg/d	2.24 IU/d	7.0 IU/d	7 IU/d	2.8-3.5 IU/kg/d
Vitamin K	2000 - 4000 µg/week	50 µg/kg/d	200 µg/d	10 µg/kg/d	2000 - 4000 µg/wk	200 µg/d	200 µg/d	10 µg/kg/d
Vitamin C	25 mg/d	15 mg/kg/d	80 mg/d	15-25 mg/kg/d	25 mg/d	15 mg/kg/d	80 mg/d	15-25 mg/kg/d
Thiamine B1	0.7 mg/d	0.38 mg/kg/d	1.2 mg/d	0.35-0.5 mg/kg/d	0.7 mg/d	0.38 mg/kg/d	1.2 mg/d	0.35-0.5 mg/kg/d
Riboflavin B2	0.83 mg/d	0.54 mg/kg/d	1.4 mg/d	0.15-0.2 mg/kg/d	0.83 mg/d	0.54 mg/kg/d	1.4 mg/d	0.15-0.2 mg/kg/d
Pyridoxine B6	0.91 mg/d	0.60 mg/kg/d	1 mg/d	0.15-0.2 mg/kg/d	0.91 mg/d	0.60 mg/kg/d	1 mg/d	0.15-0.2 mg/kg/d
Niacin	9.2 mg/d	6.0 mg/kg/d	17 mg/d	4-6.8 mg/kg/d	9.2 mg/d	6.0 mg/kg/d	17 mg/d	4-6.8 mg/kg/d
Vitamin B12	1.2 µg/d	0.75 µg/kg/d	1 µg/d	0.3 µg/kg/d	1.2 µg/d	0.75 µg/kg/d	1 µg/d	0.3 µg/kg/d

Pantothenic acid	3.5 mg/d	2.25 mg/kg/d	5 mg/d	2.5 mg/kg/d	3.5 mg/d	2.25 mg/kg/d	5 mg/d	2.5 mg/kg/d
Biotin	23 µg/d	9.0 µg/kg/d	20 µg/d	5-8 µg/kg/d	23 µg/d	9.0 µg/kg/d	20 µg/d	5-8 µg/kg/d
Folic acid	82.8 µg/d	60 µg/kg/d	80 µg/d	56 µg/kg/d	82.8 µg/d	60 µg/kg/d	80 µg/d	56 µg/kg/d

*Due to the differences in cut-off values in Rotterdam children up to 12 kg are included and in Edmonton children up to 12 months are included.

Table 5. Comparison of the standard provision of micronutrients in children between 10-30 kg and children > 30 kg of the three PEPaNIC RCT centres and the ESPGHAN guidelines.

	Children 10* – 30 kg				Children > 30 kg			
Nutrient	**Leuven**	**Rotterdam**	**Edmonton**	**ESPGHAN guidelines**	**Leuven**	**Rotterdam**	**Edmonton**	**ESPGHAN guidelines**
Sodium	7.2 mmol/kg/d	6.3 mmol/kg/d	11.5-15.4 mmol/kg/d	1-3 mmol/kg/d	7.2 mmol/kg/d	4.2 mmol/kg/d	<8.7 mmol/kg/d	1-3 mmol/kg/d
Potassium	0.73-2.92 mmol/kg/d	1.2 mmol/kg/d	2-4 mmol/kg/d	1-3 mmol/kg/d	0.73-2.92 mmol/kg/d	0.8 mmol/kg/d	2-4 mmol/kg/d	1-3 mmol/kg/d
Calcium	-	0.35 mmol/kg/d	0.25-2 mmol/kg/d	0.25-0.4 mmol/kg/d	-	0.23 mmol/kg/d	0.25-2 mmol/kg/d	0.25-0.4 mmol/kg/d
Magnesium	0.24 mmol/kg/d	0.1 mmol/kg/d	0.15-0.25 mmol/kg/d	0.1 mmol/kg/d	0.24 mmol/kg/d	0.07 mmol/kg/d	0.15-0.25 mmol/kg/d	0.1 mmol/kg/d
Phosphate	0.73-2.92 mmol/kg/d	0.5 mmol/kg/d	0.5-2 mmol/kg/d	0.2-0.7 mmol/kg/d	0.73-2.92 mmol/kg/d	0.33 mmol/kg/d	0.5-2 mmol/kg/d	0.2-0.7 mmol/kg/d
Chloride	7.2 mmol/kg/d	7.0 mmol/kg/d	13.5-17.4 mmol/kg/d	2-4 mmol/kg/d	7.2 mmol/kg/d	5.0 mmol/kg/d	<12.7 mmol/kg/d	2-4 mmol/kg/d
Iron	27.5 µg/kg/d	27.5 µg/kg/d	-	Not recommended in short-term PN	27.5 µg/kg/d	27.5 µg/kg/d	-	Not recommended in short-term PN
Zinc	126 µg/kg/d	126 µg/kg/d	125 µg/kg/d	50 µg/kg/d (max 5mg/d)	126 µg/kg/d	126 µg/kg/d	125 µg/kg/d	50 µg/kg/d (max 5mg/d)
Copper	9.5 µg/kg/d	9.5 µg/kg/d	10 µg/kg/d	20 µg/kg/d (max0.5 mg/d)	9.5 µg/kg/d	9.5 µg/kg/d	10 µg/kg/d	20 µg/kg/d (max 0.5 mg/d)
Iodine	3.2 µg/kg/d	3.2 µg/kg/d	0.5 µg/kg/d	At least 1 µg/kg/d	3.2 µg/kg/d	3.2 µg/kg/d	0.5 µg/kg/d	At least 1 µg/kg/d
Selenium	2.0 µg/kg/d	2.0 µg/kg/d	1 µg/kg/d	2-3 µg/kg/d (max 100µ/d)	2.0 µg/kg/d	2.0 µg/kg/d	1 µg/kg/d	2-3 µg/kg/d (max 100µ/d)
Manganese	1.4 µg/kg/d	1.4 µg/kg/d	-	Max 1 µg/kg/d	1.4 µg/kg/d	1.4 µg/kg/d	-	Max 1 µg/kg/d
Molybdenum	0.48 µg/kg/d	0.48 µg/kg/d	-	0.25 µg/kg/d (max 5.0 µg/d)	0.48 µg/kg/d	0.48 µg/kg/d	-	0.25 µg/kg/d (max 5.0 µg/d)
Chromium	0.25 µg/kg/d	0.25 µg/kg/d		Not advised in PN	0.25 µg/kg/d	0.25 µg/kg/d		Not advised in PN

Fluor	23.8 µgl/kg/d	23.8 µg/kg/d	-		23.8 µg/kg/d	23.8 µgl/kg/d	-	
Vitamin A	1750 µg/d	690 µg/d	690 µg/d	150 µg/d	420 µg/d	3500 µg/d	690 µg/d	150 µg/d
Vitamin D	110 IU/d	400 IU/d	400 UI/d	400-600 IU/d	80 IU/d	220 IU/d	400 UI/d	400-600 IU/d
Vitamin E	5.6 IU/d	7.0 IU/d	7 UI/d	11 IU/d	4.48 IU/d	11.2 IU/d	7 UI/d	11 IU/d
Vitamin K	5000-10.000 µg/week	200 µg/d	200 µg/d	200 µg/d	5000-10.000 µg/week	200 µg/d	200 µg/d	200 µg/d
Vitamin C	62.5 mg/d	80 mg/d	80 mg/d	80 mg/d	50 mg/d	125 mg/d	80 mg/d	80 mg/d
Thiamine B1	1.75 mg/d	2.0 mg/d	1.2 mg/d	1.2 mg/d	1.40 mg/d	3.51 mg/d	1.2 mg/d	1.2 mg/d
Riboflavin B2	2.07 mg/d	2.9 mg/d	1.4 mg/d	1.4 mg/d	1.66 mg/d	4.14 mg/d	1.4 mg/d	1.4 mg/d
Pyridoxine B6	2.265 mg/d	3.2 mg/d	1 mg/d	1.0 mg/d	1.81 mg/d	4.53 mg/d	1 mg/d	1.0 mg/d
Niacin	23 mg/d	32 mg/d	17 mg/d	17 mg/d	18.4 mg/d	46 mg/d	17 mg/d	17 mg/d
Vitamin B12	3 µg/d	4.0 µg/d	1 µg/d	1 µg/d	2.2 µg/d	6.0 µg/d	1 µg/d	1 µg/d
Pantothenic acid	8.625 mg/d	12 mg/d	5 mg/d	5 mg/d	6.9 mg/d	17.25 mg/d	5 mg/d	5 mg/d
Biotin	34.5 µg/d	48 µg/d	20 µg/d	20 µg/d	24 µg/d	69 µg/d	20 µg/d	20 µg/d
Folic acid	207 µg/d	320 µg/d	80 µg/d	140 µg/d	165 µg/d	414 µg/d	80 µg/d	140 µg/d

*Due to the differences in cut-off values in Rotterdam children from 12 kg are included and in Edmonton children from 12 months are included.

DISCUSSION

The micronutrient protocols in the three PEPaNIC centres varied widely, mostly due to practical considerations. As such, there are substantial differences in the administered vitamins, trace elements and electrolytes between the participating centres. The most prominent differences are: 1) different age or weight cut-off values determined by recommended age and weight limits of their used products; 2) Rotterdam is the only centre which included electrolytes within their micronutrient protocols as continuous infusion over 24 hours, whereas the Leuven and Edmonton protocol for continuous electrolyte administration is adaptive and nurse driven and avoids simultaneous infusion of trace-elements and phosphate; 3) vitamins and trace elements are administered either separately or simultaneously via 1-8 hours daily bolus; and 4) Edmonton is the only centre to institutionally prepare the trace elements mixtures, whereas in the other two centres commercially available products are administered. Nonetheless, these three protocols provide practical information, which can be valuable for PICUs worldwide.

Comparison between the prescribed and ESPGHAN/ESPEN/ESPR/CSPEN guideline recommended amounts yielded substantial differences for electrolytes, vitamins and trace elements, which was most frequently observed for vitamins.[8,10,11,18-25] Avoiding depletion of micronutrients seems essential during critical illness, as deficiencies have been associated with decreased organ dysfunction, muscle weakness, poor wound healing and altered immune status.[1,3] Unfortunately, there is a paucity of evidence in critically ill children regarding the clinical consequences of insufficient micronutrient provision, low serum levels or true depletion of body stores. Moreover, the redistribution of micronutrients during critical illness and the interaction with oxidative stress preclude reliable identification of true deficiencies.[11,26,27] Only two studies investigated the impact of zinc and selenium supplementation in critically ill children, unfortunately, the generated data was insufficient to provide recommendations on dose and timing of supplementation.[26,28] For *macro*nutrient prescription, the ESPGHAN/ESPEN/ESPR/CSPEN guidelines take the different phases of critical illness into consideration, but for micronutrients these phases are not taken into account. Currently, there are no specific recommendations for parenteral micronutrient provision in critically ill children and as such, the ESPGHAN/ESPEN/ESPR/CSPEN recommendations for amount and timing of parenteral micronutrient requirements are based on recommended daily intakes for healthy children and observational studies, limiting their value, particularly for PICU.

When developing a protocol for parenteral micronutrient and electrolyte administration, several important aspects have to be addressed. First, one should consider the timing of the prescription (bolus vs. continuous / day vs. night / combined vs. separated / daily vs. non-daily). Parenteral vitamins are usually administered as a mixture containing multiple vitamins, some adhering to the tubing, others at risk of degradation by daylight. Therefore, vitamin

mixtures are administered at night and shielded from daylight or delivered within a short timeframe in the PEPaNIC centres. It is important to consider that bolus injection may increase urinary losses of water-soluble vitamins. In Edmonton and Leuven, the provision is separated for vitamins and trace element mixtures, whereas in Rotterdam these mixtures are provided simultaneously for practical reasons. It is important to consider that simultaneous provision can create a possible risk – among others - of vitamin C breakdown by copper,[29] although the clinical importance of such effect has never been established. On the other hand, addition of selenium to a mixture can attenuate spontaneous vitamin C breakdown.[30] All such interactions are obviously dependent on the volume of dilution and are under-investigated. Vitamin K in Leuven is the only micronutrient not given daily. The ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommend against non-daily provision of vitamins as transiently high levels may provoke adverse effect. This is however not the case for vitamin K.[21] For trace elements, the ESPGHAN/ESPEN/ESPR/CSPEN guidelines provide no strong recommendation whether these elements should be given daily or intermittently. Nonetheless, most dose recommendations are provided per day. The value of monitoring remains debated, since serum levels don't reflect body stores.[20] The ESPGHAN/ESPEN/ESPR/CSPEN strongly recommend against early administration of iron, which is reserved for long-term PN dependency (>3 weeks), due to the risk of iron overload when bypassing the homeostatic control of gastrointestinal iron absorption. In addition, iron is a pro oxidative agent. Because of the used commercial products, Leuven and Rotterdam deviate from the guideline, as iron is supplemented from day two onwards in all children in Leuven and in older children in Rotterdam. Moreover, iron overload is primarily reported in children receiving prolonged PN

Second, the choice between provision of institutionally prepared mixtures and one of the available commercial preparations will determine the doses of vitamin and trace elements administered. Moreover, by elimination of lipid emulsion, the pharmaceutical companies are restricted by the solubility and stability of the vitamins in non-lipid emulsions. In the three PEPaNIC centres three different commercially available vitamin preparations are used, none of them fulfilling all guideline recommended requirements. Given the scarce data these guidelines are based on, it is difficult to judge the importance of such deviations.[21]

Concerning the prescription of trace elements, commercially available mixtures are used in Rotterdam and in Leuven and institutionally prepared mixtures in Edmonton.[16] The advantage of commercially available mixtures is the lower risk for microbial contamination and compounding errors prior to administration.[31-33] Furthermore, the adequate infrastructure to secure and check the quality makes locally prepared products very costly.[34] This is why most institutions prefer standard solutions to institutional solutions. Unfortunately, the currently available commercial products are insufficient to fully comply with the guideline recommendations for each trace element. Nonetheless, the ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommend only to use individually tailored

solutions when the nutritional requirements cannot be met by the available range of standard solutions, for example for critically ill children or metabolically unstable patients such as those with abnormal fluid and electrolyte losses.[35] This is not in correspondence with the ASPEN guidelines, that state that the recommended intakes of trace elements can only be achieved using individualised trace element products.[36] Hence, before prescribing commercial trace elements, one has to determine if the micronutrient mixtures are acceptable for the majority of their admitted patient population.[35,37]

Regarding the administration of electrolytes, Rotterdam is the only centre that prescribes standard continuous electrolyte infusions, in contrast with Edmonton where electrolytes are prescribed on demand and Leuven, where intermittent electrolyte infusions were given in a nurse driven approach preventing or correcting deficiencies. In Rotterdam, electrolyte infusions are diluted in commercially available glucose and sodium chloride solutions and are, mainly to equally administer glucose over the day, administered continuously over 24 hours. This practice results in higher sodium intake than the advised amounts via parenteral nutrition. Critical illness is characterised by a shift in metabolic pathways responsible for electrolyte and fluid balance. Because of several common critical illness related factors, such as impaired free water excretion, frequent administration of hypotonic fluids, and multiple morbidity and drug-related conditions, critically ill children are more susceptible to develop hyponatremia during PICU admission compared to non-critically ill children with PN dependency.[38,39] Therefore, in clinical practice, the ESPGHAN/ESPEN/ESPR/CSPEN recommended amounts targeted for non-critically ill children are often not sufficient to prevent hyponatremia during the acute phase of critical illness and higher amounts can be tolerated.[40]

CONCLUSIONS

In conclusion, practices of parenteral micronutrient administration varied substantially between the PEPaNIC research centres, and deviated from the current guideline recommendations, most prominent for vitamin administration. Lack of hard clinical supportive evidence and the inability to administer all recommended amounts with the currently available commercial products hampers implementation of these new recommendations.

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APPENDIX

Methods S1: Composition of the commercial supplements used in the PEPaNIC centres

Addaven® or Supliven®

Vial (10ml)	
Chromic chloride hexahydrate	53.33 µg
Cupric chloride dihydrate	1.02 mg
Ferric chloride hexahydrate	5.40 mg
Manganese chloride tetrahydrate	198 µg
Potassium iodide	166 µg
Sodium fluoride	2.10 mg
Sodium molybdate dihydrate	48.5 µg
Sodium selenite	173 µg
Zinc chloride	10.5 mg

Cernevit-*12*®

Vial (5ml)	
Retinol palmitate corresponding to Retinol (Vitamin A)	3500 IU
Cholecalciferol (Vitamin D3)	200 IU
DL a-tocopherol corresponding to	10.2 mg
a-tocopherol (Vitamin E)	11.2 IU
Ascorbic Acid (Vitamin C)	125 mg
Nicotinamide (Vitamin B3)	46 mg
Dexpanthenol corresponding to	16.15 mg
pantothenic acid (Vitamin B5)	17.25 mg
Pyridoxine hydrochloride corresponding to	5.5 mg
pyridoxine (Vitamin B6)	4.53 mg
Riboflavin sodium phosphate corresponding	5.67 mg
to riboflavin (Vitamin B2)	4.14 mg
Cocarboxylase tetrahydrate	5.8 mg
corresponding to thiamine (Vitamin B1)	3.51 mg
Folic Acid	414 µg
D-Biotin	60 µg
Cyanocobalamin (Vitamin B12)	5.5 µg

Also contains: Glycine 250 mg, Glycocholic acid 140 mg, Soybean lecithin 112.5 mg

MULTI-12/K1®

Vial 1 (4ml)	
Ascorbic acid	80 mg
Vitamin A	2300 IU
Vitamin D	400 IU
Thiamine (as hydrochloride)	1.2 mg
Riboflavin (as phosphate)	1.4 mg
Pyridoxine hydrochloride	1 mg
Niacinamide	17 mg
d-Panthenol	5 mg
Vitamin E (*dl*-alpha tocopheryl acetate)	7 IU

Vitamin K1	0.2 mg

Also contains: polysorbate 80, 1.4%, sodium hydroxide to adjust pH and water for injection.

Vial 2 (1ml)

Biotin	20 µg
Folic Acid	140 µg
Vitamin B12 (cyanocobalamin)	1 µg

Also contains: mannitol 7.5 %, sodium citrate and/or citric acid to adjust pH and water for injection.

Peditrace®

Vial (10ml)

zinkchloride	5.21 mg
koperchloride 2 H2O	537 µg
mangaanchloride 4 H2O	36.0 µg
natriumseleniet anhydraat	43.8 µg
natriumfluoride	1.26 mg
kaliumjodide	13.1 µg

Soluvit ® N

Vial (10ml)

Thiamine nitrate	3.1 mg
Sodium riboflavine phosphate	4.9 mg
corresponding to Vitamin B2	3.6 mg
Nicotinamide	40 mg
Pyridoxine hydrochloride	4.9 mg
corresponding to Vitamin B6	4.0 mg
Sodium pantothenate	16.5 mg
corresponding to Pantothenic acid	15.0 mg
Sodium ascorbate	113 mg
corresponding to Vitamin C	100 mg
Biotin	60 µg
Folic acid	400 µg
Cyanocobalamin	5.0 µg

Also contains: Glycine 300 mg, Sodium edetate 0,5 mg, Methyl parahydroxybenzoate 0,5 mg

Vitintra Infant®

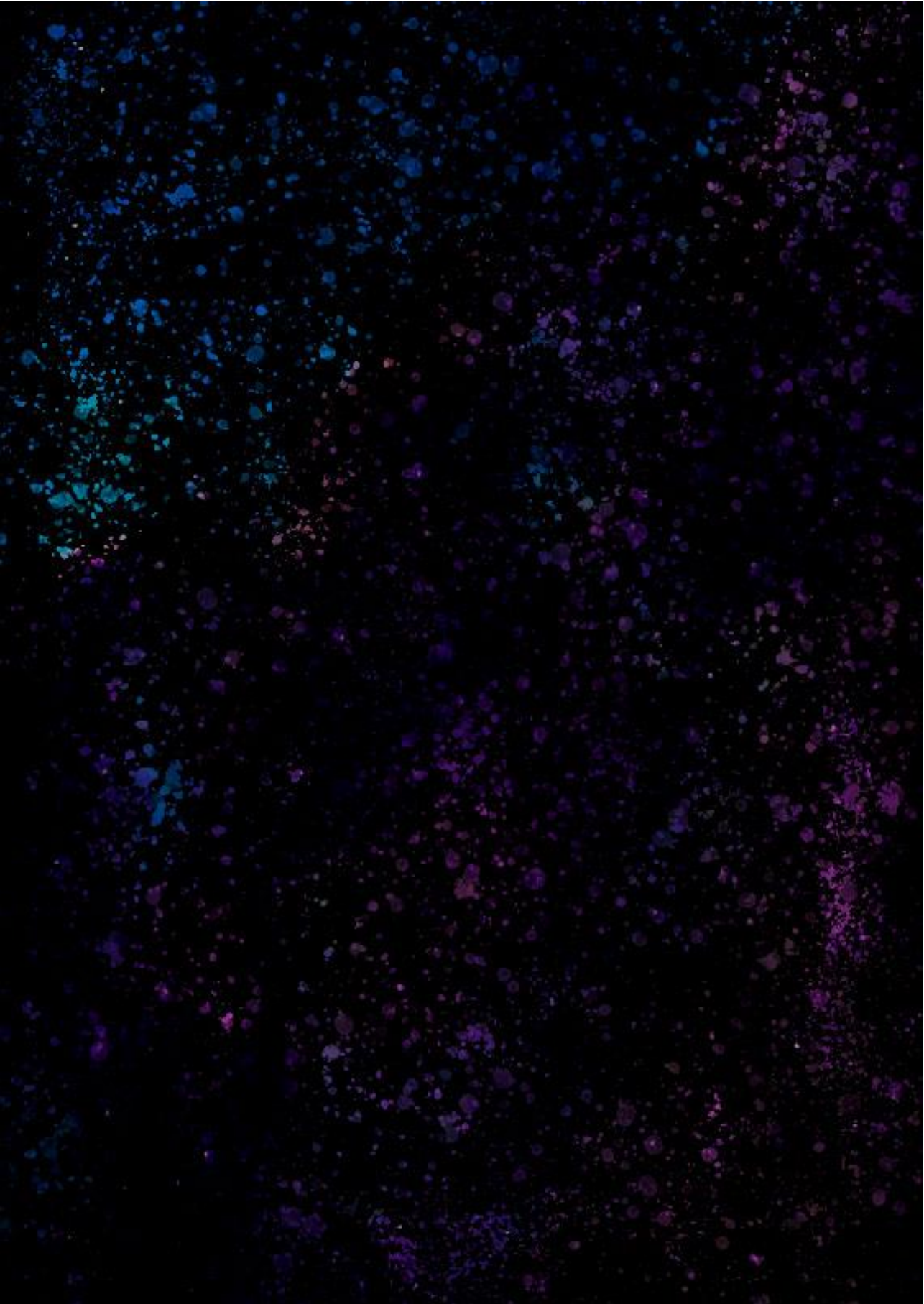
Vial (10ml)

Retinolpalmitate	135.3 µg
corresponding to retinol	69 µg
Phytomenadione	20 µg
Ergocalciferol	1.0 µg
dl - α - Tocopherol	0.64 mg

Table S1. Overview of the local fluid practices in the three PEPaNIC RCT centres

Practices	**Leuven**	**Rotterdam**	**Edmonton**
Fluid allowance	100 ml/kg/d for the first 10 kg bodyweight, 50 ml/kg/d for the next 10 kg, and 20 ml/kg/d for the bodyweight > 20 kg	<3m: 150-180 ml/kg/d 3-6m: 150 ml/kg/d 6-9m: 140 ml/kg/d 9-12m: 120 ml/kg/d > 1y: 100 ml/kg/d for the first 10 kg bodyweight, 50 ml/kg/d for the next 10 kg, and 20 ml/kg/d for the bodyweight > 20 kg	100 ml/kg/d for the first 10 kg bodyweight, 50 ml/kg/d for the next 10 kg, and 20 ml/kg/d for the bodyweight > 20 kg
Fluid allowance in restricted patients	80-110 ml/kg/d	Post-op cardiac patients: day 1 50% TFI and day 2 75% Other patients around 75%, however Individually adjusted	75% TFI for intubated patients 50% TFI for post-op cardiac patients
Maintenance fluid	NaCl 0.9%	<5kg: glucose 5% - NaCl 0.45% >5kg: glucose 2.5% / NaCl 0.45%	NaCl 0.9%

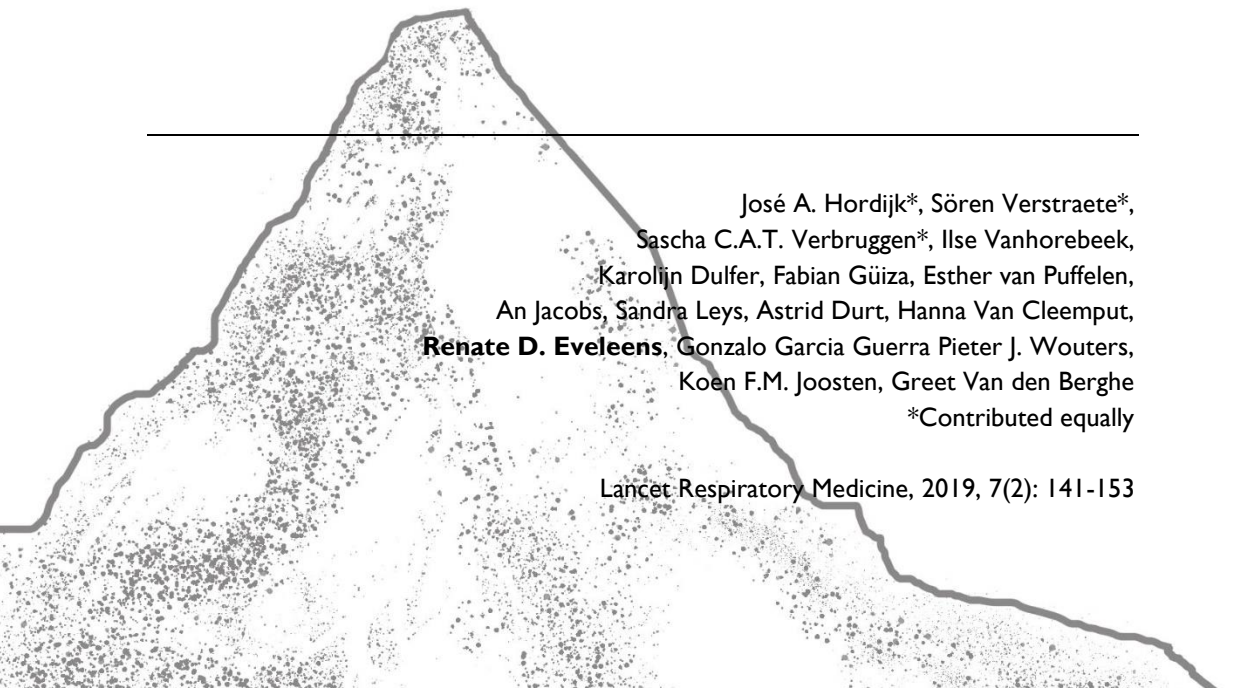
TFI, total fluid intake



PART IV

CHAPTER 11

LONG–TERM DEVELOPMENTAL EFFECTS OF WITHOLDING PARENTERAL NUTRITION FOR 1 WEEK IN THE PEDIATRIC INTENSIVE CARE UNIT: A 2–YEAR FOLLOW–UP OF THE PEPaNIC INTERNATIONAL, RANDOMISED, CONTROLLED TRIAL



José A. Hordijk*, Sören Verstraete*,
Sascha C.A.T. Verbruggen*, Ilse Vanhorebeek,
Karolijn Dulfer, Fabian Güiza, Esther van Puffelen,
An Jacobs, Sandra Leys, Astrid Durt, Hanna Van Cleemput,
Renate D. Eveleens, Gonzalo Garcia Guerra Pieter J. Wouters,
Koen F.M. Joosten, Greet Van den Berghe
*Contributed equally

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ABSTRACT

Background: The Paediatric Early versus Late Parenteral Nutrition in Critical Illness (PEPaNIC) multicentre, randomised, controlled trial showed that compared with early parenteral nutrition (Early-PN), withholding supplemental parenteral nutrition for 1 week in the paediatric intensive care unit (PICU; Late-PN) reduced infections and accelerated recovery from critical illness in children. We aimed to investigate the long-term impact on physical and neurocognitive development of early versus late parenteral nutrition (PN).

Methods: In this preplanned 2-year follow-up study, all patients included in the PEPaNIC trial (which was done in University Hospitals Leuven, Belgium; Erasmus MC–Sophia Children's Hospital, Rotterdam, the Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada) were approached for possible assessment of physical and neurocognitive development compared with healthy children who were matched for age and sex, and who had never been admitted to a neonatal ICU or a PICU. Assessed outcomes comprised anthropometric data; health status; parent/caregiver-reported executive functions, and emotional and behavioural problems; and tests for intelligence, visual-motor integration, alertness, motor coordination, inhibitory control, cognitive flexibility, and memory. To address partial responses among the children tested, we did multiple data imputation by chained equations before univariable and multivariable linear and logistic regression analyses adjusted for risk factors.

Findings: At the 2-years follow-up, 60 (8%) of 717 children who received Late-PN and 63 (9%) of 723 children who received Early-PN had died (p=0.81). 68 (9%) of 717 children who received Late-PN and 91 (13%) of 723 children who received Early-PN were too disabled for neurocognitive assessment (p=0.059), and 786 patients (395 assigned to Late-PN and 391 assigned to Early-PN) consented for testing. 786 patients and 405 healthy control children underwent long-term outcomes testing between August 4, 2014, and January 19, 2018, and were included in the imputation model for subsequent multivariable analyses. Late-PN did not adversely affect anthropometric data, health status, or neurological functioning, and improved parent/caregiver-reported executive functioning (Late-PN vs Early-PN β estimate –2.258, 95% CI –4.012 to –0.504; p=0.011), more specifically inhibition (–3.422, –5.171 to –1.673; p=0.0001), working memory (–2.016, –3.761 to –0.270; p=0.023), and meta-cognition (–1.957, –3.694 to –0.220; p=0.027). Externalising behavioural problems (β estimate –1.715, 95% CI –3.325 to –0.106; p=0.036) and visual-motor integration (0.468, 0.087 to 0.850; p=0.016) were also improved in the Late-PN group compared with the Early-PN group. After Bonferroni correction for multiple comparisons, the effect on inhibitory control remained significant (p=0.0001).

Interpretation: Withholding early PN for 1 week in the PICU did not negatively affect survival, anthropometrics, health status, and neurocognitive development, and improved inhibitory control 2 years after PICU admission.

INTRODUCTION

The Paediatric Early versus Late Parenteral Nutrition in Critical Illness (PEPaNIC) multicentre, randomised, controlled trial revealed that withholding parenteral nutrition (PN) for up to 1 week in the paediatric intensive care unit (PICU), when enteral nutrition (EN) was insufficient, was clinically superior to providing full nutrition up to caloric targets with supplemental PN.[1] Indeed, not giving PN during the first week in PICU and thus, in most patients, accepting low caloric and macronutrient intake reduced the incidence of new infections and accelerated recovery.[1] Despite these short-term clinical benefits, concerns have been raised about potential adverse long-term consequences of low caloric and macronutrient intake for the patients' length, bodyweight, head circumference, health status and neurocognitive development.[2,3] To evaluate long-term value for patients, patient-reported outcomes or rather, in case of children, parent/caregiver-reported outcomes should also be investigated.[4] Any such adverse patient-centred long-term consequences would discourage withholding PN early in the course of paediatric critical illness. Children who have been treated in the PICU tend to have adverse long-term developmental and neurocognitive outcomes.[5] In view of the potential benefits of fasting-induced responses for removal of cell damage and prevention of neurodegeneration,[6,7] we hypothesised that withholding PN early during the course of critical illness in children could also bring about beneficial effects in the long term, in particular for neurocognitive development.

We aimed to investigate whether withholding supplemental PN during the first week in PICU, rather than giving PN to reach nutritional targets as soon as possible, while adequately providing micronutrients, has an impact on survival, health status, and anthropometrics, clinically assessed neurological function, and parent/caregiver-reported and clinically tested neurocognitive outcomes at the 2-year follow-up, compared with matched healthy children.

METHODS

Study design and participants

This study is the preplanned 2-year follow-up of the PEPaNIC trial, in which 1440 critically ill children admitted to the participating PICUs (University Hospitals Leuven, Belgium; Erasmus-MC Sophia Children's Hospital, Rotterdam, Netherlands; Stollery Children's Hospital, Edmonton, AB, Canada) had been enrolled between 2012 and 2015. The full study protocol and acute outcome results have been published.[1,8]

Parents or legal guardians had provided written informed consent on admission to the PICU to contact them for long-term follow-up testing of their child. Survival status was determined by assessment of hospital notes, national registers, or contact with the general practitioner or referring paediatrician. All PICU survivors and their parents or caregivers

were first sent a standardised patient information letter. Subsequently, they were contacted by phone to obtain consent for scheduling an appointment for the medical and neurocognitive assessment. Participating patients (Appendix) were assessed either at the hospital or at home; the latter was offered whenever parents or caregivers considered the burden of coming to the hospital too high. Neonates and infants enrolled in the PEPaNIC trial were assessed at the age of 2.5 years because the youngest appropriate age for parent/caregiver-reported executive functioning (with the Behaviour Rating Inventory of Executive Function [BRIEF] and a general intelligence test, Wechsler Preschool and Primary Scale of Intelligence [WPPSI]) is 2.5 years.

405 healthy control children were recruited for a medical and neurocognitive assessment similar to that of the PEPaNIC patients. These children were demographically matched to the patients for age and sex. To control as much as possible for genetic, socioeconomic, and environmental background, siblings and relatives of the patients were preferably recruited into this control group besides unrelated children recruited from the same geographical area. Exclusion criteria for the control group were previous admission to a neonatal ICU or a PICU, or hospital admission for at least 7 days with need for an intravenous line, history of suspicious or established inborn chronic metabolic diseases requiring a specific diet, such as diabetes, and history of short bowel syndrome on home PN or other conditions that require home PN.

Written informed consent was obtained from the parents or legal guardians or from the adolescent according to local regulations. The institutional review boards at each participating site approved this follow-up study (ML8052; NL49708.078; Pro00038098). The protocol is available online.

Procedures, randomization and masking

In the PEPaNIC trial,[1] after having obtained consent, children who were admitted to the PICU were randomly allocated (1:1) to receive Early-PN, which was initiating PN within 24 hours of PICU admission to supplement EN whenever 80% of targeted calories per age and bodyweight categories was not reached, or Late-PN. Late-PN meant that, for up to 1 week, patients received a mixture of glucose 5% and sodium chloride 0.9% without other forms of PN (lipid or protein infusions) being administered, corresponding to no PN in the majority of children. After 1 week, for both groups equally, PN could be administered if necessary. When EN covered 80% or more of calculated targets, supplemental PN was discontinued. Total macronutrient doses administered on each of the first 7 days in PICU are shown in the appendix. EN was initiated early for both groups equally, and all patients received intravenous micronutrients until fully enterally fed.

Outcome assessors were physicians and experienced paediatric psychologists who had not been involved in the management of the patients during their stay in the PICU and who

were strictly blinded for the randomised allocation to either Late-PN or Early-PN. Parents had not been masked during the time the child was treated in the PICU and were not actively informed about the initial PEPaNIC study results.

Outcomes

In this 2-year follow-up study, the primary outcomes assessed were growth, physical ability, health status, and clinical, neurological, and neurocognitive outcomes. Death and severe disability precluding neurocognitive testing were a priori defined as safety endpoints. Neurocognitive testability was determined by screening of the medical file or clinical judgment, before the start of the neurocognitive assessment, by the physician or psychologist and confirmed by the parents or caregivers.

For children who were examined at follow-up, head circumferences, bodyweights, and heights were measured. A clinical neurological examination was done to assess gross neurological abnormalities. A structured interview with the parents or caregivers assessed whether the child had been diagnosed with a somatic or psychiatric illness, or had been admitted to a hospital for medical or surgical reasons during the preceding 2 years for healthy control children and during the 2 years following the index PICU admission for patients.

Validated, internationally recognised questionnaires and clinical tests with adequate normative data were used to score performance for a broad range of neurocognitive functions.[9] Patient-reported outcome questionnaires were completed by parents or caregivers. They reported executive functioning in their child with the BRIEF preschool version for children aged 2.5-5 years or BRIEF for patients aged 6-18 years. Overlapping scales of both questionnaires (inhibition, flexibility, emotional control, working memory, and planning and organization), the overlapping index (meta-cognition, comprising the scales working memory and planning and organization), and the total score were reported (T scores, with mean 50 [SD 10]).[10,11] Parents or caregivers completed the Child Behaviour Checklist (CBCL 1.5–5 years or CBCL 6–18 years)[12,13] to assess emotional and behavioural problems. Internalising, externalising, and total problems were analysed (T scores, with mean 50 [SD 10]).[12,13]

Clinical tests were used to evaluate neurocognitive functions. General intellectual ability was assessed with use of age-appropriate versions of the Wechsler intelligence quotient (IQ). WPPSI-III-NL[14] was used for children aged between 2.5 years and 5 years 11 months, the Wechsler Intelligence Scale for Children (WISC-III-NL)[15] was used for children aged between 6 years and 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL)[16] for adolescents or young adults who were 17 years or older. For all of these tests, total IQ, verbal IQ, and performance IQ scores (test mean 100 [SD 15]) were computed. The Beery Developmental Test of Visual–Motor Integration[17] was used for children aged

2.5 years and older to assess the ability to integrate visual and motor functions (total scaled score, with test mean 10 [SD 3]). The validated computerised Amsterdam Neuropsychological Tasks (ANT) program was used to measure attention, motor coordination, and executive functions in children aged 4 years or older.[18] ANT-Baseline Speed was used to evaluate alertness (reaction time and SD), ANT-Tapping to assess motor coordination (number of taps), and Response Organization Objects to measure inhibitory control and cognitive flexibility (differences in reaction time and in number of errors between tests of increasing demand). Memory was assessed with use of 4 tests from the Children's Memory Scale (CMS) for children aged between 5 years and 16 years 11 months.[19] CMS-Numbers assessed short-term verbal memory span and verbal working memory load (scaled score, with test mean 10 [SD 3]). The CMS-Word Pairs assessed short-term and long-term verbal memory, and recognition; CMS-Picture Locations assessed immediate visual memory; and CMS-Dot Locations assessed immediate and delayed visual memory (proportion of correct responses, ranging from 0 to 1). The CMS-Learning index represents learning abilities of the child (standard score, with mean 100 [SD 15]). The extended description of the parent/caregiver-reported outcome questionnaires and of the clinical and neuropsychological test battery is available in the appendix.

Statistical analysis

After taking into account estimations for the safety endpoints (death and severe disability precluding neurocognitive testing), we estimated that about 30% of the patients among the critically ill patients who had been included in the PEPaNIC trial and who were alive and testable at the 2-year follow-up would be lost to follow-up, on the basis of earlier experience.[9] We calculated that such a sample size had >80% power to detect, with a certainty of >95%, clinically relevant differences between the 2 randomization arms, in the same order of magnitude as those we had previously documented with blood glucose control in the PICU.[9] For the healthy control group, we calculated that with a sample size of 405 children, we would be able to detect, with a power of >80% and certainty of >95%, outcome differences between patients and healthy children of the same order of magnitude as those previously documented.[9]

The inability to fully complete any of the neurocognitive tests would introduce bias in univariable analyses of these test results, because this in itself might suggest poor function. Hence, to correctly address partial responses, multiple data imputation by chained equations was required,[20] with use of all available data per individual (Appendix). For tests validated for a specific age range (alertness, motor coordination, inhibitory control and flexibility in children aged 4 years or older, and memory in children who are between 5 and 16 years old), we imputed data within these age ranges only. To avoid bias and instability in this imputation model, the percentage of missing data per variable could not exceed 30%[20] and to minimise loss of statistical power, the number of iterative imputations was set at 31.[20]

Comparison of the observed and imputed values and the imputation predictor are shown in the appendix.

To analyses the differences in outcomes between PEPaNIC participants and healthy control children, and to investigate the long-term outcome differences between patients randomly allocated to Late-PN or Early-PN during PICU stay, we did multivariable linear and logistic regression analyses on the 31 imputed datasets with the β estimates or odds ratios reported as pooled results, preceded by a pooled univariable comparison with use of Fisher's exact test, Student's *t* test, or Wilcoxon rank-sum test as appropriate (Appendix). All multivariable analyses were adjusted for the following risk factors: age, centre, race,[21] sex, geographic origin,[21] language, hand preference, history of malignancy, diabetes, a predefined syndrome (Appendix), and the educational and occupational status of parents (Appendix). For the comparison between Late-PN and Early-PN groups, further adjustment was done for diagnosis and severity of illness (with the Paediatric Index of Mortality 3 and paediatric logistic organ dysfunction scores) on PICU admission, risk of malnutrition, and parental smoking behaviour before PICU admission. We calculated p values for interaction between age group and randomization to assess whether patients who were infants (aged <1 years) at randomization behaved differently from older children.

We did explanatory statistical analyses with further adjustment to investigate whether any eventual impact of Late-PN versus Early-PN on the long-term outcomes might have been mediated by its acute effects on new PICU infections and duration of PICU stay, and thus possibly indirectly also number of post-randomization hypoglycemic events or the duration of post-randomization treatments such as mechanical ventilatory support, hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics, and α2-agonists. Data are presented as β estimates and odds ratios with 95% CIs, means and SDs, or numbers and proportions, as appropriate. Statistical analyses were done with R version 3.4.3, MICE version 2.46.0, and JMP version 13.0.0. Two-sided p-values of 0.05 or less were considered statistically significant. Bonferroni corrections for the multiple comparisons (n=45) were done as a sensitivity analysis, which altered the required level of p value for significance to 0.001 or less.

RESULTS

Of the total patient population (n=1440), 60 (8%) of 717 children in the Late-PN group and 63 (9%) of 723 children in the Early-PN group had died 2 years after admission to a PICU (p=0.81; Figure 1). 68 (9%) patients in the Late-PN group and 91 (13%) patients in the Early-PN group were identified as too disabled to assess for neurocognitive development (p=0.059). 372 (26%) patients survived, but declined participation or could not be reached. No differences in reasons for loss to follow-up between randomization groups were

observed (p=0.27). 786 patients (395 assigned to Late-PN and 391 assigned to Early-PN) and 405 healthy controls underwent long-term outcome testing between August 4, 2014 and January 19 2018, and were included in the imputation model for subsequent multivariable analyses. Of the healthy control children, 332 (82%) were assessed at the hospital compared with 502 (64%) PEPaNIC children (p<0.001), with similar proportions for the Early-PN 458 (64%) and Late-PN 461 (64%) groups being assessed at the hospital (p=0.79). Demographic and medical characteristics of PEPaNIC participants and healthy control children are shown in Table 1. Patients who were tested at follow-up were overall comparable to the initial PEPaNIC study population (Table 1).

Overall, PEPaNIC participants had worse outcomes at the 2-year follow-up for height, body weight, and head circumference, for health status, clinically assessed neurological functioning, parent/caregiver-reported executive functioning, and emotional and behavioural problems, and for clinical tests for intelligence, visual-motor integration, alertness, and memory than did healthy control children, assessed via univariable and via multivariable comparisons (Table 2; Table 3).

Patients in the Late-PN group and those in the Early-PN group were similar in terms of height, bodyweight, body-mass index, and head circumference, and for health status, and clinically assessed neurological functioning in univariable and multivariable analyses (Table 2; Table 3) However, in the univariable comparisons, patients in the Late-PN group performed better than did those in the Early-PN group on parent/caregiver-reported inhibitory control, working memory, meta-cognition, and overall executive functioning, and on clinical tests for visual-motor integration, verbal-auditory recognition, and for one motor coordination task (synchronous tapping; Table 2). Adjusted for multiple comparisons, the better inhibitory control of patients in the Late-PN group than that of patients in the Early-PN group remained significant (p=0.0001). After multivariable adjustment for risk factors, parents/caregivers of patients in the Late-PN group reported better overall executive functioning than did parents/caregivers of patients in the Early-PN group (β estimate –2.258, 95% CI –4.012 to –0.504; p=0.011), more specifically for inhibition (–3.422, –5.171 to –1.673; p=0.0001), working memory (–2.016, –3.761 to –0.270; p=0.023), and metacognition (–1.957, –3.694 to –0.220; p=0.027; Table 3; Figure 2). Furthermore, patients in the Late-PN group had fewer externalising behavioural problems (–1.715, 95% CI –3.325 to –0.106; p=0.036) as reported by parents/caregivers and scored better on visual-motor integration (0.468, 0.087 to 0.850; p=0.016) than did patients in the Early-PN group (Table 3; Appendix).

For overall executive functioning, inhibition, meta-cognition, and externalising problems as reported by parents/caregivers, patients in the Late-PN group were not different from healthy control children (p values of ≥0.12; Appendix). After further correction for multiple comparisons, the better inhibitory control of patients in the Late-PN group than of those in the Early-PN group remained significant (p=0.0001; Table 3). Sensitivity analyses for the

missing-at-random assumption and with imputing worst test scores for the severely disabled and thus non-testable children, as presented in the appendix, further supported the robustness of these results.

The effects of Late-PN versus Early-PN were more pronounced in the subgroup of patients who were infants at randomization than in older children (interaction p values of ≤0.03): β estimates for Late-PN versus Early-PN among infants for parent/caregiver-reported overall executive functioning (-3.843, 95% CI -6.361 to -1.325; p=0.0029), meta-cognition (-3.749, -6.244 to -1.254; p=0.0034), and working memory (-3.594, -6.052 to -1.135; p=0.0043; Appendix).

The impact of Late-PN versus Early-PN on long-term outcomes did not appear to be mediated by its acute effects on new PICU infections, duration of PICU stay, exposure to hypoglycemia, or duration of potentially hazardous post-randomization treatments during the PICU stay (Appendix). The use of benzodiazepines and of corticosteroids was independently associated with poorer outcomes, whereas treatment with α2 agonists was associated with better overall executive functioning and visual-motor integration (Appendix).

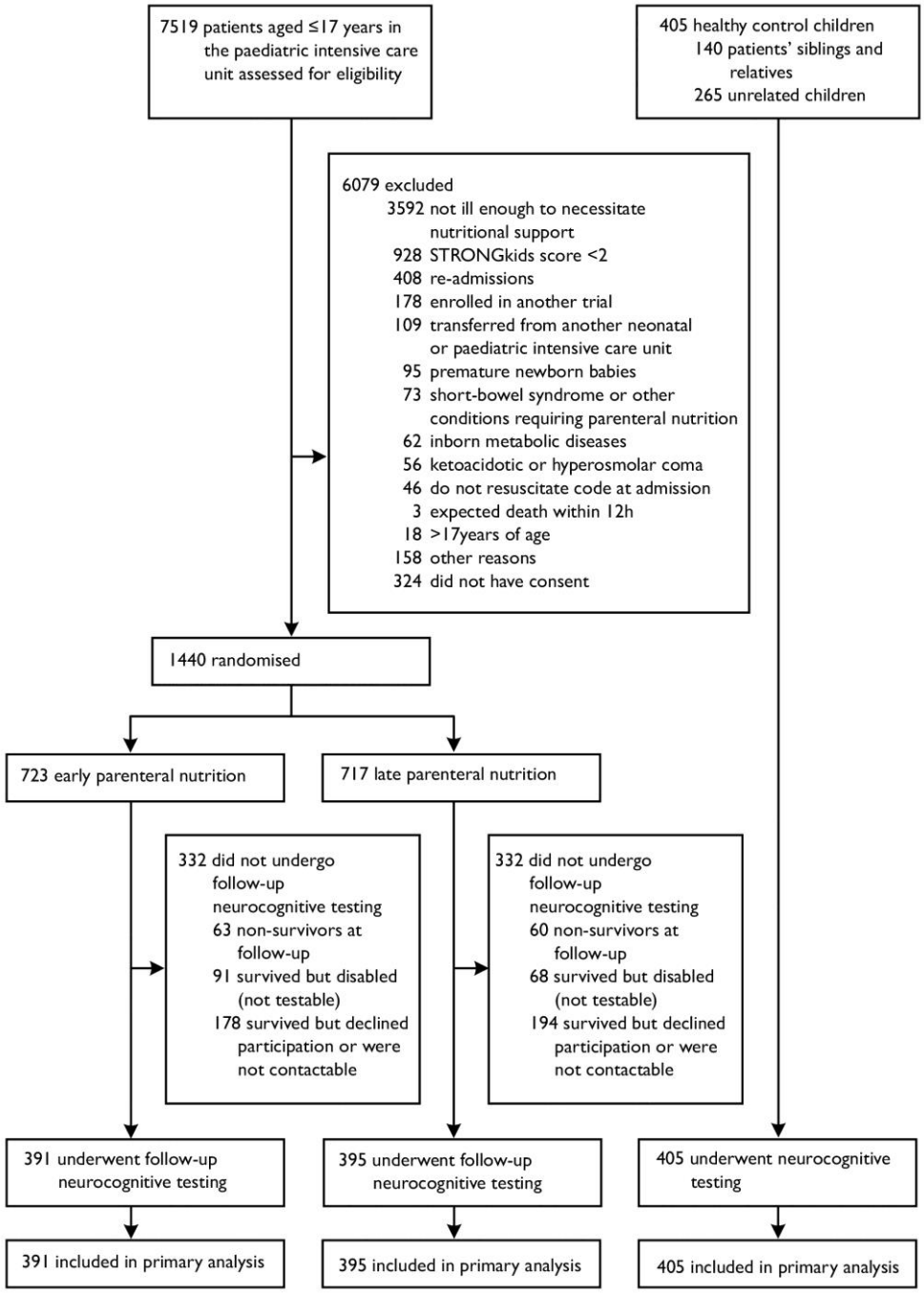
DISCUSSION

Two years after inclusion in the PEPaNIC multicentre, randomised, controlled trial, PICU survivors had worse developmental outcomes than did healthy control children. However, no adverse effect of withholding PN during the first week in the PICU could be detected for survival, anthropometrics health status, and neurocognitive development. In fact, omitting Early-PN in the PICU improved parent/caregiver-reported executive functioning 2 years later compared with Early-PN, in particular resulting in a better inhibitory control. Moreover, of the patients who survived, fewer were too disabled to be tested in the Late-PN group than in the Early-PN group.

The long-term legacy of problems in executive functioning, as reported in this article by parents or caregivers of patients admitted to the PICU, has been described previously, although mostly limited to the results of clinical neurocognitive testing.[9,22]

Figure 1. CONSORT flow diagram of the study participants

PN, parenteral nutrition, STRONGkids, Screening Tool for Risk on Nutritional Status and Growth



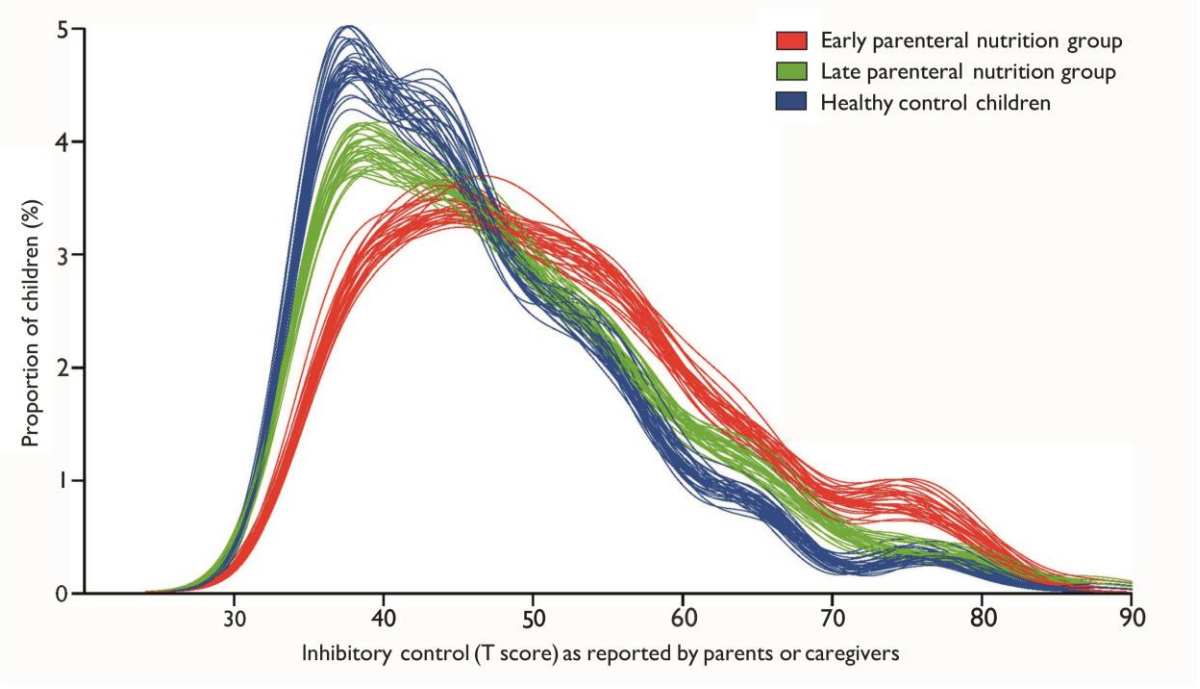


Figure 2. Density estimates for inhibitory function as reported by parents or caregivers

Each line corresponds to an imputed dataset. Densities, which correspond to the proportions of children with a certain score (equivalent to a smoothed histogram), are shown separately for healthy control children and for paediatric early versus late parenteral nutrition in critical illness (PEPaNIC) participants who had been randomly assigned to receive late parenteral nutrition (no parenteral nutrition in the first week after admission to a paediatric intensive care unit [PICU]) or early parenteral nutrition (within 24 h after PICU admission when enteral nutrition alone was insufficient). Higher scores indicate worse functioning.

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested population[a]		Total population	PEPaNIC	Tested population[b]	PEPaNIC
	Healthy control children (N=405)	PEPaNIC patients (N=786)	Early-PN (N=723)	Late-PN (N=719)	Early-PN (N=391)	Late-PN (N=395)
Demographic						
Age at 2-year follow-up - years	6.0 (4.7)	5.7 (4.5)	NA	NA	5.7 (4.4)	5.6 (4.5)
Sex						
Female	186 (46%)	331 (42%)	331 (42%)	305 (43%)	161 (41%)	170 (43%)
Male	219 (54%)	455 (58%)	415 (57%)	412 (57%)	230 (59%)	225 (57%)
Known non-white race[c]	33 (8%)	63 (8%)	50 (7%)	33 (5%)	38 (10%)	25 (6%)
Known non-European origin[c]	54 (13%)	152 (19%)	161 (22%)	128 (18%)	88 (23%)	64 (16%)
Known not exclusive Dutch or English language	76 (19%5)	184 (23%)	122 (17%)	106 (15%)	95 (24%)	89 (23%)
Socioeconomic status						
Parent[d] educational level 1	13 (3%)	37 (5%)	NA	NA	12 (3%)	25 (6%)
Parent[d] educational level 1.5	23 (6%)	54 (7%)	NA	NA	28 (7%)	26 (7%)
Parent[d] educational level 2	55 (14%)	184 (23%)	NA	NA	96 (25%)	88 (22%)
Parent[d] educational level 2.5	76 (19%)	131 (17%)	NA	NA	60 (15%)	71 (18%)
Parent[d] educational level 3	215 (53%)	200 (26%)	NA	NA	100 (26%)	100 (25%)
Parent[d] educational level unknown	23 (6%)	180 (23%)	NA	NA	95 (24%)	85 (22%)
Parent[e] occupational level 1	2 (<1%)	10 (1%)	NA	NA	2 (<1%)	8 (2%)
Parent[e] occupational level 1.5	25 (6%)	76 (10%)	NA	NA	33 (8%)	43 (11%)
Parent[e] occupational level 2	47 (12%)	127 (16%)	NA	NA	61 (16%)	66 (17%)
Parent[e] occupational level 2.5	26 (6%)	77 (10%)	NA	NA	44 (11%)	33 (8%)
Parent[e] occupational level 3	83 (21%)	121 (15%)	NA	NA	54 (14%)	67 (17%)
Parent[e] occupational level 3.5	40 (10%)	54 (7%)	NA	NA	32 (8%)	22 (6%)
Parent[e] occupational level 4	116 (29%)	108 (14%)	NA	NA	53 (14%)	55 (14%)
Parent[e] occupational level unknown	66 (16%)	213 (27%)	NA	NA	112 (29%)	101 (26%)
Infant (age<1y) at randomization	NA	363 (46%)	328 (45%)	325 (45%)	177 (45%)	186 (47%)
STRONGkids risk level[f]						
Medium	NA	707 (90%)	644 (89%)	644 (90%)	351 (90%)	356 (90%)
High	NA	79 (10%)	79 (11%)	73 (10%)	40 (10%)	39 (10%)

PeLOD score, first 24h in PICU[g]	NA	20.0 (11.6)	19.7 (12.0)	20.1 (12.3)	20.0 (11.6)	20.0 (11.5)
PIM3 score[h]	NA	–3.5 (1.4)	–3.2 (1.6)	–3.2 (1.7)	–3.4 (1.4)	–3.5 (1.3)
PIM3 probability of death, %[h]	NA	6.7 (11.8)	9.4 (15.9)	9.1 (17.4)	6.8 (12.0)	6.5 (11.6)
Diagnostic category						
Surgical: abdominal	NA	70 (9%)	53 (7%)	60 (8%)	34 (9%)	36 (9%)
Surgical: burns	NA	2 (<1%)	5 (<1%)	5 (<1%)	1 (<1%)	1 (<1%)
Surgical: cardiac	NA	339 (43%)	279 (39%)	268 (37%)	173 (44%)	166 (42%)
Surgical: neurosurgery or traumatic brain injury	NA	71 (9%)	63 (9%)	53 (7%)	39 (10%)	32 (8%)
Surgical: thoracic	NA	42 (5%)	34 (5%)	27 (4%)	23 (6%)	19 (5%)
Surgical: transplantation	NA	14 (2%)	7 (1%)	17 (2%)	4 (1%)	10 (3%)
Surgical: orthopedic surgery or trauma	NA	23 (3%)	28 (4%)	26 (4%)	14 (4%)	9 (2%)
Surgical: other	NA	27 (3%)	21 (3%)	27 (4%)	10 (3%)	17 (4%)
Medical: cardiac	NA	26 (3%)	30 (4%)	31 (4%)	10 (3%)	16 (4%)
Medical: gastrointestinal or hepatic	NA	3 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	2 (<1%)
Medical: oncologic or hematologic	NA	8 (1%)	8 (1%)	7 (1%)	5 (1%)	3 (<1%)
Medical: neurologic	NA	44 (6%)	51 (7%)	52 (7%)	21 (5%)	23 (6%)
Medical: renal	NA	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Medical: respiratory	NA	83 (11%)	99 (14%)	96 (13%)	38 (10%)	45 (11%)
Medical: other	NA	34 (4%)	42 (6%)	43 (6%)	18 (5%)	16 (4%)
Malignancy	0 (0.0)	42 (5%)	51 (7%)	33 (5%)	26 (7%)	16 (4%)
Diabetes	0 (0.0)	1 (<1%)	3 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Syndrome[i]	5 (1.2)	79 (10%)	123 (17%)	118 (16%)	34 (9%)	45 (11%)
Known parental smoking between birth and PICU admission	NA	149 (19%)	NA	NA	72 (18%)	77 (20%)
Acute effect of randomization and post-randomization treatment in PICU						
Duration of stay in the PICU - days	NA	7.4 (15.1)	9.2 (21.3)	6.5 (10.0)	8.4 (18.4)	6.4 (10.8)
Patients who acquired a new infection in PICU	NA	105 (13%)	134 (19%)	77 (11%)	66 (17%)	39 (10%)
Duration of mechanical ventilatory support - days	NA	4.7 (11.0)	6.4 (18.6)	4.4 (7.3)	5.5 (13.9)	3.9 (7.1)
No. of days with hypoglycemia <40mg/dl - days	NA	0.1 (0.5)	0.1 (0.6)	0.2 (0.6)	0.1 (0.5)	0.2 (0.6)
Duration of antibiotic treatment - days	NA	5.1 (13.4)	6.7 (19.0)	4.6 (8.7)	5.8 (16.4)	4.3 (9.5)
Duration of hemodynamic support - days	NA	2.5 (7.2)	3.0 (7.4)	2.4 (6.2)	2.6 (7.6)	2.3 (6.8)
Duration of treatment with opioids - days	NA	4.7 (8.8)	6.1 (16.5)	4.1 (6.2)	5.4 (10.8)	4.1 (6.2)
Duration of treatment with benzodiazepines - days	NA	4.2 (9.8)	5.4 (16.7)	4.0 (8.8)	4.5 (9.9)	3.9 (9.7)
Duration of treatment with hypnotics - days	NA	1.4 (5.6)	1.8 (6.3)	1.3 (3.1)	1.6 (7.4)	1.2 (2.9)

Duration of treatment with α2-agonists - days	NA	1.0 (6.4)	1.1 (8.7)	1.0 (6.0)	0.9 (5.9)	1.1 (6.8)
Duration of treatment with corticosteroids) - days	NA	1.2 (3.7)	1.6 (4.3)	1.3 (3.9)	1.3 (4.2)	1.0 (3.1)

Data are mean (SD) or n (%). BMI, body mass index; NA, not applicable (values only known when the patients were seen at follow-up, or not applicable for healthy control children); PeLOD, Paediatric Logistic Organ Dysfunction score; PICU, paediatric intensive care unit; PIM3, Paediatric Index of Mortality 3 score; PN, parenteral nutrition; SEM, standard error of the mean.

a 708 (59%) of 1191 participating children were tested in Belgium, 463 (39%) in the Netherlands, and 20 (2%) in Canada.

b No differences in demographics, allocation to Late or Early-PN, and PICU- or hospital-related primary and secondary study endpoints were observed between the PEPaNIC patients who were tested and those who survived, but declined participation or could not be reached (n=372; all p>0.15).

c Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.

d The education level is the mean of the paternal and maternal educational level, and calculated on the basis of the 3-point scale (1=low, 2=middle, 3-high; Appendix) subdivisions as made by the Algemene Directie Statistiek (Belgium) and the Centraal Bureau voor de Statistiek (The Netherlands).

e The occupation level is the mean of the paternal and maternal occupation level, which is calculated on the basis of the International Isco System 4-point scale for professions (Appendix).

f STRONGkids scores range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

g PeLOD scores range from 0 to 71, with higher scores indicating more severe illness.

h PIM3 probability of death, ranging from 0-100% with high percentage indicating a higher probability of death in PICU.

i A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Appendix)

Table 2. Pooled univariable analyses of the differences assessed at 2-year follow-up between patients and healthy control children and between Late-PN and Early-PN patient groups

	Number (%) of available data per outcome before imputation (N=1191)	Tested populations			Tested PEPaNIC population		
		Healthy control children (N=405)	PEPaNIC patients (N=786)	P-value	Early-PN (N=391)	Late-PN (N=395)	P-value
Height – cm	1126 (95%)	114.6 (27.4)	110.6 (26.5)	0.0018[a]	111.2 (25.9)	109.9 (27.0)	0.16
SD score[b]	1126 (95%)	0.370 (1.1)	-0.066 (1.3)	<0.0001[a]	-0.016 (1.2)	-0.115 (1.4)	0.47
Weight – kg	1135 (96%)	24.6 (16.7)	23.0 (16.2)	0.0020	23.0 (15.2)	23.0 (17.0)	0.20
SD score[b]	1135 (96%)	0.425 (0.9)	0.154 (1.2)	<0.0001	0.187 (1.1)	0.122 (1.1)	0.30
Body-mass index – kg/m^3	1126 (95%)	16.9 (2.7)	17.0 (5.1)	0.27	16.9 (3.1)	17.2 (6.5)	0.51
SD score[b]	1126 (95%)	0.306 (1.0)	0.249 (1.2)	0.043	0.259 (1.2)	0.240 (1.2)	0.61
Head circumference – cm	1060 (89%)	51.5 (2.6)	50.9 (2.8)	<0.0001	51.0 (2.8)	50.8 (2.8)	0.14
SD score[b]	1060 (89%)	0.504 (1.1)	0.107 (1.3)	<0.0001	0.139 (1.3)	0.076 (1.3)	0.35
Diagnosed with a somatic illness	957 (81%)	140 (35%)	507 (65%)	<0.0001	259 (66%)	248 (63%)	0.31
Diagnosed with a psychiatric illness	1160 (98%)	16 (4%)	52 (7%)	<0.0001	30 (8%)	22 (6%)	0.23
Admitted to hospital for a medical or surgical reason	1191 (100%)	72 (18%)	425 (54%)	<0.0001	216 (55%)	209 (53%)	0.51
Clinical neurological evaluation score (range 0-8)[c]	1116 (94%)	0.22 (0.6)	0.71 (1.5)	<0.0001	0.81 (1.6)	0.61 (1.3)	0.096
Executive functioning as reported by parents/caregivers - T-score[c]							
Inhibition	850 (72%)	46.3 (11.5)	49.9 (15.2)	<0.0001	51.4 (14.4)	48.4 (13.2)	<0.0001
Flexibility	851 (72%)	46.7 (11.3)	49.9 (15.3)	<0.0001	50.5 (14.3)	49.4 (13.3)	0.12
Emotional control	851 (72%)	47.7 (11.2)	49.7 (13.5)	0.0052	50.0 (12.7)	49.4 (12.4)	0.34
Working memory	845 (71%)	46.7 (12.1)	51.4 (16.7)	<0.0001	52.3 (15.4)	50.6 (14.1)	0.055
Planning and organization	847 (72%)	46.9 (11.9)	50.3 (14.7)	0.0001	50.8 (13.8)	49.8 (12.9)	0.18
Meta-cognition index	842 (71%)	46.8 (12.5)	50.2 (15.2)	<0.0001	51.0 (14.1)	49.5 (13.5)	0.059
Total score	841 (71%)	45.9 (11.6)	50.2 (15.4)	<0.0001	51.1 (14.5)	49.3 (13.7)	0.029
Emotional and behavioural problems as reported by parents/caregivers - T-score[c]							

Internalising problems	1014 (86%)	46.7 (10.7)	51.1 (13.5)	<0.0001	51.4 (13.3)	50.8 (12.5)	0.53
Externalising problems	1014 (86%)	46.8 (10.1)	49.8 (13.2)	<0.0001	50.5 (12.7)	49.1 (12.0)	0.11
Total problems	1014 (86%)	46.1 (10.4)	50.9 (13.2)	<0.0001	51.6 (13.0)	50.2 (12.3)	0.12
Intelligence (range 45-155)[d]							
Total IQ	1066 (90%)	100.7 (13.0)	90.6 (16.5)	<0.0001	90.3 (16.6)	90.9 (15.8)	0.57
Verbal IQ	1052 (89%)	100.8 (14.1)	92.0 (18.2)	<0.0001	91.6 (18.2)	92.4 (17.3)	0.55
Intelligence (range 45-155)[d]							
Performance IQ	1071 (90%)	100.7 (13.8)	91.5 (16.4)	<0.0001	91.4 (16.7)	91.7 (15.6)	0.54
Visual-motor integration (range 0.9-20)[d]	1097 (93%)	9.6 (2.4)	8.2 (3.5)	<0.0001	8.0 (3.5)	8.5 (2.9)	0.010
Alertness[c, e]							
Reaction time right hand - ms	413 (78%)	480.8 (290.2)	561.1 (700.4)	0.0064	591.4 (581.8)	527.6 (489.9)	0.082
Within-person SD of repeated tests	413 (78%)	219.3 (176.0)	278.8 (715.0)	0.056	296.3 (559.0)	259.5 (510.8)	0.29
Reaction time left hand - ms	418 (79%)	459.7 (239.2)	536.2 (538.1)	0.038	557.1 (460.6)	513.0 (412.5)	0.11
Within-person SD of repeated tests	418 (79%)	217.3 (222.4)	287.4 (542.7)	0.063	196.0 (454.0)	177.8 (401.8)	0.23
Motor coordination (number of taps in 10 s) [d, e]							
Number of right hand taps	433 (82%)	41.4 (16.1)	37.9 (41.1)	0.095	37.2 (32.6)	38.8 (28.8)	0.29
Number of left hand taps	433 (82%)	36.3 (14.4)	34.9 (36.6)	0.30	33.7 (29.1)	36.2 (25.9)	0.19
Number of valid alternating taps	392 (74%)	18.3 (23.2)	18.6 (63.8)	0.35	17.4 (49.4)	20.0 (45.7)	0.36
Number of valid synchronous taps	392 (74%)	23.9 (15.1)	21.9 (35.8)	0.19	20.4 (27.6)	23.5 (26.5)	0.041
Inhibition and flexibility[c, e]							
Difference in reaction time (inhibition) - ms	383 (72%)	234.5 (411.0)	264.2 (1207.6)	0.24	286.5 (937.0)	239.6 (826.2)	0.17
Difference in no of errors (inhibition)	385 (73%)	2.1 (12.7)	4.1 (38.6)	0.053	4.2 (28..5)	4.0 (27.3)	0.73
Difference in reaction time (flexibility) - ms	369 (70%)	427.9 (445.3)	445.8 (1149.2)	0.31	458.7 936.0)	431.6 (782.9)	0.49
Difference in numbers of errors (flexibility)	370 (70%)	2.4 (10.8)	4.8 (35.7)	0.067	4.6 (26.8)	5.0 (24.8)	0.64

Memory[d, e]							
Verbal-auditory							
Numbers (range 1-19)							
Memory span (forward)	331 (83%)	10.2 (2.9)	8.6 (5.7)	<0.0001	8.6 (5.0)	8.7 (4.4)	0.66
Working memory (backward)	318 (80%)	10.3 (3.0)	8.7 (4.5)	<0.0001	8.9 (4.3)	8.4 (3.7)	0.38
Word pairs (% of correct responses)							
Learning	287 (72%)	0.50 (0.2)	0.43 (0.8)	0.047	0.42 (0.7)	0.45 (0.5)	0.26
Immediate memory	285 (72%)	0.47 (0.2)	0.33 (0.6)	<0.0001	0.31 (0.5)	0.35 (0.4)	0.13
Delayed memory	282 (71%)	0.40 (0.3)	0.31 (0.8)	0.0059	0.30 (0.7)	0.32 (0.5)	0.43
Recognition	279 (70%)	0.95 (0.2)	0.87 (0.5)	0.0003	0.85 (0.4)	0.89 (0.3)	0.043
Non-verbal, visual-spatial							
Pictures (% of correct responses)	319 (80%)	0.85 (0.1)	0.789 (0.3)	0.0001	0.77 (0.2)	0.79 (0.2)	0.29
Dots (% of correct responses)							
Learning	305 (77%)	0.86 (0.2)	0.78 (0.5)	0.010	0.79 (0.4)	0.78 (0.4)	0.57
Immediate memory	305 (77%)	0.87 (0.2)	0.80 (0.8)	0.058	0.80 (0.6)	0.80 (0.5)	0.70
Delayed memory	299 (75%)	0.87 (0.2)	0.80 (0.8)	0.094	0.79 (0.6)	0.80 (0.5)	0.59
Learning index (range 50-150)	280 (71%)	100.2 (22.5)	92.2 (85.5)	0.025	91.9 (69.2)	92.5 (54.9)	0.50

Results are the combined number (%) and means (SD) from 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption for the 786 post-PICU patients and 405 healthy control children. IQ, intelligence quotient; PN, parenteral nutrition.

a Statistically significant after Bonferroni correction for multiple comparisons.

b Age-specific and sex-specific SD scores were calculated with the use of reference data from the WHO Growth Charts. The mean change in Z-scores from admission to a PICU to 2-year follow-up in the tested PEPaNIC population was 0.073 (SD 0.781) for height, 0.533 (1.101) for bodyweight, and 0.673 (1.393) for body-mass index. The mean change in Z-scores from PICU admission to 2-year follow-up for patients who received Late-PN versus those who received Early-PN in the tested PEPaNIC population was 0.027 (SD 1.899) versus 0.119 (1.656; p=0.84) for height, -0.366 (1.314) versus -0.397 (1.316; p=0.34) for bodyweight, and 0.605 (1.429) versus 0.739 (1.355; p=0.31) for body-mass index.

c Higher scores reflect worse performance.

d Higher scores reflect better performance.

e For alertness, motor coordination, executive functions, applicable imputation was limited to relevant age ranges.

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 2-year follow-up between patients and healthy control children and between Late-PN and Early-PN patient groups

	Number (%) of available data per outcome before imputation (N=1191)	**Beta-estimate or odds ratio (95% CI) for the comparison patients vs controls, adjusted for risk factors[a]**	**P-value**	**Beta-estimate or odds ratio (95% CI) for the comparison Late-PN vs Early-PN, adjusted for risk factors[b]**	**P-value**
Height – cm	1126 (95%)	-1.717 (-2.670;-0.763)	0.0004[c]	-0.538 (-3.358;2.282)	0.70
Weight – kg	1135 (96%)	-0.318 (-1.052;0.417)	0.39	0.278 (-1.639;2.194)	0.77
Body-mass index – kg/m^3	1126 (95%)				
Head circumference – cm	1060 (89%)	-0.461 (-0.701;-0.221)	0.0001[c]	-0.150 (-0.496;0.197)	0.39
Diagnosed with a somatic illness	957 (81%)	2.940 (2.199;3.931)[d]	<0.0001[c]	0.881 (0.625;1.242)[d]	0.74
Diagnosed with a psychiatric illness	1160 (98%)	2.137 (1.104;4.136)[d]	0.024	0.764 (0.403;1.448)[d]	0.40
Admitted to hospital for a medical or surgical reason	1191 (100%)	4.781 (3.485;6.559)[d]	<0.0001[c]	0.867 (0.634;1.186)[d]	0.37
Clinical neurological evaluation score (range 0-8)[e]	1116 (94%)	0.296 (0.154;0.439)	<0.0001[c]	-0.134 (-0.308;0.040)	0.13
Executive functioning as reported by parents/caregivers - T-score[f]					
Inhibition	850 (72%)	2.067 (0.507;3.628)	0.0095	-3.422 (-5.171;-1.673)	0.0001[c]
Flexibility	851 (72%)	1.611 (0.107;3.114)	0.035	-1.146 (-2.841;0.550)	0.18
Emotional control	851 (72%)	0.678 (-0.796;2.152)	0.36	-0.861 (-2.500;0.778)	0.30
Working memory	845 (71%)	2.834 (1.196;4.471)	0.0007[c]	-2.016 (-3.761;-0.270)	0.023
Planning and organization	847 (72%)	2.008 (0.426;3.590)	0.031	-1.139 (-2.807;0.529)	0.18
Meta-cognition index	842 (71%)	1.783 (0.145;3.421)	0.032	-1.957 (-3.694;-0.220)	0.027
Total score	841 (71%)	2.445 (0.882;4.008)	0.0022	-2.258 (-4.012;-0.504)	0.011
Emotional and behavioural problems as reported by parents/caregivers - T-score[e]					

Internalising problems	1014 (86%)	3.153 (1.705;4.600)	<0.0001[c]	-0.837 (-2.535;0.860)	0.33
Externalising problems	1014 (86%)	1.675 (0.261;3.088)	0.020	-1.715 (-3.325;-0.106)	0.036
Total problems	1014 (86%)	3.206 (1.757;4.655)	<0.0001[c]	-1.590 (-3.268;0.088)	0.063
Intelligence (range 45-155)[e]					
Total IQ	1066 (90%)	-5.508 (-7.254;-3.761)	<0.0001[c]	0.044 (-1.947;2.034)	0.96
Verbal IQ	1052 (89%)	-4.301 (-6.197;-2.405)	<0.0001[c]	0.237 (-1.980;2.455)	0.83
Performance IQ	1071 (90%)	-5.650 (-7.462;-3.838)	<0.0001[c]	-0.158 (-2.201;1.885)	0.87
Visual-motor integration (range 0.9-20)[f]	1097 (93%)	-0.925 (-1.256;-0.594)	<0.0001[c]	0.468 (0.087;0.850)	0.016
Alertness[e, g]					
Reaction time right hand - ms	413 (78%)	55.695 (6.319;105.071)	0.027	-55.418 (-121.649;10.813)	0.10
Within-person SD of repeated tests	413 (78%)	48.403 (0.632;96.174)	0.047	-34.167 (-91.313;22.978)	0.23
Reaction time left hand - ms	418 (79%)	54.996 (10.192;99.799)	0.016	-40.166 (-106.821;26.488)	0.23
Within-person SD of repeated tests	418 (79%)	49.624 (4.158;95.089)	0.032	-17.296 (-75.374;40.783)	0.55
Motor coordination (number of taps in 10 s)[f, g]					
Number of right hand taps	433 (82%)	-2.429 (-5.171;0.314)	0.081	0.863 (-2.181;3.907)	0.57
Number of left hand taps	433 (82%)	-1.536 (-4.077;1.004)	0.23	1.998 (-0.878;4.874)	0.17
Number of valid alternating taps	392 (74%)	0.707 (-4.391;5.805)	0.78	2.085 (-2.653;6.823)	0.38
Number of valid synchronous taps	418 (79%)	-1.354 (-3.998;1.289)	0.31	2.650 (-0.375;5.675)	0.085
Inhibition and flexibility[e, g]					
Difference in reaction time (inhibition) - ms	383 (72%)	25.177 (-51.033;101.387)	0.51	-53.416 (-125.105;18.274)	0.14
Difference in numbers of errors (inhibition)	385 (73%)	1.422 (-0.788;3.632)	0.20	-0.326 (-2.145;1.492)	0.72
Difference in reaction time (flexibility) - ms	369 (70%)	40.680 (-47.657;129.017)	0.36	-22.794 (-110.737;65.148)	0.60
Difference in numbers of errors (flexibility)	370 (70%)	2.085 (-0.062;4.231)	0.056	0.631 (-1.083;2.344)	0.46
Memory[f, g]					
Verbal-auditory					

Numbers (range 1-19)					
Memory span (forward)	331 (83%)	-1.113 (-1.883;-0.342)	0.0048	0.037 (-0.859;0.933)	0.93
Working memory (backward)	318 (80%)	-0.927 (-1.638;-0.216)	0.010	-0.393 (-1.286;0.500)	0.38
Word pairs (proportion of correct responses)					
Learning	287 (72%)	-0.065 (-0.121;-0.008)	0.025	0.039 (-0.027;0.104)	0.24
Immediate memory	285 (72%)	-0.110 (-0.165;-0.055)	0.0001[c]	0.047 (-0.014;0.109)	0.13
Delayed memory	282 (71%)	-0.078 (-0.132;-0.025)	0.0046	0.017 (-0.044;0.078)	0.57
Recognition	279 (70%)	-0.058 (-0.096;-0.021)	0.0027	0.035 (-0.013;0.083)	0.14
Non-verbal, visual-spatial					
Pictures (proportion of correct responses)	319 (80%)	-0.056 (-0.088;-0.024)	0.0006[c]	0.009 (-0.033;0.052)	0.66
Dots (proportion of correct responses)					
Learning	305 (77%)	-0.050 (-0.095;-0.005)	0.029	-0.016 (-0.064;0.032)	0.51
Immediate memory	305 (77%)	-0.051 (-0.114;0.012)	0.11	-0.013 (-0.077;0.052)	0.69
Delayed memory	299 (75%)	-0.058 (-0.122;0.006)	0.073	-0.002 (-0.069;0.064)	0.94
Learning index (range 50-150)	280 (71%)	-6.328 (-12.555;-0.101)	0.046	0.487 (-5.590;6.565)	0.87

Results are the combined beta-estimates and odds ratios from 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption for the 786 post-PICU patients and 405 healthy control children. Sensitivity analyses to the missing-at-random assumption and with imputing worst test-scores for the severely disabled and thus non-testable children, as specified in the appendix, further supported the robustness of these results. IQ, intelligence quotient; PeLOD score, Paediatric Logistic Organ Dysfunction Score; PICU, paediatric intensive care unit; PIM3 score, Paediatric Index of Mortality 3 score; PN, parenteral nutrition; SD, standard deviation; STRONGkids, Screening Tool Risk On Nutritional Status and Growth.

a Estimates and odds ratios were adjusted for the following risk factors: age, centre, race, sex, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined syndrome, and the educational and occupational status of parents; b Estimates and odds ratios were adjusted for the following risk factors: age, centre, race, sex, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined syndrome, the educational and occupational status of parents, PIM3 score and PeLOD score upon PICU admission, STRONGkids risk category, and parental smoking behaviour prior to PICU admission; c Statistically significant after Bonferroni correction for multiple comparisons; d These values are odds ratios; e Higher scores reflect worse performance; f Higher scores reflect better performance; g For alertness, motor coordination, executive functions, applicable imputation was limited to relevant age ranges.

Executive dysfunction comprises problems in complex decision making and goal-oriented behaviour with implications for daily life[23] and has been associated with externalising problems such as antisocial and aggressive behaviour.[10,24] Indeed, poor inhibitory control in children is known to contribute to impulsive and destructive behaviours that upset or harm others.[24] Hence, the possible beneficial effects of delaying PN in paediatric critical illness on the longer-term parent/caregiver-reported inhibitory function, further supported by better scores for other executive functions, externalising behaviour, and visual-motor integration (comparisons that lost significance after Bonferroni correction), are relevant. Indeed, the consequences for daily life and for the social environment are otherwise difficult to quantify by existing clinical neurocognitive tests.

The most robust protection of executive functioning of delayed PN was observed for the ability to suppress immediate responses, as measured by the parent/caregiver- reported inhibition score; this finding suggests potential damage induced by Early-PN to frontal lobe areas that coordinate inhibition.[25] The frontal lobe appears to be particularly vulnerable to metabolic insults during critical illness, with inflammation and neuronal damage described, which can be partially prevented by avoiding excessive hyperglycaemia.[26] A previous randomised, controlled trial[9] that documented the long-term neurocognitive impact of preventing hyperglycemia in the PICU also found some improvement of executive functioning. We speculate that harm induced by Early-PN to executive functioning might also be a direct metabolic insult on the developing brains of young children, because it was not statistically explained by the acute effects of the intervention, such as increased incidence of new infections or delayed recovery, or by other potentially hazardous post-randomization treatments given during the PICU stay, such as use of benzodiazepines. The larger benefit observed for critically ill infants than for older children provides support for this speculation. Whether other periods of age or development, such as puberty, also represent special vulnerability remains to be investigated.

Unlike our current findings in patients admitted to the PICU early in life, studies in other paediatric settings and otherwise healthy children have shown that insufficient rather than abundant nutritional intake, both prenatally and during childhood, can result in impaired growth and neurocognitive development.[27,28] These differing results could be explained by the context. Indeed, specifically in the context of critical illness, fasting-induced responses brought about during the first days after an insult might generate beneficial effects through (autophagy-induced) cell damage removal and prevention of neuronal loss.[26,29] The early administration of amino acids, the most powerful suppressors of autophagy,[29] rather than glucose or lipids was found to explain the short-term harm by Early-PN in critically ill children.[30] However, the exact underlying mechanisms of any long-term effect of not forcefully feeding patients early during critical illness remain speculative. Among others, alterations in DNA methylation in promoters or bodies of genes involved in neuronal growth, axonal guidance, and signal transduction could play a part,[31] since such epigenetic

changes have been previously associated with executive dysfunction.[23] Moreover, the potential involvement of telomere shortening, which has been shown to be accelerated by early initiation of PN during paediatric critical illness, should be further investigated.[32]

This study has limitations. First, the young age of PEPaNIC patients precluded complete and reliable results for certain neurocognitive tests. For these tests, the statistical power and thus the odds of identifying a difference between treatment groups was reduced. Second, neuroimaging studies were not done. Third, information on physiotherapy in the PICU and on the regular ward (i.e., after PICU but before hospital discharge) was not recorded. Fourth, data on follow-up consultations and therapies beyond the study protocol were not systematically available for all centres and all diagnostic subgroups. Fifth, after conservative Bonferroni correction, only the impact of withholding PN early in the PICU on long-term inhibitory control remained significant. However, given that inhibition is an important cognitive function involved in many aspects of daily life, and given the absence of any harm, this finding is relevant for endorsing implementation of withholding early PN in the PICU.

CONCLUSIONS

Patients admitted to the PICU early in life had worse outcomes at the 2-year follow-up for anthropometrics, health status, and neurocognitive development than did healthy control children. Withholding early PN for 1 week in the PICU did not negatively affect survival, anthropometrics, health status and neurocognitive development, and improved inhibitory control 2 years later.

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APPENDIX

Methods S1: Definition of educational and occupational level of parents

Educational level of parents

The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): low (=1), middle (=2) and high (=3) educational level.

Occupational level of parents

The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (http://www.ilo.org/public/english/bureau/stat/isco/).[1] In case one of the parents filled in two jobs in the questionnaire, the highest Isco code level was used. In case "unemployed", "disabled", "student", or "housewife/houseman" was filled in, an Isco code level of 1 was given to that parent. When the parents described their profession as "employee", "worker", "liberal profession", or "retired", they were given an Isco code level of 2.

Methods S2: Definition of "Syndrome"

A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development, and which is subdivided in the following categories:

- Genetically confirmed syndrome or pathogenic chromosomal abnormality
- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown etiology
- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumor or tumor with intracranial metastatic disease
- Pedopsychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré
- Resuscitation and/or need for extracorporeal membrane oxygenation prior to randomization
- Severe convulsions or stroke prior to randomization

Methods S3: Detailed description of outcome measures

Medical assessment

Anthropometric data

Height (in cm), body weight (in kg) and head circumference (in cm) were measured.

Health status

In an interview with the parents, the need for medical support of all kind during the past two years for healthy control children and during the 2 years following the index PICU admission for patients, was recorded. The hospital admissions because of surgery or a medical reason, and the occurrence of a psychiatric diagnosis were documented.

Clinical neurological examination

In order to assess whether there were gross neurological abnormalities, during a structured clinical neurological examination, signs of major neurologic dysfunction were detected in the following domains: interaction/language skills, gross motor function, involuntary movements, reflexes, coordination and balance, fine motor function, cranial nerves, and special senses (sensory, visual, and auditory function). These were all scored normal or abnormal. An abnormal result for each of these domains was given 1 point and the sum was made of all the abnormal results, with a range of 0-8.

Neurocognitive testing

A broad range of neurocognitive functions, including general intellectual functioning, visual-motor integration, attention, motor coordination, inhibitory control and cognitive flexibility, verbal and visual-spatial learning, and memory were evaluated, as previously reported.[2]

Patient/Parents-reported outcomes (PROs)

Executive functioning was measured with the Behaviour Rating Inventory of Executive Function (BRIEF-P 2.5-5 years, BRIEF 6-18 years), filled out by the parents or caregivers of the child. Overlapping scales and indices of both questionnaires (Inhibition, Flexibility, Emotional Control, Working Memory, Planning and Organization, Meta-cognition) and a Total Score were analysed (T-scores, with mean 50 and SD 10).[3,4] Emotional and behavioural problems were assessed by the parent or caregiver with the Child Behaviour Checklist (CBCL 1.5-5 years or CBCL 6-18 years).[5,6] NREF 4 Internalising, externalising, and total problems were analysed (T-scores, with mean 50 and SD 10).[5,6]

Intelligence

General intellectual ability was assessed with use of age-appropriate versions of the Wechsler Intelligence Quotient (IQ) tests. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)[7] was used for children aged 2.5 years to 5 years 11 months (one version for age range 2 years 6 months to 3 years 11 months, and another version for age range 4 years to 5 years 11 months), the Wechsler Intelligence Scale for Children (WISC-

III-NL)[8] was used for children aged 6 years to 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL)[9] for adolescents who were 17 years or older. For all these tests Total IQ, Verbal IQ, and Performance IQ scores (Test-mean 100, SD 15) were computed.

Visual-motor integration

We used the Beery Developmental Test of Visual-Motor Integration, 6th Edition (VMI) to assess the ability to integrate their visual and motor functions (total Scaled Score, Test-mean 10, SD 3). This involves eye-hand coordination.[10]

Alertness, motor-coordination, and executive functions

To measure alertness, motor-coordination and executive function, the validated Amsterdam Neuropsychological Tasks (ANT) program was used.[11] The ANT is a computer-aided assessment battery of reaction time (RT) tasks that allows for the systematic evaluation of information processing capacities.

Children 4 years and older performed ANT-Baseline Speed (BS), ANT-Tapping (TP), and Response Organization Objects (ROO). The ANT-BS evaluated alertness by measuring simple RT to visual stimuli (mean RT and SD of RT were obtained for the right and left hand separately). The ANT-TP assessed motor coordination for the right hand, left hand, bimanual alternating, and bimanual synchronous. The ANT-ROO measured inhibitory control and cognitive flexibility by calculating the differences in RT and the differences in number of errors between tests of increasing demand.

Memory

Auditory/verbal memory and Visual-spatial/non-verbal memory were assessed with use of four tests from the Children's Memory Scale (CMS) for children between 5 and 16 years 11 months.[12] As to verbal memory, CMS-Numbers assessed short-term verbal memory span (forward digit recall) and verbal working memory load (backward digit recall). The CMS-Word Pairs (recall a list of word pairs) assessed short-term and long-term verbal memory, and recognition. As to non-verbal memory, CMS-Picture Locations (remembering and recall of pictures in various locations) assessed immediate visual memory. CMS-Dot Locations (remembering and recall of the location of dots) assessed immediate and delayed visual memory. For CMS-Numbers, raw scores for verbal memory span, CMS-numbers forward, and verbal working memory load, CMS-numbers backward were reported. For CMS-Word Pairs, CMS-Picture Locations, and CMS-Dot Locations, proportional scores were analysed (proportion of correct responses ranging from 0 to 1, with higher scores reflecting better performance). The CMS-Learning index is a standardised score of the sum of the three learning trials of the CMS-Word Pairs and the learning trial of the CMS-Dot Locations subtests. The range of the score is 50-150, with a higher score representing a better learning ability.

Methods S4: Imputation

Missing data (excluding the deceased and the severely disabled whereby non-testable children) were handled by **multiple data imputation with chained equations under a 'missing at random' assumption.** There were no missing data in the baseline variables. Predictors for missing values included all covariates listed below, and were retained in the predictor models with a minimum correlation of 0.1 with the prediction target. Predictive mean matching[13] was used for numeric variables except for factors with two levels (which were imputed based on logistic regression) and factors with more than two levels (for which polytomous (unordered) regression was used). A monotonous visiting scheme was used such that variables for imputation were visited in increasing order of the number of missing data. Imputation convergence was assessed visually and set at 70 iterations (Figure S1). Since there were no more than 30% missing observations for all variables, 31 complete imputed datasets were used in the analyses,[14] and pooled results were obtained across datasets using Rubin's rules.[15]

Plausibility of the imputations was assessed visually via the densities of the observed data and that resulting from the imputed values (Figure S2). **Sensitivity of results to the 'missing at random' assumption** was assessed with use of pattern mixture models [15-17] assuming the original imputed values were either too high or too low by a factor of 0.1 for the main result of inhibition as reported by parents. Under this assumption, the obtained beta-estimates and P-values for randomization to Late-PN vs. Early-PN for the multivariable linear regression analyses performed to determine significant and independent associations between risk factors and inhibition as reported by the parents at two-year follow-up within the tested patient population (Table S1-1) ranged from -2.962 ($p<0.0001$) to -2.396 ($p=0.032$). The effect-sizes thus remained of the same order of magnitude, sign, and statistical significance as were observed for the original imputed datasets, which suggested that the analyses were robust against the investigated 'missing at random' violation.

To further evaluate the robustness of the main findings, the analyses were repeated after imputing a **penalised test result for all severely disabled and thus non-testable patients,** defined as the worst result in the observed patients or controls, plus or minus one, as appropriate for each test. In this case, the obtained beta-estimates (p-values) for randomization to Late-PN vs. Early-PN for the multivariable linear regression analyses were respectively: A) -3.382 ($p<0.0001$) for inhibition as reported by parents; B) -1.928 ($p=0.031$) for meta-cognition as reported by parents; C) -1.992 ($P=0.026$) for working memory as reported by parents; D) -2.224 ($p=0.014$) for overall executive functioning as reported by parents; E) -1.668 ($p=0.045$) for externalising emotional and behavioural problems as reported by parents; and F) 0.464 ($p=0.017$) for visual-motor integration. These sensitivity

analyses corresponded closely to the primary results as reported in Table 2 of the main manuscript.

All multiple data imputation analyses were performed with R version 3.4.3 and MICE version 2.46.0.

List of variables used for multiple data imputation by chained equations

Demographics of patients and control children and patient characteristics upon PICU admission, Centre, randomization for Late-PN or Early-PN, patient vs. controls, race, gender, geographic origin, language, hand preference, history of malignancy, history of diabetes, a predefined "syndrome", educational and occupational status of parents, diagnosis, PIM3 and PeLOD scores upon PICU admission, risk of malnutrition (STRONGkids category), parental smoking behaviour prior to PICU admission, age at randomization, age group at randomization.

Acute effects of randomization and post-randomization treatments in PICU

Acquisition of new PICU infections, duration of PICU stay, duration of mechanical ventilatory support, hypoglycemia, duration of treatment with hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and α2-agonists.

At two-year follow-up

Age, test location, height, weight, head circumference, composite endpoint "diagnosed with a somatic illness", composite endpoint "diagnosed with a psychiatric illness", composite endpoint "admitted to hospital for a medical or surgical reason", clinical neurological examination, verbal IQ, performance IQ, total IQ, visual motor integration, reaction time left hand, reaction time right hand, within subject SD of reaction time left hand, within subject SD of reaction time left hand, number of unimanual taps right hand, number of unimanual taps left hand, number of valid alternating taps, number of valid synchronous taps, delta reaction time inhibition, delta number of errors inhibition, delta reaction time flexibility, delta number of errors flexibility, numbers memory span forward, numbers working memory backward, word pairs learning, word pairs immediate memory, word pairs delayed memory, word pairs recognition, pictures, dots learning, dots immediate memory, dots delayed memory, learning index, executive functioning as reported by parents/caregivers (inhibition, flexibility, emotional control, working memory, planning and organization, meta-cognition index, and total score), emotional and behavioural problems as reported by parents/caregivers (internalising problems, externalising problems, and total problems). Interactions between age group and randomization were not included in the imputation models.

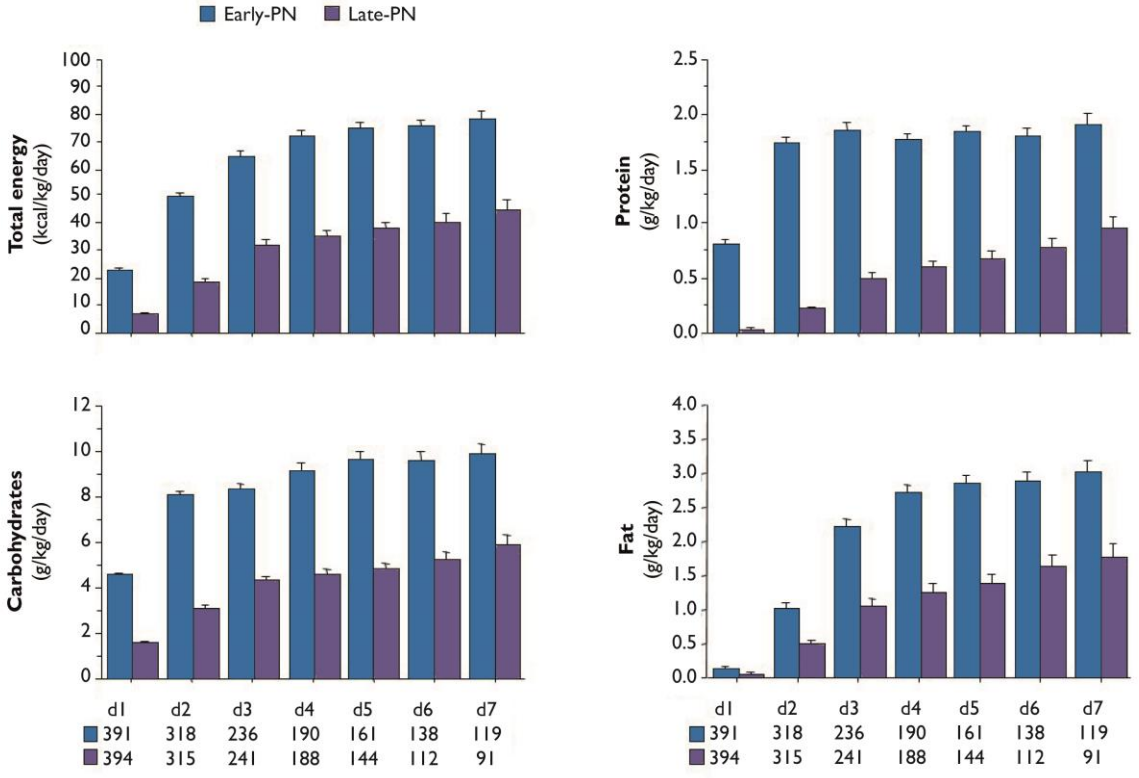

Figure S1. Macronutrient doses during the first week in PICU administered to the tested population

Daily amount of total energy in kcal/kg/day, and the daily amounts of total substrates in g/kg/day are shown for the first 7 days in the paediatric intensive care unit (PICU). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the Early-PN group and the green bars represent the Late-PN group.

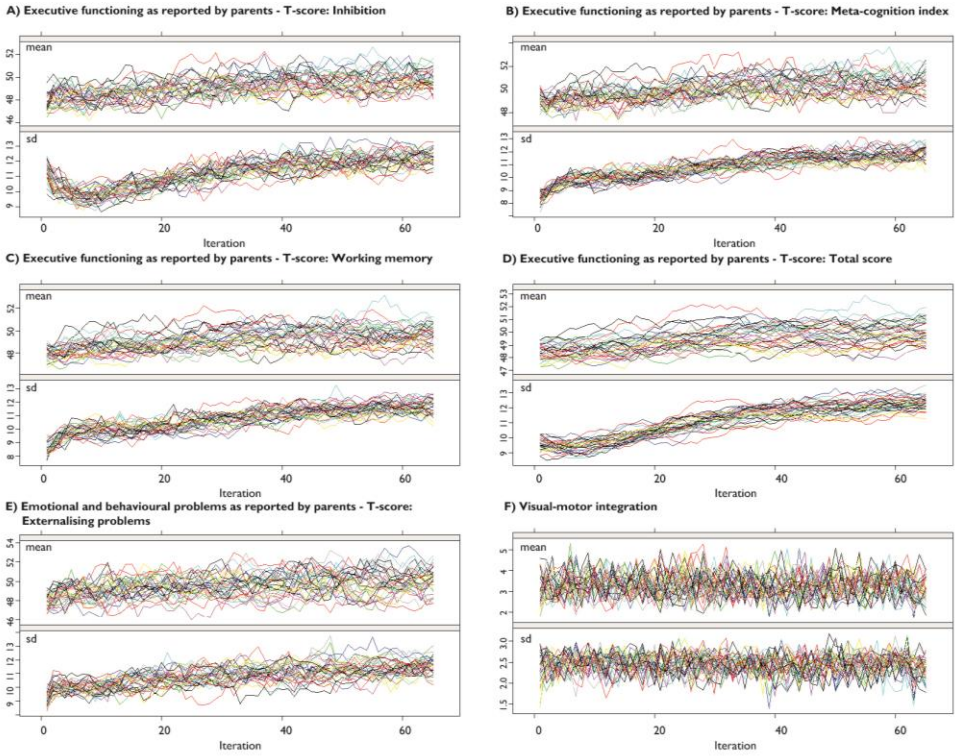

Figure S2. Imputation convergence for selected neurocognitive test results
Mean and standard deviation of imputed values in each of 31 datasets over 70 iterations for
A) Executive functioning as reported by parents/caregivers - T-score: Inhibition;
B) Meta-cognition index;
C) Working memory;
D) Total score;
E) Emotional and behavioural problems as reported by parents/caregivers - T-score: Externalising problems;
F) Visual-motor integration.

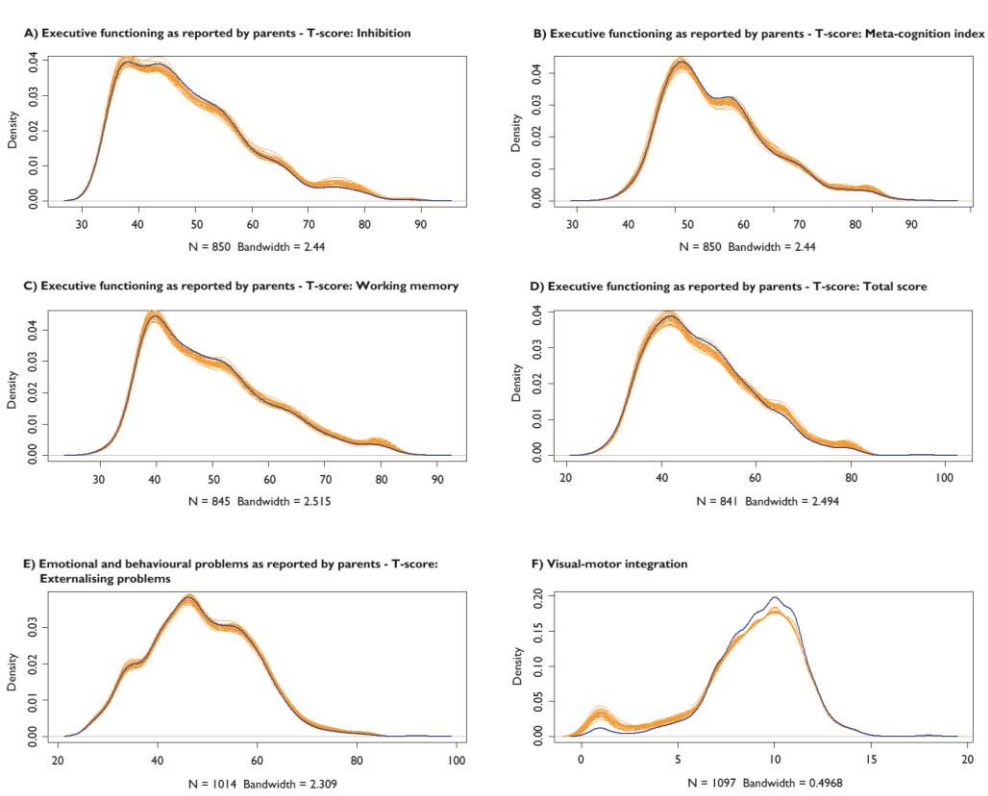

Figure S3. Density estimates of the observed and imputed values for selected neurocognitive test results

Density estimated for observed values (in blue) and for each imputed dataset (in orange) for

A) Executive functioning as reported by parents/caregivers - T-score: Inhibition;

B) Meta-cognition index;

C) Working memory;

D) Total score;

E) Emotional and behavioural problems as reported by parents - T-score: Externalising problems;

F) Visual-motor integration.

Figure S4. Multiple imputation predictor variables

Missing values for the variables in each row are imputed based on models that use as predictors only the column variables highlighted in blue. The predictor variables are selected as described in Methods S4

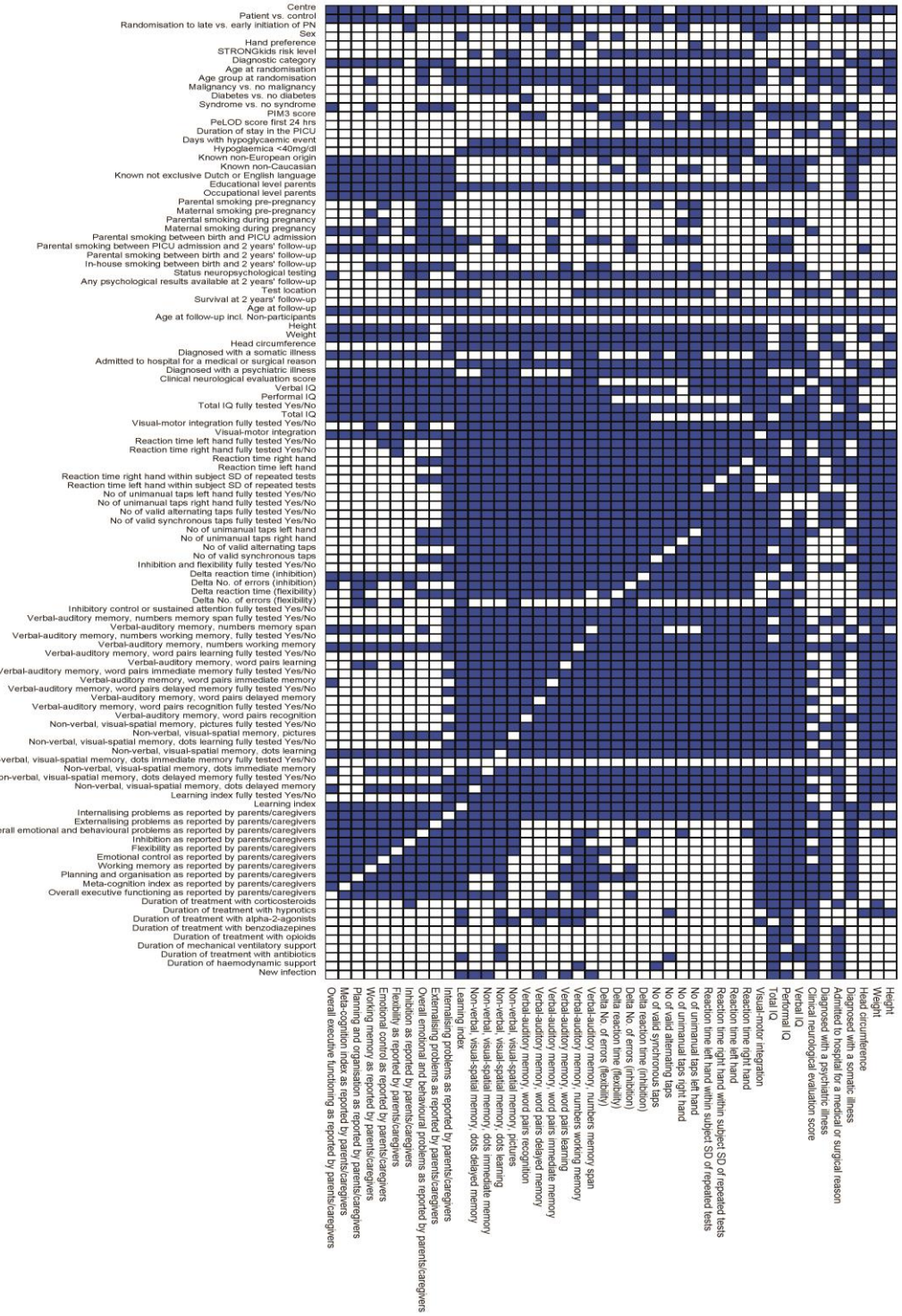

Table S1-1. Multivariable linear regression analyses determining significant and independent associations between risk factors and inhibition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Randomization to late vs. early initiation of PN	***-3.422***	***-5.171***	***-1.673***	***0.00013***	***-3.373***	***-5.140***	***-1.605***	***0.00020***
Centre								
Leuven vs. Edmonton	1.752	-5.864	9.369	0.65	2.306	-5.392	10.004	0.55
Rotterdam vs. Edmonton	1.683	-6.012	9.377	0.66	1.307	-6.456	9.069	0.74
Male vs. female sex	1.098	-0.740	2.937	0.24	1.162	-0.675	2.999	0.21
Right vs. left hand preference	0.280	-2.548	3.109	0.84	0.284	-2.492	3.060	0.83
Medium vs. high STRONGkids risk level[a]	0.592	-2.543	3.726	0.71	0.562	-2.620	3.745	0.72
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-0.800	-4.510	2.911	0.67	-0.634	-4.338	3.070	0.73
Burns	-1.969	-17.860	13.923	0.80	-3.540	-19.912	12.833	0.67
Neurosurgery - traumatic brain injury	1.988	-1.662	5.638	0.28	1.640	-2.005	5.285	0.37
Thoracic	-1.293	-5.670	3.084	0.56	-1.225	-5.650	3.200	0.58
Transplantation	5.434	-2.598	13.465	0.18	3.995	-5.157	13.148	0.38
Orthopedic surgery-trauma	0.485	-5.186	6.157	0.86	0.184	-5.522	5.889	0.94
Other	3.419	-1.470	8.309	0.17	2.611	-2.369	7.591	0.30
Medical								
Cardiac	2.694	-2.638	8.026	0.32	2.291	-3.295	7.877	0.42
Gastrointestinal-hepatic	10.927	-5.325	27.179	0.18	10.591	-5.610	26.792	0.19
Hematologic-oncologic	3.951	-4.925	12.828	0.38	0.637	-8.789	10.063	0.89

Neurologic	0.691	-3.535	4.918	0.74	-0.297	-4.658	4.064	0.89
Respiratory	0.374	-3.370	4.118	0.84	-0.161	-4.032	3.710	0.93
Other	0.096	-4.640	4.832	0.96	-0.307	-5.197	4.582	0.90
Infant (age<1y) vs. child at randomization	0.315	-1.635	2.265	0.75	0.331	-1.719	2.382	0.75
Malignancy vs. no malignancy	-1.620	-5.794	2.554	0.44	-1.907	-6.129	2.314	0.37
Diabetes vs. no diabetes	-5.169	-28.229	17.890	0.65	-3.412	-26.465	19.642	0.77
Syndrome vs. no syndrome[b]	3.447	0.314	6.581	0.031	3.727	0.571	6.884	0.020
PIM3 score (per point added)[c]	0.071	-0.780	0.922	0.87	-0.006	-0.883	0.871	0.98
PeLOD score first 24 hrs (per point added)[d]	0.067	-0.047	0.181	0.24	0.051	-0.064	0.167	0.38
Known non-European origin vs. other[e]	-0.582	-4.367	3.202	0.76	-0.625	-4.407	3.158	0.74
Known non-Caucasian vs. other[e]	-1.931	-6.585	2.724	0.41	-1.560	-6.231	3.112	0.51
Known not exclusive Dutch or English language vs. other	0.359	-2.480	3.198	0.80	0.379	-2.456	3.214	0.79
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.090	-8.471	2.292	0.25	-2.468	-7.907	2.970	0.37
Educational level 2	-2.097	-6.648	2.453	0.36	-1.634	-6.226	2.958	0.48
Educational level 2.5	-3.730	-8.625	1.164	0.13	-3.127	-8.047	1.792	0.21
Educational level 3	-4.590	-9.509	0.329	0.067	-4.043	-8.996	0.909	0.10
Educational level unknown	-0.579	-6.400	5.242	0.84	-0.111	-5.963	5.742	0.97
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	3.634	-4.260	11.527	0.36	3.091	-4.810	10.992	0.44
Occupational level 2	3.086	-4.721	10.893	0.43	2.380	-5.448	10.208	0.55
Occupational level 2.5	3.803	-4.335	11.941	0.35	2.995	-5.176	11.166	0.47
Occupational level 3	3.047	-4.923	11.017	0.45	2.400	-5.583	10.382	0.55

Occupational level 3.5	0.490	-7.969	8.950	0.90	-0.224	-8.701	8.253	0.95
Occupational level 4	4.074	-4.163	12.312	0.33	3.139	-5.147	11.426	0.45
Occupational level unknown	2.458	-5.483	10.399	0.54	1.882	-6.074	9.839	0.64
Parental smoking between birth and PICU admission vs. no smoking	1.530	-0.787	3.847	0.19	1.635	-0.671	3.942	0.16
New infection vs. no new infection					-0.420	-3.898	3.058	0.81
Duration of stay in the PICU (per day added)					0.033	-0.258	0.323	0.82
Days with hypoglycemic event (per day added)					-0.331	-2.299	1.637	0.74
Duration of mechanical ventilatory support (per day added)					-0.089	-0.291	0.113	0.38
Duration of treatment with antibiotics (per day added)					-0.049	-0.321	0.223	0.72
Duration of hemodynamic support (per day added)					-0.100	-0.305	0.104	0.33
Duration of treatment with corticosteroids (per day added)					0.229	-0.101	0.558	0.17
Duration of treatment with opioids (per day added)					-0.082	-0.368	0.204	0.57
Duration of treatment with benzodiazepines (per day added)					0.323	0.056	0.590	0.017
Duration of treatment with hypnotics (per day added)					0.073	-0.211	0.356	0.61
Duration of treatment with α2-agonists (per day added)					-0.186	-0.449	0.078	0.16

PeLOD, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3, paediatric index of mortality 3 score; PN, parenteral nutrition. For inhibition as reported by parents, higher scores reflect worse performance. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1-3 indicating medium risk, and a score of 4-5 indicating high risk. b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods S2) c Paediatric Index of Mortality 3(PIM3) scores, with higher scores indicating a higher risk of mortality. d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.me Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl):Low(=1), middle(=2) and high(=3) educational level (Methods S1). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-2. Multivariable linear regression analyses determining significant and independent associations between risk factors and working memory as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Randomization to late vs. early initiation of PN	***-2.016***	***-3.761***	***-0.270***	***0.023***	***-1.961***	***-3.728***	***-0.194***	***0.029***
Centre								
Leuven vs. Edmonton	0.686	-6.879	8.250	0.85	1.356	-6.400	9.112	0.73
Rotterdam vs. Edmonton	0.107	-7.564	7.779	0.97	-0.082	-7.943	7.778	0.98
Male vs. female sex	1.266	-0.523	3.055	0.16	1.220	-0.564	3.005	0.17
Right vs. left hand preference	0.222	-2.353	2.797	0.86	0.287	-2.274	2.849	0.82
Medium vs. high STRONGkids risk level [a]	-0.120	-3.331	3.092	0.94	0.180	-3.084	3.444	0.91
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.737	-6.574	1.100	0.16	-2.573	-6.423	1.277	0.18
Burns	-1.793	-17.437	13.850	0.82	-2.819	-18.998	13.361	0.73
Neurosurgery - traumatic brain injury	2.159	-1.515	5.833	0.24	1.930	-1.752	5.612	0.30
Thoracic	-3.357	-7.670	0.956	0.12	-3.286	-7.666	1.094	0.14
Transplantation	6.273	-1.387	13.934	0.10	5.872	-2.856	14.599	0.18
Orthopedic surgery-trauma	0.651	-4.851	6.153	0.81	0.536	-4.962	6.034	0.84
Other	4.021	-0.885	8.927	0.10	3.462	-1.543	8.467	0.17
Medical								
Cardiac	3.986	-1.280	9.252	0.13	3.125	-2.477	8.727	0.27
Gastrointestinal-hepatic	13.673	-1.652	28.999	0.080	13.484	-1.816	28.784	0.083
Hematologic-oncologic	-1.926	-10.690	6.838	0.66	-4.287	-13.541	4.967	0.36

Neurologic	0.246	-3.909	4.402	0.90	-0.369	-4.582	3.843	0.86
Respiratory	-2.172	-5.908	1.563	0.25	-2.735	-6.583	1.113	0.16
Other	-1.210	-5.913	3.493	0.61	-1.545	-6.405	3.314	0.53
Infant (age<1y) vs. child at randomization	-0.737	-2.690	1.216	0.45	-0.703	-2.721	1.315	0.49
Malignancy vs. no malignancy	1.704	-2.413	5.821	0.41	1.688	-2.471	5.847	0.42
Diabetes vs. no diabetes	0.527	-22.272	23.326	0.96	1.951	-20.856	24.757	0.86
Syndrome vs. no syndrome[b]	5.298	2.181	8.414	0.00094	5.324	2.167	8.481	0.0010
PIM3 score (per point added)[c]	0.280	-0.614	1.173	0.53	0.191	-0.737	1.120	0.68
PeLOD score first 24 hrs (per point added)[d]	0.011	-0.101	0.124	0.84	-0.004	-0.118	0.110	0.94
Known non-European origin vs. other[e]	1.118	-2.771	5.007	0.57	1.112	-2.781	5.005	0.57
Known non-Caucasian vs. other[e]	-3.969	-9.097	1.158	0.12	-3.744	-8.870	1.382	0.15
Known not exclusive Dutch or English language vs. other	0.316	-2.338	2.970	0.81	0.365	-2.305	3.036	0.78
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.391	-8.554	1.773	0.19	-2.870	-8.119	2.379	0.28
Educational level 2	-2.230	-6.603	2.144	0.31	-1.745	-6.159	2.669	0.43
Educational level 2.5	-3.950	-8.584	0.683	0.094	-3.314	-7.974	1.346	0.16
Educational level 3	-4.174	-8.873	0.524	0.081	-3.631	-8.376	1.114	0.13
Educational level unknown	-1.527	-7.153	4.099	0.59	-1.042	-6.754	4.669	0.71
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.618	-7.159	8.394	0.87	0.162	-7.632	7.956	0.96
Occupational level 2	0.579	-7.203	8.362	0.88	0.055	-7.752	7.863	0.98
Occupational level 2.5	0.286	-7.808	8.381	0.94	-0.453	-8.571	7.665	0.91
Occupational level 3	-0.860	-8.803	7.082	0.83	-1.442	-9.390	6.506	0.72

Occupational level 3.5	-3.143	-11.577	5.292	0.46	-3.740	-12.188	4.708	0.38
Occupational level 4	0.358	-7.869	8.585	0.93	-0.426	-8.692	7.840	0.91
Occupational level unknown	0.378	-7.667	8.422	0.92	-0.162	-8.241	7.918	0.96
Parental smoking between birth and PICU admission vs. no smoking	1.230	-1.255	3.715	0.32	1.315	-1.174	3.803	0.29
New infection vs. no new infection					0.674	-2.783	4.131	0.70
Duration of stay in the PICU (per day added)					0.001	-0.287	0.289	0.99
Days with hypoglycemic event (per day added)					-0.166	-2.167	1.835	0.87
Duration of mechanical ventilatory support (per day added)					-0.103	-0.300	0.095	0.30
Duration of treatment with antibiotics (per day added)					0.034	-0.239	0.307	0.80
Duration of hemodynamic support (per day added)					-0.066	-0.266	0.134	0.51
Duration of treatment with corticosteroids (per day added)					0.095	-0.226	0.415	0.56
Duration of treatment with opioids (per day added)					-0.150	-0.435	0.134	0.29
Duration of treatment with benzodiazepines (per day added)					0.337	0.075	0.598	0.011
Duration of treatment with hypnotics (per day added)					0.066	-0.214	0.346	0.64
Duration of treatment with α2-agonists (per day added)					-0.207	-0.465	0.050	0.11

PeLOD, Paediatric Logistic Organ Dysfunction score; PICU, paediatric intensive care unit; PIM3, Paediatric Index of Mortality 3 score; PN, parenteral nutrition. For working memory as reported by parents, higher scores reflect worse performance. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk. b A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods S2). c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality. d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness. e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S1). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-3. Multivariable linear regression analyses determining significant and independent associations between risk factors and meta-cognition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Randomization to late vs. early initiation of PN	***-1.957***	***-3.694***	***-0.220***	***0.027***	***-1.914***	***-3.668***	***-0.159***	***0.032***
Centre								
Leuven vs. Edmonton	1.562	-5.918	9.041	0.68	2.358	-5.310	10.026	0.54
Rotterdam vs. Edmonton	0.874	-6.632	8.380	0.81	0.959	-6.726	8.644	0.80
Male vs. female sex	0.936	-0.884	2.755	0.31	0.883	-0.934	2.699	0.33
Right vs. left hand preference	0.355	-2.296	3.006	0.79	0.456	-2.136	3.049	0.72
Medium vs. high STRONGkids risk level[a]	-0.073	-3.217	3.071	0.96	0.190	-3.019	3.398	0.90
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.385	-6.209	1.438	0.22	-2.290	-6.145	1.565	0.24
Burns	-0.358	-16.758	16.043	0.96	-1.153	-18.197	15.892	0.89
Neurosurgery - traumatic brain injury	1.129	-2.417	4.674	0.53	0.907	-2.639	4.453	0.61
Thoracic	-3.311	-7.540	0.919	0.12	-3.228	-7.490	1.034	0.13
Transplantation	5.501	-2.154	13.157	0.15	5.628	-3.204	14.460	0.20
Orthopedic surgery-trauma	1.015	-4.352	6.381	0.71	0.939	-4.431	6.310	0.73
Other	3.183	-1.648	8.015	0.19	2.623	-2.336	7.581	0.29
Medical								
Cardiac	2.776	-2.502	8.053	0.30	2.040	-3.474	7.553	0.46
Gastrointestinal-hepatic	13.837	-1.403	29.076	0.074	13.620	-1.592	28.832	0.079
Hematologic-oncologic	0.069	-8.634	8.773	0.98	-1.756	-11.000	7.488	0.70

Neurologic	-0.205	-4.378	3.967	0.92	-0.703	-4.941	3.536	0.74
Respiratory	-1.146	-5.067	2.776	0.56	-1.620	-5.670	2.430	0.43
Other	-1.400	-6.082	3.282	0.55	-1.681	-6.540	3.179	0.49
Infant (age<1y) vs. child at randomization	-0.047	-1.996	1.901	0.96	-0.008	-2.034	2.017	0.99
Malignancy vs. no malignancy	0.192	-3.858	4.243	0.92	0.267	-3.816	4.350	0.89
Diabetes vs. no diabetes	2.021	-20.625	24.666	0.86	3.172	-19.481	25.826	0.78
Syndrome vs. no syndrome[b]	4.615	1.484	7.746	0.0040	4.650	1.463	7.838	0.0044
PIM3 score (per point added)[c]	0.140	-0.764	1.044	0.76	0.057	-0.887	1.002	0.90
PeLOD score first 24 hrs (per point added)[d]	0.005	-0.111	0.121	0.93	-0.011	-0.128	0.106	0.85
Known non-European origin vs. other [e]	1.902	-2.060	5.864	0.34	1.933	-2.039	5.904	0.33
Known non-Caucasian vs. other[e]	-4.294	-9.338	0.750	0.094	-4.159	-9.193	0.874	0.10
Known not exclusive Dutch or English language vs. other	-0.479	-3.185	2.227	0.72	-0.525	-3.243	2.193	0.70
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.383	-8.510	1.743	0.19	-2.849	-8.040	2.342	0.28
Educational level 2	-2.252	-6.601	2.098	0.30	-1.850	-6.234	2.533	0.40
Educational level 2.5	-3.961	-8.586	0.663	0.092	-3.364	-8.009	1.280	0.15
Educational level 3	-3.754	-8.451	0.943	0.11	-3.251	-7.998	1.496	0.17
Educational level unknown	-2.156	-7.533	3.221	0.42	-1.668	-7.105	3.770	0.54
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	1.617	-6.176	9.410	0.68	1.218	-6.597	9.034	0.75
Occupational level 2	1.903	-5.876	9.682	0.63	1.382	-6.410	9.174	0.72
Occupational level 2.5	1.416	-6.695	9.528	0.73	0.718	-7.412	8.847	0.86
Occupational level 3	0.828	-7.068	8.724	0.83	0.237	-7.661	8.135	0.95

Occupational level 3.5	-2.904	-11.297	5.489	0.49	-3.499	-11.894	4.896	0.41
Occupational level 4	1.026	-7.130	9.183	0.80	0.218	-7.962	8.399	0.95
Occupational level unknown	1.409	-6.541	9.359	0.72	0.899	-7.064	8.861	0.82
Parental smoking between birth and PICU admission vs. no smoking	0.770	-1.592	3.131	0.51	0.858	-1.503	3.219	0.47
New infection vs. no new infection					0.261	-3.320	3.843	0.88
Duration of stay in the PICU (per day added)					-0.042	-0.328	0.244	0.77
Days with hypoglycemic event (per day added)					-0.262	-2.237	1.714	0.79
Duration of mechanical ventilatory support (per day added)					-0.090	-0.288	0.108	0.36
Duration of treatment with antibiotics (per day added)					0.070	-0.206	0.346	0.61
Duration of hemodynamic support (per day added)					-0.048	-0.249	0.153	0.63
Duration of treatment with corticosteroids (per day added)					0.053	-0.279	0.386	0.75
Duration of treatment with opioids (per day added)					-0.103	-0.389	0.183	0.48
Duration of treatment with benzodiazepines (per day added)					0.328	0.067	0.590	0.014
Duration of treatment with hypnotics (per day added)					0.032	-0.254	0.319	0.82
Duration of treatment with α2-agonists (per day added)					-0.235	-0.495	0.025	0.076

PeLOD, Paediatric Logistic Organ Dysfunction score; PICU, paediatric intensive care unit; PIM3, Paediatric Index of Mortality 3 score; PN, parenteral nutrition. For meta-cognition as reported by parents, higher scores reflect worse performance. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk. b A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods S2). c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality. d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness. e Paarticipants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S1). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-4. Multivariable linear regression analyses determining significant and independent associations between risk factors and overall executive functioning as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Randomization to late vs. early initiation of PN	***-2.258***	***-4.012***	***-0.504***	***0.011***	***-2.181***	***-3.953***	***-0.409***	***0.015***
Centre								
Leuven vs. Edmonton	3.856	-3.580	11.291	0.30	4.479	-3.043	12.001	0.24
Rotterdam vs. Edmonton	3.164	-4.370	10.699	0.40	2.874	-4.744	10.493	0.45
Male vs. female sex	0.990	-0.826	2.806	0.28	0.977	-0.841	2.796	0.29
Right vs. left hand preference	0.295	-2.397	2.986	0.82	0.404	-2.232	3.039	0.76
Medium vs. high STRONGkids risk level[a]	-0.324	-3.425	2.777	0.83	-0.053	-3.211	3.106	0.97
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.051	-5.824	1.722	0.28	-1.943	-5.732	1.847	0.31
Burns	1.883	-14.275	18.041	0.81	0.303	-16.376	16.983	0.97
Neurosurgery - traumatic brain injury	2.165	-1.441	5.770	0.23	1.896	-1.712	5.505	0.30
Thoracic	-1.916	-6.216	2.383	0.38	-1.812	-6.154	2.529	0.41
Transplantation	6.550	-0.796	13.896	0.080	6.490	-1.812	14.793	0.12
Orthopedic surgery-trauma	0.235	-5.239	5.710	0.93	0.026	-5.466	5.517	0.99
Other	4.937	0.015	9.858	0.049	4.123	-0.923	9.168	0.10
Medical								
Cardiac	2.858	-2.373	8.089	0.28	1.891	-3.581	7.362	0.49
Gastrointestinal-hepatic	13.977	-1.084	29.038	0.068	13.632	-1.377	28.640	0.074
Hematologic-oncologic	1.544	-7.245	10.333	0.73	-0.418	-9.711	8.875	0.92

Neurologic	-0.445	-4.596	3.706	0.83	-1.077	-5.314	3.160	0.61
Respiratory	-0.999	-4.628	2.631	0.58	-1.492	-5.206	2.223	0.42
Other	-0.949	-5.599	3.701	0.68	-1.363	-6.189	3.464	0.57
Infant (age<1y) vs. child at randomization	0.317	-1.608	2.242	0.74	0.386	-1.634	2.406	0.70
Malignancy vs. no malignancy	-0.038	-4.162	4.085	0.98	-0.131	-4.290	4.028	0.95
Diabetes vs. no diabetes	2.475	-20.377	25.328	0.83	4.192	-18.640	27.025	0.71
Syndrome vs. no syndrome[b]	5.082	2.013	8.152	0.0012	5.296	2.202	8.390	0.00086
PIM3 score (per point added)[c]	0.194	-0.695	1.082	0.66	0.121	-0.805	1.048	0.79
PeLOD score first 24 hrs (per point added)[d]	0.026	-0.089	0.140	0.66	0.009	-0.107	0.125	0.88
Known non-European origin vs. other[e]	1.782	-2.000	5.563	0.35	1.779	-2.001	5.559	0.35
Known non-Caucasian vs. other[e]	-4.530	-9.283	0.222	0.061	-4.265	-9.022	0.492	0.078
Known not exclusive Dutch or English language vs. other	0.066	-2.585	2.718	0.96	-0.003	-2.665	2.659	0.99
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.958	-9.112	1.196	0.13	-3.283	-8.492	1.927	0.21
Educational level 2	-2.614	-7.009	1.782	0.24	-2.119	-6.552	2.314	0.34
Educational level 2.5	-4.118	-8.777	0.541	0.083	-3.422	-8.103	1.259	0.15
Educational level 3	-4.625	-9.360	0.111	0.055	-4.032	-8.806	0.742	0.097
Educational level unknown	-0.202	-5.678	5.273	0.94	0.386	-5.139	5.910	0.89
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	2.929	-4.880	10.738	0.46	2.240	-5.573	10.053	0.57
Occupational level 2	3.469	-4.305	11.244	0.38	2.652	-5.129	10.433	0.50
Occupational level 2.5	3.334	-4.693	11.361	0.41	2.298	-5.752	10.348	0.57
Occupational level 3	2.959	-4.955	10.873	0.46	2.159	-5.758	10.077	0.59

Occupational level 3.5	-0.484	-8.917	7.948	0.91	-1.317	-9.760	7.125	0.75
Occupational level 4	3.326	-4.857	11.508	0.42	2.245	-5.979	10.468	0.59
Occupational level unknown	2.792	-5.114	10.698	0.48	2.085	-5.836	10.006	0.60
Parental smoking between birth and PICU admission vs. no smoking	1.022	-1.242	3.285	0.37	1.144	-1.108	3.396	0.31
New infection vs. no new infection					-0.356	-3.782	3.070	0.83
Duration of stay in the PICU (per day added)					0.045	-0.236	0.326	0.75
Days with hypoglycemic event (per day added)					-0.670	-2.632	1.293	0.50
Duration of mechanical ventilatory support (per day added)					-0.123	-0.323	0.076	0.22
Duration of treatment with antibiotics (per day added)					-0.017	-0.282	0.247	0.89
Duration of hemodynamic support (per day added)					-0.071	-0.272	0.130	0.48
Duration of treatment with corticosteroids (per day added)					0.073	-0.251	0.396	0.65
Duration of treatment with opioids (per day added)					-0.102	-0.381	0.177	0.47
Duration of treatment with benzodiazepines (per day added)					0.368	0.111	0.625	0.0050
Duration of treatment with hypnotics (per day added)					0.078	-0.206	0.363	0.58
Duration of treatment with α2-agonists (per day added)					-0.260	-0.516	-0.003	0.047

PeLOD, Paediatric Logistic Organ Dysfunction score; PICU, paediatric intensive care unit; PIM3, Paediatric Index of Mortality 3 score; PN, parenteral nutrition. For overall executive functioning as reported by parents, higher scores reflect worse performance. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 in-dicating medium risk, and a score of 4 to 5 indicating high risk. b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods S2). c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality. d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness. e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S1). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-5. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalising problems as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Randomization to late vs. early initiation of PN	***-1.715***	***-3.325***	***-0.106***	***0.036***	***-1.810***	***-3.441***	***-0.179***	***0.029***
Centre								
Leuven vs. Edmonton	4.664	-1.959	11.287	0.16	4.377	-2.421	11.175	0.20
Rotterdam vs. Edmonton	3.024	-3.740	9.787	0.37	2.464	-4.455	9.383	0.48
Male vs. female sex	1.483	-0.241	3.207	0.091	1.427	-0.303	3.157	0.10
Right vs. left hand preference	0.103	-2.410	2.616	0.93	0.159	-2.327	2.645	0.89
Medium vs. high STRONGkids risk level[a]	-0.069	-2.880	2.742	0.96	0.170	-2.702	3.042	0.90
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	0.597	-2.874	4.068	0.73	0.672	-2.793	4.138	0.70
Burns	8.641	-6.396	23.679	0.25	8.965	-6.524	24.454	0.25
Neurosurgery - traumatic brain injury	3.809	0.528	7.089	0.022	3.699	0.412	6.985	0.027
Thoracic	-1.001	-5.006	3.004	0.62	-0.765	-4.811	3.280	0.70
Transplantation	7.503	0.677	14.328	0.031	8.683	0.985	16.381	0.027
Orthopedic surgery-trauma	-0.017	-5.137	5.102	0.99	-0.105	-5.263	5.053	0.96
Other	2.924	-1.639	7.487	0.20	2.192	-2.432	6.815	0.35
Medical								
Cardiac	2.955	-2.044	7.954	0.24	2.199	-3.080	7.479	0.41
Gastrointestinal-hepatic	10.723	-4.646	26.091	0.17	10.571	-4.771	25.913	0.17

Hematologic-oncologic	7.972	-0.416	16.361	0.062	7.727	-1.147	16.600	0.087
Neurologic	2.384	-1.535	6.303	0.23	2.119	-1.908	6.146	0.30
Respiratory	1.392	-1.909	4.693	0.40	1.040	-2.386	4.467	0.55
Other	-0.018	-4.367	4.330	0.99	-0.257	-4.787	4.273	0.91
Malignancy vs. no malignancy	-3.056	-7.042	0.931	0.13	-3.143	-7.173	0.887	0.12
Diabetes vs. no diabetes	15.073	-6.806	36.951	0.17	15.892	-5.983	37.767	0.15
Syndrome vs. no syndrome[b]	1.066	-1.763	3.895	0.45	1.180	-1.693	4.052	0.41
PIM3 score (per point added)[c]	0.067	-0.752	0.886	0.87	-0.051	-0.904	0.801	0.90
PeLOD score first 24 hrs (per point added)[d]	0.054	-0.052	0.161	0.31	0.041	-0.067	0.150	0.45
Known non-European origin vs. other[e]	-0.480	-4.171	3.210	0.79	-0.425	-4.123	3.272	0.82
Known non-Caucasian vs. other[e]	-2.054	-6.511	2.404	0.36	-1.933	-6.383	2.517	0.39
Known not exclusive Dutch or English language vs. other	2.015	-0.467	4.496	0.11	1.989	-0.496	4.474	0.11
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-1.008	-5.866	3.851	0.68	-0.433	-5.377	4.510	0.86
Educational level 2	0.382	-3.730	4.494	0.85	0.763	-3.413	4.939	0.71
Educational level 2.5	-1.791	-6.206	2.624	0.42	-1.300	-5.762	3.163	0.56
Educational level 3	-2.165	-6.604	2.274	0.33	-1.684	-6.184	2.815	0.46
Educational level unknown	1.718	-2.986	6.422	0.47	2.140	-2.621	6.900	0.37
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.469	-7.078	8.015	0.90	0.079	-7.465	7.624	0.98
Occupational level 2	2.858	-4.657	10.373	0.45	2.361	-5.147	9.869	0.53
Occupational level 2.5	1.806	-5.933	9.546	0.64	1.312	-6.437	9.060	0.73
Occupational level 3	1.638	-6.002	9.277	0.67	1.398	-6.242	9.039	0.71

Occupational level 3.5	-0.323	-8.366	7.719	0.93	-0.465	-8.512	7.583	0.90
Occupational level 4	0.810	-7.026	8.647	0.83	0.287	-7.581	8.154	0.94
Occupational level unknown	0.795	-6.737	8.326	0.83	0.450	-7.064	7.963	0.90
Parental smoking between birth and PICU admission vs. no smoking	2.017	-0.063	4.096	0.057	2.142	0.071	4.214	0.042
New infection vs. no new infection					-0.771	-3.886	2.344	0.62
Duration of stay in the PICU (per day added)					0.112	-0.157	0.381	0.41
Days with hypoglycemic event (per day added)					1.425	-0.477	3.328	0.14
Duration of mechanical ventilatory support (per day added)					-0.113	-0.295	0.070	0.22
Duration of treatment with antibiotics (per day added)					-0.062	-0.314	0.189	0.62
Duration of hemodynamic support (per day added)					-0.101	-0.286	0.084	0.28
Duration of treatment with corticosteroids (per day added)					-0.055	-0.363	0.253	0.72
Duration of treatment with opioids (per day added)					-0.111	-0.371	0.150	0.40
Duration of treatment with benzodiazepines (per day added)					0.304	0.064	0.544	0.013
Duration of treatment with hypnotics (per day added)					0.042	-0.226	0.310	0.76
Duration of treatment with α2-agonists (per day added)					-0.200	-0.446	0.046	0.11

PeLOD, Paediatric Logistic Organ Dysfunction score; PICU, paediatric intensive care unit; PIM3, Paediatric Index of Mortality 3 score; PN, parenteral nutrition. For externalising problems as reported by parents, higher scores reflect worse performance. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk. b A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods S2). c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality. d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness. e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S1). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-6. Multivariable linear regression analyses determining significant and independent associations between risk factors and visual-motor integration at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Randomization to late vs. early initiation of PN	***0.468***	***0.087***	***0.850***	***0.016***	***0.422***	***0.037***	***0.807***	***0.031***
Centre								
Leuven vs. Edmonton	5.647	3.729	7.566	<0.0001	5.449	3.506	7.391	<0.0001
Rotterdam vs. Edmonton	4.879	3.032	6.727	<0.0001	4.834	2.961	6.708	<0.0001
Male vs. female sex	-0.789	-1.178	-0.400	<0.0001	-0.794	-1.185	-0.403	<0.0001
Right vs. left hand preference	0.544	-0.091	1.179	0.092	0.542	-0.101	1.185	0.098
Medium vs. high STRONGkids risk level[a]	0.339	-0.334	1.013	0.32	0.270	-0.417	0.958	0.44
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	0.449	-0.358	1.255	0.27	0.372	-0.436	1.180	0.36
Burns	0.585	-3.065	4.235	0.75	1.054	-2.699	4.807	0.58
Neurosurgery - traumatic brain injury	-0.037	-0.786	0.713	0.92	0.031	-0.717	0.778	0.93
Thoracic	0.630	-0.273	1.533	0.17	0.528	-0.380	1.436	0.25
Transplantation	-1.738	-3.224	-0.253	0.021	-1.099	-2.725	0.527	0.18
Orthopedic surgery-trauma	-2.207	-3.346	-1.069	0.00015	-2.236	-3.378	-1.094	0.00013
Other	0.245	-0.849	1.340	0.65	0.289	-0.817	1.395	0.60
Medical								
Cardiac	0.128	-1.022	1.277	0.82	0.333	-0.894	1.560	0.59
Gastrointestinal-hepatic	0.245	-2.770	3.260	0.87	0.239	-2.761	3.239	0.87

Hematologic-oncologic	1.275	-0.776	3.326	0.22	1.891	-0.263	4.045	0.085
Neurologic	-0.472	-1.371	0.427	0.30	-0.268	-1.189	0.652	0.56
Respiratory	0.506	-0.233	1.246	0.17	0.445	-0.315	1.206	0.25
Other	-0.180	-1.188	0.827	0.72	-0.279	-1.324	0.767	0.60
Infant (age<1y) vs. child at randomization	1.228	0.799	1.657	<0.0001	1.179	0.736	1.622	<0.0001
Malignancy vs. no malignancy	0.014	-0.945	0.972	0.97	0.196	-0.771	1.163	0.69
Diabetes vs. no diabetes	0.511	-4.802	5.823	0.85	-0.090	-5.383	5.204	0.97
Syndrome vs. no syndrome[b]	-1.336	-1.985	-0.687	<0.0001	-1.474	-2.125	-0.823	<0.0001
PIM3 score (per point added)[c]	0.017	-0.169	0.203	0.85	0.028	-0.163	0.219	0.77
PeLOD score first 24 hrs (per point added)[d]	-0.015	-0.039	0.010	0.23	-0.012	-0.037	0.013	0.34
Known non-European origin vs. other[e]	-0.144	-0.901	0.613	0.70	-0.133	-0.888	0.622	0.72
Known non-Caucasian vs. other[e]	-0.278	-1.197	0.642	0.55	-0.333	-1.250	0.585	0.47
Known not exclusive Dutch or English language vs. other	0.350	-0.231	0.932	0.23	0.381	-0.201	0.962	0.19
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	0.121	-1.036	1.279	0.83	0.029	-1.143	1.201	0.96
Educational level 2	0.500	-0.469	1.469	0.31	0.413	-0.565	1.391	0.40
Educational level 2.5	0.419	-0.614	1.451	0.42	0.319	-0.717	1.355	0.54
Educational level 3	0.988	-0.062	2.037	0.062	0.883	-0.173	1.939	0.10
Educational level unknown	0.235	-0.769	1.238	0.64	0.080	-0.931	1.091	0.87
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.643	-1.186	2.472	0.49	0.807	-1.015	2.630	0.38
Occupational level 2	0.687	-1.140	2.515	0.46	0.808	-1.016	2.631	0.38
Occupational level 2.5	0.899	-0.990	2.789	0.35	1.075	-0.812	2.961	0.26

Occupational level 3	1.079	-0.766	2.924	0.25	1.228	-0.610	3.065	0.19
Occupational level 3.5	0.669	-1.295	2.634	0.50	0.766	-1.193	2.725	0.44
Occupational level 4	0.392	-1.520	2.304	0.68	0.625	-1.286	2.536	0.52
Parental smoking between birth and PICU admission vs. no smoking	-0.247	-0.729	0.235	0.31	-0.293	-0.765	0.180	0.22
New infection vs. no new infection					0.043	-0.672	0.759	0.90
Duration of stay in the PICU (per day added)					-0.026	-0.089	0.037	0.41
Days with hypoglycemic event (per day added)					0.256	-0.175	0.687	0.24
Duration of mechanical ventilatory support (per day added)					0.026	-0.015	0.068	0.21
Duration of treatment with antibiotics (per day added)					0.027	-0.033	0.086	0.37
Duration of hemodynamic support (per day added)					-0.025	-0.068	0.019	0.26
Duration of treatment with corticosteroids (per day added)					-0.078	-0.148	-0.007	0.030
Duration of treatment with opioids (per day added)					0.022	-0.039	0.084	0.47
Duration of treatment with benzodiazepines (per day added)					-0.035	-0.093	0.022	0.22
Duration of treatment with hypnotics (per day added)					-0.053	-0.118	0.011	0.10
Duration of treatment with α2-agonists (per day added)					0.078	0.021	0.134	0.0074

PeLOD, Paediatric Logistic Organ Dysfunction score; PICU, paediatric intensive care unit; PIM3, Paediatric Index of Mortality 3 score; PN, parenteral nutrition. For visual-motor integration, higher scores reflect better performance. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk. b A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods S2). c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality. d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness. e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S1). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S2. Comparison of patients randomised to late parenteral nutrition during PICU stay with healthy control children for the tests significantly affected by the randomised intervention

Neurocognitive function	**P-value**
Visual-motor integration	0.00052
Externalising problems as reported by parents/caregivers	0.34
Inhibition as reported by parents/caregivers	0.66
Working memory as reported by parents/caregivers	0.032
Meta-cognition index as reported by parents/caregivers	0.34
Overall executive functioning as reported by parents/caregivers	0.12

Table S3. Impact of late versus early parenteral nutrition in infants for tests showing a significant interaction P-value with age group

Variable	**Beta-estimate**	**Confidence interval**		**P-value**
Overall executive functioning	-3.843	-6.361	-1.325	0.0029
Meta-cognition	-3.749	-6.244	-1.254	0.0034
Working memory	-3.594	-6.052	-1.135	0.0043

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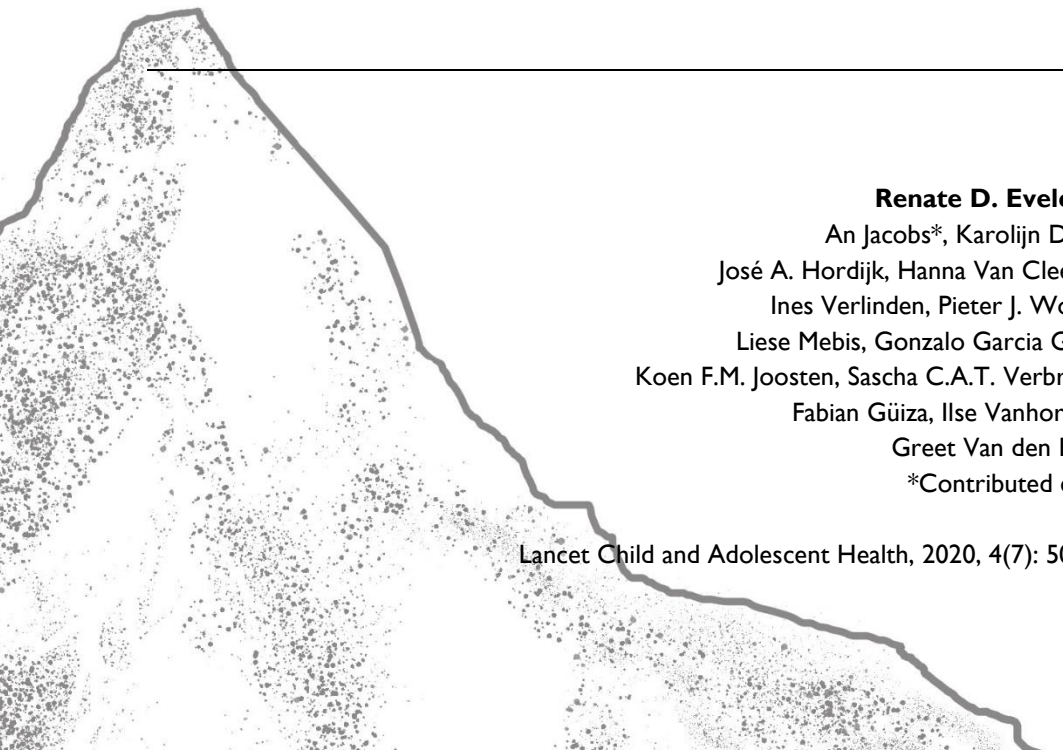
CHAPTER 12

LONG–TERM DEVELOPMENTAL EFFECTS OF WITHOLDING PARENTERAL NUTRITION IN PEDIATRIC INTENSIVE CARE UNITS: A 4–YEAR FOLLOW–UP OF THE PEPANIC RANDOMISED CONTROLLED TRIAL



Renate D. Eveleens*,
An Jacobs*, Karolijn Dulfer*,
José A. Hordijk, Hanna Van Cleemput,
Ines Verlinden, Pieter J. Wouters,
Liese Mebis, Gonzalo Garcia Guerra,
Koen F.M. Joosten, Sascha C.A.T. Verbruggen,
Fabian Güiza, Ilse Vanhorebeek,
Greet Van den Berghe
*Contributed equally

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ABSTRACT

Background: PEPaNIC randomised controlled trial, which recruited 1440 critically ill infants and children in 2012–15, showed that withholding parenteral nutrition for 1 week (late-parenteral nutrition), compared with early supplementation within 24 h of admission to the paediatric intensive care unit (early-parenteral nutrition), prevented infections, accelerated recovery, and improved neurocognitive development assessed 2 years later. Because several neurocognitive domains can only be thoroughly assessed from age 4 years onwards, we aimed to determine the effect of late-parenteral nutrition versus early-parenteral nutrition on physical, neurocognitive, and emotional and behavioural development 4 years after randomization.

Methods: This is a preplanned, blinded, 4-year follow-up study of participants included in the PEPaNIC trial (done at University Hospitals Leuven, Belgium; Erasmus Medical Centre Sophia Children's Hospital, Rotterdam, Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada) and of matched healthy children. Studied outcomes were anthropometrics; health status; parent-reported or caregiver-reported executive functions, and emotional and behavioural problems; and clinical tests for intelligence, visual-motor integration, alertness, motor coordination, and memory. Through multivariable linear and logistic regression analyses, after imputation for missing values (≤30%) and adjustment for risk factors, we investigated the effect of early-parenteral nutrition versus late-parenteral nutrition.

Findings: Between March 8, 2016, and Nov 8, 2019, 684 children from the original PEPaNIC trial (356 from the late parenteral nutrition group and 328 from the early-parenteral nutrition group) were assessed for neurocognitive development at 4-years follow-up. Compared with the control group (369 healthy children), children who had critical illness had lower height (β-estimate –2.11 [95% CI –3.15 to –1.06]; p<0.0001) and head circumference (–0.42 [–0.67 to –0.18]; p=0.00077); and worse health status (e.g., hospital admission odds ratio 4.27 [95% CI 3.12 to 5.84]; p<0.0001), neurocognitive (e.g., parent-reported or caregiver-reported total executive functioning β-estimate 3.57 [95% CI 1.95 to 5.18], p<0.0001; total intelligence quotient –7.35 [–9.31 to –5.39], p<0.0001), and parent-reported or caregiver-reported emotional and behavioural developmental outcomes (internalising 2.73 [1.19 to 4.28], p=0.00055; externalising 1.63 [0.19 to 3.08], p=0.027; and total behavioural problems 2.95 [1.44 to 4.46], p=0.00013), adjusted for risk factors. Outcomes were never worse in the late-parenteral nutrition group compared with the early-parenteral nutrition group, but patients in the late-parenteral nutrition group had fewer parent-reported or caregiver-reported internalising (β-estimate –1.88 [95% CI –3.69 to –0.07]; p=0.042), externalising (–1.73 [–3.43 to –0.03]; p=0.046), and total emotional and behavioural problems (–2.44 [–4.22 to –0.67]; p=0.0070) than patients who had received

early-parenteral nutrition, after adjusting for risk factors, and were no longer different from healthy controls for these outcomes.

Interpretation: Omitting early parenteral nutrition use for critically ill children did not adversely affect long-term outcomes 4 years after randomization and protected against emotional and behavioural problems, further supporting the de-implementation of early parenteral nutrition.

INTRODUCTION

Critical illness in children is associated with impaired physical, neurocognitive, emotional, and behavioural development, which often persists for years after discharge from the paediatric intensive care unit and hospital.[1,2] Over the past decade, avoidable intensive care-related factors contributing to some long-term effects have been identified; these include hyperglycemia, phthalates leaching into the blood from indwelling medical devices, and the use of early-parenteral nutrition.[3–5] The multicentre randomised controlled PEPaNIC trial[6] showed that postponing parenteral nutrition for 1 week in the paediatric intensive care unit (late-parenteral nutrition) has benefits over initiating parenteral nutrition within 24 h after admission to supplement insufficient enteral nutrition (early-parenteral nutrition), such as improved intensive care outcomes, as well as better executive functioning and visual-motor integration and reduced externalising behavioural problems at 2 years after admission to the intensive care unit.[5] The improvements in neurocognitive development in the late-parenteral nutrition group were found to be mediated by the differential DNA methylation status, in particular of 37 CpG sites related to genes involved in brain development.[7]

A methodological limitation of the 2-year follow-up study of the PEPaNIC trial[5] was the large proportion of patients who were younger than 4 years old when tested neurocognitively. Because of rapid brain development during the first years of life, assessment of most neurocognitive domains is only possible when the child is 4 years of age or older.[8,9] As the child develops, impairments in physical or neurocognitive domains that were observed at 2 years follow-up could persist or disappear and other problems might emerge. Taken together, assessments at a later time point after critical illness are of value. We therefore did a 4-year follow-up study of the children included in the PEPaNIC trial to assess their health status, neurocognitive development, and emotional and behavioural outcomes. We aimed to compare these outcomes with data from matched children who had not had a critical illness, and to investigate the longer term effects of late-parenteral nutrition compared with early-parenteral nutrition.

METHODS

Study design and participants

In the PEPaNIC trial,[6] 1440 critically ill infants and children admitted to the participating paediatric intensive care units at University Hospitals Leuven, Leuven, Belgium; Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam, Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada were enrolled from 2012 to 2015. The study protocol has been published.10 This study represents the preplanned 4-year follow-up of the original PEPaNIC trial.[6]

As described previously,[5] during admission to a paediatric intensive care unit, parents or legal guardians of the patients provided consent to contact them for long-term follow-up testing. First, survival status was assessed by reviewing hospital notes, obtained through the national register or through contact with the general practitioner or referring paediatrician. After receiving a standardised information letter, survivors and parents or caregivers were contacted by telephone to obtain consent for scheduling an appointment for the medical and neurocognitive assessment, either at the hospital or at the patient's home. For patients who could not be reached by telephone, survival status was reassessed at the end of the study.

For comparison, 369 healthy children, demographically matched to the patients for age and sex, were recruited to a control group and underwent identical medical and neurocognitive assessment. Alongside unrelated children, healthy siblings and relatives of the patients were included to control as much as possible for genetic, socioeconomic, and environmental background. Healthy children were only included if they had not been previously admitted to a neonatal or paediatric intensive care unit, or admitted to hospital with need for an intravenous line for 7 days or more. History of inborn chronic metabolic diseases requiring a specific diet, such as diabetes, and conditions that require home parenteral nutrition, such as short bowel syndrome, were additional exclusion criteria.

Parents, legal guardians, or patients (if they were ≥18 years old), gave written informed consent according to local regulations. The institutional review boards at each participating site approved this follow-up study (ML8052; NL49708.078; Pro00038098).

Procedures, randomization, and masking

After obtaining informed consent, children in the PEPaNIC trial6 were randomly assigned (1:1) to receive early parenteral nutrition, with parenteral nutrition initiated within 24 h of admission to the intensive care unit to supplement enteral nutrition whenever 80% of targeted calories per age and weight categories had not been reached, or late-parenteral nutrition, which meant that all parenteral nutrition was withheld for up to 1 week in the intensive care unit. For the late-parenteral nutrition group, this corresponded to no parenteral nutrition in most children. When enteral nutrition covered more than 80% of calculated targets, supplemental parenteral nutrition was discontinued. Total macronutrient doses administered on each of the first 7 days of admission are shown in the appendix. After 1 week in the paediatric intensive care unit, parenteral nutrition could be administered when necessary in both groups. Enteral nutrition was initiated early in both groups equally, and all patients received intravenous micronutrients until fully enterally fed.

Outcome assessors of the 4-year follow-up study were physicians and experienced paediatric psychologists who had not been involved in the management of the patients during their stay in the paediatric intensive care unit and who were strictly masked to

treatment allocation. Parents and caregivers were not masked while the child was treated in the paediatric intensive care unit and they were not actively informed about the initial PEPaNIC study results or the 2-year outcome results (which only became available near the end of the inclusions in the 4-year follow-up study).[6]

Outcomes

As done in the 2-year follow-up study,[5] at 4-year follow-up, head circumference, body weight, and height were measured. A clinical neurological examination was done to assess gross neurological abnormalities. We used structured interviews with the parents or caregivers to assess whether the children had been diagnosed with a somatic or psychiatric illness, and whether they had been admitted to a hospital for medical or surgical reasons during the past 4 years (for the control group) and during the 4 years following admission to the paediatric intensive care unit (for the PEPaNIC participants). Neurocognitive testability was determined by screening the medical file or on clinical judgement before the start of the neurocognitive assessment by the physician or psychologist and confirmed by the parents or caregivers.

To score performance for a broad range of neurocognitive functions, validated internationally recognised questionnaires and clinical tests with adequate normative data were used. Parent-reported questionnaires included the Behaviour Rating Inventory of Executive Function[11,12] (executive functioning, T scores, with mean 50 and SD 10) and the Child Behaviour Checklist[13,14] (emotional and behavioural problems, T scores, with mean 50 and SD 10). On both questionnaires, higher scores indicate more problems. Clinical tests consisted of the age-appropriate versions of the Wechsler Intelligence Quotient Scale[15-17] (intelligence, standard scores, with mean 100 and SD 15), the Beery Developmental Test of Visual-Motor Integration[18] (visuomotor integration, scaled score, with mean 10 and SD 3), tasks of the Amsterdam Neuropsychological Task Battery[9] (for children aged 4 years or older), and the Children's Memory Scale[8] (for children aged 5–16 years). Tasks of the Amsterdam Neuropsychological Task Battery consisted of Amsterdam Neuropsychological Task Battery-Baseline Speed (alertness and reaction time) and Amsterdam Neuropsychological Task Battery-Tapping (motor coordination as number of taps). Tasks of the Children's Memory Scale were Children's Memory Scale-Numbers (verbal short-term memory and working memory, scaled scores with mean 10 and SD 3), Children's Memory Scale-Word Pairs (short-term and long-term verbal memory, and recognition, proportion of correct responses ranging from 0 to 1), Children's Memory Scale-Picture Locations (short-term visual memory as the proportion of correct responses), and Children's Memory Scale-Dot Locations (short-term and long-term visual memory proportion of correct responses). The Children's Memory Scale-Learning index represents learning abilities of the child (standard score, with mean 100 and SD 15). For the clinical tests, a higher score indicates better functioning, with the exception of Amsterdam Neuropsychological Task

Battery-Baseline Speed. An extended description of the questionnaires and of the clinical and neuropsychological test battery is reported in the appendix.

Statistical analysis

For patients in the PEPaNIC trial who were alive and testable 4 years later, we estimated a loss to follow-up of about 30%, on the basis of previous studies.[3,5] With this sample size, we calculated that we would have more than 80% statistical power to detect, with a certainty of more than 95%, a minimal clinically relevant four point difference in intelligence quotient (IQ) and clinically relevant differences of a median 5.8% (IQR 3.8–8.0) or mean of 7.6% (SD 7.9) in the other outcomes between patients in the early-parenteral nutrition and late parenteral nutrition groups, based on previous data.[3,5] For the healthy control group, a sample size of 369 allows detection, with a power of more than 80% and certainty of more than 95%, of a difference in IQ of four points with the patients and median differences between patients and the control group of 5.2% (IQR 3.5–7.3) and a mean difference of 7.9% (11.2) in the other outcomes that were studied previously.[3,5]

Inability to fully complete the neurocognitive test battery could indicate poor neurocognitive function and thus introduce bias. Similarly to the 2-year follow-up study,5 missing values were imputed by chained equations, with use of all available data for each individual (Appendix).[19] Imputation of data for age specific tests was only done within the respective age group. Bias and instability of the imputation model was minimised by only including outcomes with no more than 30% missing data.[19] The number of imputation models was set at 31 to avoid the loss of statistical power (Appendix).[19]

Univariable comparison of the pooled data from the imputed models was done with the Fisher exact test, Student *t* test, or Wilcoxon rank-sum test as appropriate. Multivariable linear and logistic regression analyses were done on the 31 imputed datasets with the pooled β-estimates or odds ratios reported to investigate the differences in outcomes between patients and healthy control children, and to analyse the differences between the two groups in PEPaNIC.[5] All multivariable analyses adjusted for covariates, as pre-specified in the statistical analysis plan, and the analyses were done as reported in the 2-year follow-up study.5,10 For the comparison of patients who were critically ill with children in the control group, the analyses adjusted for the baseline risk factors, age, treatment centre, sex, race, geographic origin, language, hand preference, history of malignancy, a predefined syndrome (Appendix), and the educational and occupational status of the parents and caregivers (Appendix). Additional adjustment for admission diagnosis, severity of illness upon paediatric intensive care unit-admission (paediatric index of mortality 3 and paediatric logistic organ dysfunction scores), risk of malnutrition (Screening Tool for Risk On Nutritional Status and Growth), and parental smoking behaviour before admission to the paediatric intensive care unit was done for the comparison of the late-parenteral nutrition group with the early-parenteral nutrition group. Acute effects of the random allocation on acquisition of new

infections and on the duration of hypoglycemia, ventilatory support, and stay in the paediatric intensive care unit could potentially mediate any long-term effect and thus further adjustment for these factors was done in the multivariable models. In addition, further adjustment was done for other post-randomization treatments that could theoretically play a role (duration of hemodynamic support, treatment with antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics, and α2-agonists). Statistical analyses were done with use of R (version 3.5.3), MICE (versions 3.4.0 and 3.6.0), and JMP (version 14.0.0). Two-sided p values of 0.05 or less were considered statistically significant. As the studied developmental outcomes are not independent (Appendix), correction for multiple comparisons was not done.[7,20]

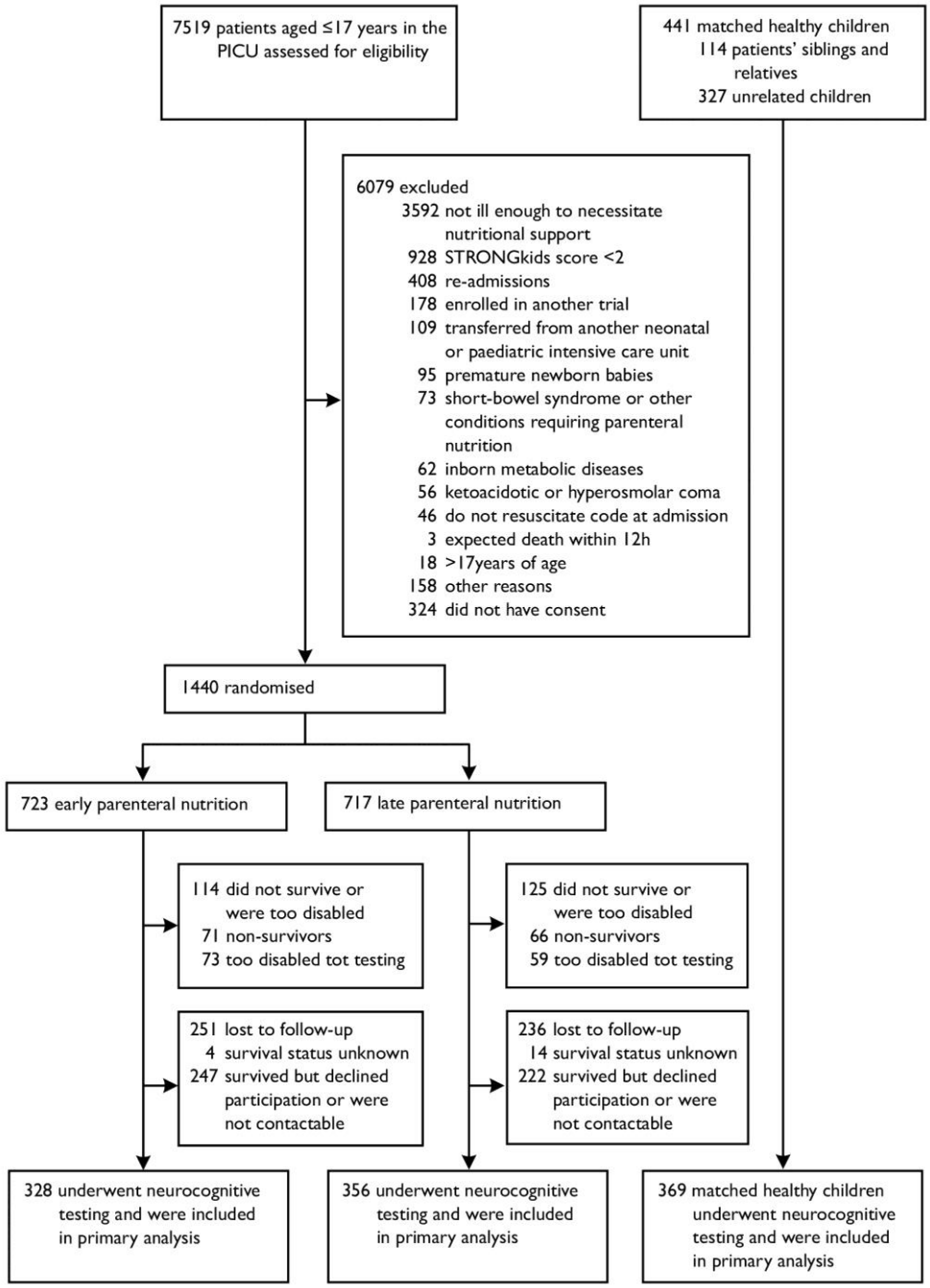
RESULTS

Of the children included in the original PEPaNIC trial, done between June 18, 2012, and July 27, 2015, 71 (10%) of 723 patients in the early-parenteral nutrition group and 66 (9%) of 717 patients in the late-parenteral nutrition group did not survive to 4 years follow-up (p=0.69; Figure 1). For 18 patients survival status was unknown. A total of 247 patients in the early-parenteral nutrition group and 222 patients in the late-parenteral nutrition group survived but declined participation or were not contactable (p=0.47). Hence, loss to follow-up was 34% (487 of 1440). At follow-up, 73 (10%) patients in the early-parenteral nutrition group and 59 (8%) patients in the late parenteral nutrition group were too disabled for neurocognitive testing (p=0.21) and were excluded from the analyses. For transparency, any available clinical data or questionnaire results for these patients are provided in the appendix, (pp 15–17). 684 (48%) children from the original study and 369 healthy controls underwent neurocognitive testing between March 8, 2016, and November 8, 2019, and were included in the imputation models for subsequent multivariable analyses. Neurocognitive testing was done at the hospital for 442 (65%) children who had been critically ill and 301 (82%) children in the control group (p<0.0001), with no differences in the place of assessment between patients in the late-parenteral nutrition and the early-parenteral nutrition groups (p=0.99). Demographics and medical characteristics of children who had been critically ill and children in the control group are shown in Table 1. Overall, random assignment and primary and secondary intensive care outcomes of patients who were tested at 4-year follow-up were similar to the initial PEPaNIC study population.

In univariable and multivariable comparison, at 4-years follow-up children who had been critically ill had worse outcomes for height, weight, head circumference, health status, clinically assessed neurological functioning, parent-reported or caregiver-reported executive functioning and emotional and behavioural problems and clinical tests for intelligence, visual-motor integration, alertness, motor-coordination, and memory than children in the control group (Table 2).

Figure 1. Study profile

PICU, paediatric intensive care unit. STRONGkids, Screening Tool Risk On Nutritional Status and Growth



Compared with patients who had been allocated to early parenteral nutrition, patients in the late-parenteral nutrition group had similar height, weight, body-mass index, and head circumference, and clinically assessed neurological functioning in univariable and multivariable analysis (Table 2). In univariable analyses, fewer patients in the late parenteral nutrition group were admitted to hospital and parents or caregivers of these children reported fewer internalising, externalising, and total emotional and behavioural problems and fewer problems regarding flexibility compared with patients who received early parenteral nutrition (Table 2; Figure 2). After adjustment for risk factors, the finding of fewer internalising, externalising, and total emotional and behavioural problems in the late parenteral nutrition group than in the early-parenteral nutrition group remained (Table 2; Appendix). For internalising and externalising problems as well as total emotional and behavioural problems, children in the late parenteral nutrition group were not different from children in the control group (Appendix).

Differences in intensive care outcomes of the randomised intervention and other post-randomization factors overall did not explain the observed differences at 4-years follow-up (Appendix). Of note, treatment with benzodiazepines was independently associated with worse outcome, whereas α2-agonist treatment was associated with better outcome.

DISCUSSION

4 years after critical illness, children were found to still have a disease legacy characterised by broad abnormalities in all investigated developmental domains, including growth, health status, and neurocognitive, and emotional and behavioural functioning, a finding that confirmed previously reported observations.[3] Our results show that omission of supplemental parenteral nutrition in the first week of the child's time in the intensive care unit did not harm physical and neurocognitive development and that these patients had fewer emotional and behavioural problems compared with children who received early-parenteral nutrition.

At 4-year follow-up, the legacy of critical illness affected all developmental domains. The extent to which these abnormalities are acquired during intensive care remains debated.22 However, the developmental legacy documented 4 years after critical illness was found to remain present after adjustment for all known baseline risk factors at intensive care unit admission. The documented developmental abnormalities are relevant because they are known to have direct implications for daily life and hamper future societal perspectives.[2,23,24] Moreover, the developmental impairment after paediatric critical illness is at least as pronounced as what has been reported for children who survived cancer[25–27] and for children with chronic diseases such as type 1 diabetes and chronic kidney disease.[28,29]

Of note, the emotional and behavioural problems—such as internalising, externalising, and other issues—were preventable by omitting the use of early-parenteral nutrition in the paediatric intensive care unit. Internalising problems are evidenced by anxious and depressive symptoms, and by social withdrawal,[13,14] which are the consequences of over-controlling behaviour. Externalising problems are externally directed problems that affect the environment and become apparent in aggressive and delinquent behaviour, which result in conflicts with others. The total score for the emotional and behavioural problems includes internalising and externalising behavioural problems, sleep problems for younger children, and social, thinking, and attention problems for older children. Such issues are thought to be in part a consequence of poor development of executive functions, such as poor inhibitory control.[30,31] This might explain why, at 2-year follow-up, we found that not being exposed to early-parenteral nutrition predominantly reduced abnormal inhibitory control;[5] whereas, 2 years later, the effect on the emotional and behavioural problems became more apparent.

The developing brain of children thus appears vulnerable to metabolic insults during periods of critical illness. We previously showed that tight glycemic control during intensive care prevented impaired motor coordination 4 years after admission,[3] an impairment that was less apparent in patients of the PEPaNIC trial, who had received at least some form of blood glucose control. In addition to avoiding pronounced hyperglycemia, omitting early-parenteral nutrition during critical illness protected the normal development of other neurobiological pathways that coordinate emotions and behaviour. This indicates that the neurocognitive legacy of paediatric critical illness is multifactorial, and improvement can only be expected by a stepwise elimination of various causal factors. The stepwise elimination of harmful factors will need the support of clinical guidelines to help the implementation or de-implementation of certain interventions, such as the latest European Society for Paediatric Gastroenterology Hepatology and Nutrition, European Society for Clinical Nutrition and Metabolism, European Society for Paediatric Research, and Chinese Society of Parenteral and Enteral Nutrition joint guidelines on paediatric parenteral nutrition.[32] Nevertheless, even though progress has been made, our findings show that children who have been critically ill clearly still face important developmental problems. Thus, the setting up of a structured post critical illness follow-up consultation is necessary for these children, with referral to a specialised health-care professional (e.g., clinical psychologist or psychiatrist) who can initiate an appropriate intervention when warranted.

This study has some limitations to highlight. First, for the clinical tests that assessed inhibition and flexibility, missing data for more than 30% of the population did not allow imputation and thus no information on differences between the groups could be provided. Second, neuroimaging studies were not done because of ethical and practical considerations. Third, we did not correct for multiple comparisons because the studied developmental outcomes are not independent, as shown by the correlations in the outcomes reported, which makes

use of the stringent Bonferroni correction inappropriate. Although the risk of false-positive findings cannot be completely excluded, we did find a significant effect of early-parenteral nutrition versus late-parenteral nutrition on caregiver-reported emotional and behavioural problems. The strengths of the study include the limited loss to follow-up compared with other long-term follow-up studies of children with critical illness[33,34] and the broad assessment of the physical, neurocognitive, and emotional and behavioural development of patients and matched control children.

CONCLUSIONS

4 years after critical illness, an important physical, neurocognitive, and emotional and behavioural legacy was reported. The omission of early-parenteral nutrition did not harm any of the developmental domains and protected patients against parent-reported or caregiver-reported emotional and behavioural problems, which were no longer overrepresented in patients in the late parenteral nutrition group compared with healthy controls. These data support de-implementation of the use of parenteral nutrition early during critical illness in infants and children. The findings also open perspectives for future identification of other modifiable risk factors related to intensive care management.

Table 1. Demographics, post-randomization treatments in the PICU, and acute outcomes of patients and healthy control children

	Tested populations		Total PICU population		Tested PICU population	
	Healthy control children N=369	**Patients N=684**	**Early-PN N=723**	**Late-PN N=717**	**Early-PN N=328**	**Late-PN N=356**
Demographics						
Age at 4-years' follow-up - yr	7.5 (4.3)	7.3 (4.3)	NA	NA	7.4 (4.3)	7.2 (4.2)
Sex						
Male	202 (54.7%)	393 (57.5%)	415 (57.4%)	412 (52.5%)	187 (57.0%)	206 (57.9%)
Female	167 (45.3%)	291 (42.5%)	308 (42.6%)	305 (42.5%)	141 (43.0%)	150 (42.1%)
Known non-Caucasian race[a]	27 (7.3%)	53 (7.8%)	50 (6.9%)	33 (4.6%)	33 (10.1%)	20 (5.6%)
Known non-European origin[a]	45 (12.2%)	129 (18.9%)	161 (22.3%)	128 (17.9%)	73 (22.3%)	56 (15.7%)
Known not exclusive Dutch or English language	71 (19.2%)	158 (23.1%)	122 (16.9%)	106 (14.8%)	78 (23.8%)	80 (22.5%)
Socioeconomic status						
Educational level parents[b]						
Educational level 1	12 (3.3%)	30 (4.4%)	NA	NA	10 (3.1%)	20 (5.6%)
Educational level 1.5	13 (3.5%)	51 (7.5%)	NA	NA	29 (8.5%)	22 (6.2%)
Educational level 2	47 (12.7%)	157 (23.0%)	NA	NA	75 (22.9%)	82 (23.0%)
Educational level 25	68 (18.4%)	116 (17.0%)	NA	NA	53 (16.2%)	63 (17.7%)
Educational level 3	207 (56.1%)	183 (26.8%)	NA	NA	86 (26.2%)	97 (27.3%)
Educational level unknown	22 (6.0%)	147 (21.5%)	NA	NA	75 (22.9%)	72 (20.2%)
Occupational level parents[c]						
Occupational level 1	2 (0.5%)	7 (1.0%)	NA	NA	1 (0.3%)	6 (1.7%)
Occupational level 1.5	20 (5.4%)	63 (9.2%)	NA	NA	23 (7.0%)	40 (11.2%)
Occupational level 2	42 (11.4%)	108 (15.8%)	NA	NA	50 (15.2%)	58 (16.3%)
Occupational level 2.5	25 (6.8%)	69 (10.1%)	NA	NA	39 (11.9%)	30 (8.4%)
Occupational level 3	80 (21.7%)	118 (17.3%)	NA	NA	52 (15.9%)	66 (18.5%)
Occupational level 3.5	40 (10.8%)	53 (7.8%)	NA	NA	30 (9.2%)	23 (6.5%)
Occupational level 4	117 (31.7%)	102 (14.9%)	NA	NA	44 (13.4%)	58 (16.3%)
Occupational level unknown	43 (11.7%)	164 (24.0%)	NA	NA	89 (27.1%)	75 (21.1%)
Patient characteristics upon PICU admission						
Infant (age<1y) at randomization	NA	331 (48.4%)	328 (45.4%)	325 (45.3%)	153 (46.7%)	178 (50.0%)
STRONGkids risk level[d]						

Medium	NA	613 (89.6%)	644 (89.1%)	644 (89.8%)	291 (88.7%)	322 (90.5%)
High	NA	71 (10.4%)	79 (10.9%)	73 (10.2%)	37 (11.3%)	34 (10.0%)
PeLOD score, first 24h in PICU [e]	NA	20.0 (11.6)	19.7 (12.0)	20.1 (12.3)	19.4 (11.6)	20.5 (11.5)
PIM3 score[f]	NA	-3.5 (1.4)	-3.2 (1.6)	-3.2 (1.7)	-3.4 (1.4)	-3.5 (1.3)
PIM3 probability of death - % [g]	NA	6.6 (11.7)	9.4 (15.9)	9.1 (17.4)	6.9 (11.9)	6.4 (11.7)
Diagnostic category						
Surgical						
Abdominal	NA	68 (9.9%)	53 (7.3%)	60 (8.4%)	34 (10.4%)	34 (10.0%)
Burns	NA	3 (0.4%)	5 (0.7%)	5 (0.7%)	2 (0.6%)	1 (0.3%)
Cardiac	NA	291 (42.5%)	279 (38.6%)	268 (37.4%)	137 (41.8%)	154 (43.3%)
Neurosurgery-Traumatic brain injury	NA	58 (8.5%)	63 (8.7%)	53 (7.4%)	31 (9.5%)	27 (7.6%)
Thoracic	NA	38 (5.6%)	34 (4.7%)	27 (3.8%)	21 (6.4%)	17 (4.8%)
Transplantation	NA	11 (1.6%)	7 (1.0%)	17 (2.4%)	3 (0.9%)	8 (2.3%)
Orthopedic surgery-Trauma	NA	19 (2.8%)	28 (3.9%)	26 (3.6%)	12 (3.7%)	7 (2.0%)
Other	NA	25 (3.7%)	21 (2.9%)	27 (3.8%)	11 (3.4%)	14 (3.9%)
Medical						
Cardiac	NA	23 (3.4%)	30 (4.2%)	31 (4.3%)	8 (2.4%)	15 (4.2%)
Gastrointestinal-Hepatic	NA	2 (0.3%)	2 (0.3%)	4 (0.6%)	1 (0.3%)	1 (0.3%)
Oncologic-Hematologic	NA	6 (0.9%)	8 (1.1%)	7 (1.0%)	2 (0.6%)	4 (1.1%)
Neurologic	NA	42 (6.1%)	51 (7.1%)	52 (7.3%)	19 (5.8%)	23 (6.5%)
Renal	NA	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Respiratory	NA	70 (10.2%)	99 (13.7%)	96 (13.4%)	33 (10.1%)	37 (10.4%)
Other	NA	28 (4.1%)	42 (5.8%)	43 (6.0%)	14 (4.3%)	14 (3.9%)
Malignancy	0 (0.0%)	38 (5.6%)	51 (7.1%)	33 (4.6%)	22 (6.7%)	16 (4.5%)
Diabetes	0 (0.0%)	0 (0.0%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Syndrome[h]	2 (0.5%)	63 (9.2%)	123 (17.0%)	118 (16.5%)	26 (7.9%)	37 (10.4%)
Known parental smoking between birth and PICU admission	NA	151 (22.1%)	NA	NA	69 (23.1%)	82 (24.5%)
Acute effects of randomization in PICU						
Duration of stay in the PICU – days	NA	7.8 (16.0)	9.2 (21.3)	6.5 (10.0)	9.3 (19.8)	6.5 (11.2)
Patients who acquired a new infection in PICU	NA	96 (14.0%)	134 (18.5%)	77 (10.7%)	59 (18.0%)	37 (10.4%)

Duration of mechanical ventilatory support – days	NA	5.0 (11.7)	6.4 (18.6)	4.4 (7.3)	6.0 (15.0)	4.0 (7.4)
Number of days with hypoglycemia <40 mg/dl – days	NA	0.1 (0.5)	0.1 (0.6)	0.2 (0.6)	0.1 (0.5)	0.2 (0.6)
Post-randomization treatments effects						
Duration of antibiotic treatment – days	NA	5.4 (14.2)	6.7 (19.0)	4.6 (8.7)	6.6 (17.7)	4.4 (9.8)
Duration of hemodynamic support – days	NA	2.7 (7.7)	3.0 (7.4)	2.4 (6.2)	2.9 (8.2)	2.5 (7.3)
Duration of treatment with opioids – days	NA	5.0 (9.3)	6.1 (16.5)	4.1 (6.2)	5.8 (11.5)	4.2 (6.5)
Duration of treatment with benzodiazepines – days	NA	4.4 (10.2)	5.4 (16.7)	4.0 (8.8)	4.9 (10.5)	4.0 (10.0)
Duration of treatment with hypnotics – days	NA	1.5 (6.0)	1.8 (6.3)	1.3 (3.1)	1.8 (8.1)	1.1 (3.0)
Duration of treatment with alpha-2-agonists – days	NA	1.1 (6.8)	1.1 (8.7)	1.0 (6.0)	1.1 (6.4)	1.1 (7.1)
Duration of treatment with corticosteroids - days	NA	1.2 (3.9)	1.6 (4.3)	1.3 (3.9)	1.4 (4.5)	1.1 (3.3)

Data are n (%) or mean (SD). a Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance. b The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4). c The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4). d Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk. e Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness. f Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality. g Paediatric Index of Mortality 3 (PIM3) probability of death, ranging from 0% to 100%, with higher percentages indicating a higher probability of death in PICU. h A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3). BMI, body mass index; NA, not applicable (values only known when the patients were seen at follow-up, or not applicable for healthy control children); PeLOD, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3, paediatric index of mortality 3 score; PN, parenteral nutrition; SD, standard deviation. i Overall, demographics upon PICU admission, allocation to late or early parenteral nutrition, and ICU or hospital-related primary and secondary study endpoints were comparable between the PEPaNIC patients who were tested (N=684) and those patients who survived, but declined participation or could not be reached (N=469, Table S2).

Table 2. Pooled univariable analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between late-PN and early-PN patient groups

		Tested populations			Tested PICU population		
Outcomes assessed at 4 years' follow-up[a]	**No. (%) available data per outcome prior to imputation N=1053**	**Healthy control children N=369**	**Patients N=684**	**P-value**	**Early-PN N=328**	**Late-PN N=356**	**P-value**
Height – cm	1012 (96.1%)	124.7 (23.4)	121.1 (23.2)	0.02	122.1 (23.1)	120.8 (23.2)	0.26
Z-score[b]	1012 (96.1%)	0.40 (0.99)	-0.03 (1.23)	<0.0001	0.04 (1.22)	-0.09 (1.25)	0.16
Weight – kg	1004 (95.3%)	28.0 (16.5)	27.0 (17.1)	0.33	27.2 (16.5)	26.7 (17.5)	0.70
Z-score[b]	1004 (95.3%)	0.32 (0.87)	0.12 (1.17)	0.005	0.17 (1.18)	0.08 (1.17)	0.55
BMI - kg/m^2	1003 (95.3%)	16.68 (2.94)	16.86 (3.33)	0.69	16.84 (3.13)	16.89 (3.50)	0.56
Z-score[b]	1003 (95.3%)	0.12 (1.00)	0.21 (1.17)	0.25	0.17 (1.43)	0.09 (1.26)	0.19
Head circumference – cm	1008 (95.7%)	52.5 (2.3)	52.0 (2.7)	0.001	52.1 (2.8)	51.8 (2.6)	0.27
Z-score[b]	1008 (95.7%)	0.49 (1.08)	0.13 (1.34)	<0.0001	0.17 (1.43)	0.09 (1.26)	0.19
Diagnosed with a somatic illness	840 (79.8%)	120 (32.4)	370 (54.0)	<0.0001	180 (54.6)	190 (53.5)	0.70
Diagnosed with a psychiatric illness	960 (91.2%)	16 (4.3)	63 (9.2)	0.005	32 (9.5)	31 (8.9)	0.81
Admitted to hospital for a medical or surgical reason	1011 (96.0%)	101 (27.3)	453 (66.2)	<0.0001	230 (70.0)	223 (62.7)	0.05
Clinical neurological evaluation score (range, 0-8)[a]	970 (92.1%)	0.2 (0.6)	0.6 (1.3)	<0.0001	0.7 (1.4)	0.5 (1.2)	0.09
Executive functioning as reported by parents/caregivers - T-score [a c]							

Inhibition	918 (89.9%)	45.7 (9.8)	49.8 (13.2)	<0.0001	50.8 (13.3)	49.0 (12.6)	0.07
Flexibility	919 (90.0%)	45.7 (8.5)	49.3 (11.8)	<0.0001	50.2 (12.2)	48.5 (11.2)	0.05
Emotional control	919 (90.0%)	46.2 (9.4)	48.9 (11.2)	<0.0001	49.5 (11.3)	48.4 (11.0)	0.18
Working memory	918 (89.9%)	46.4 (9.6)	51.9 (13.5)	<0.0001	52.7 (13.7)	51.1 (12.6)	0.12
Planning and organization	917 (89.8%)	46.3 (9.5)	50.4 (12.8)	<0.0001	50.6 (12.8)	50.2 (12.0)	0.60
Meta-cognition index	916 (89.7%)	45.6 (9.8)	50.6 (13.2)	<0.0001	50.9 (13.5)	50.2 (12.4)	0.51
Total score	915 (89.6%)	44.8 (9.8)	49.9 (13.2)	<0.0001	50.5 (13.3)	49.2 (12.5)	0.18
Emotional and behavioural problems as reported by parents/caregivers - T-score [a c]							
Internalising problems	940 (92.1%)	46.7 (10.5)	51.0 (12.3)	<0.0001	52.1 (12.1)	50.0 (12.2)	0.02
Externalising problems	940 (92.1%)	45.6 (9.7)	48.8 (11.2)	<0.0001	49.7 (11.0)	47.9 (11.1)	0.03
Total problems	940 (92.1%)	45.4 (9.9)	50.1 (11.9)	<0.0001	51.5 (11.6)	48.8 (11.9)	0.003
Intelligence (range, 45-155) [a]							
Total IQ	940 (92.1%)	105.7 (13.4)	93.1 (18.2)	<0.0001	93.2 (17.0)	93.0 (18.2)	0.89
Verbal IQ	940 (92.1%)	107.5 (14.4)	95.2 (19.0)	<0.0001	93.2 (16.0)	92.5 (16.2)	0.56
Performance IQ	940 (92.1%)	102.7 (13.2)	92.9 (16.2)	<0.0001	94.8 (18.3)	95.6 (18.6)	0.56
Visual-motor integration (range, 0.9-20) [a]	1025 (97.3%)	10.0 (2.1)	8.7 (3.1)	<0.0001	8.7 (3.1)	8.7 (2.7)	0.88
Alertness and motor coordination [a c]							
Alertness [a c d]							
Reaction time right hand – Z-score	739 (72.0%)	0.8 (4.3)	1.7 (12.6)	0.03	1.7 (8.9)	1.7 (9.4)	0.65
Within subject SD of repeated tests – Z-score	739 (72.0%)	1.1 (3.4)	2.0 (8.5)	<0.0001	2.0 (6.1)	2.0 (6.4)	0.68
Reaction time left hand – Z-score	752 (73.3%)	0.3 (2.5)	1.0 (5.8)	<0.0001	1.0 (4.3)	1.1 (4.5)	0.64

Within subject SD of repeated tests – Z-score	752 (73.3%)	1.0 (2.5)	1.7 (4.0)	<0.0001	1.6 (3.3)	1.7 (3.2)	0.59
Motor coordination (No of taps in 10s) [a c]							
No of unimanual taps							
Right hand	816 (79.5%)	34.6 (29.6)	32.6 (52.3)	0.12	32.7 (40.0)	32.5 (37.0)	0.76
Left hand	816 (79.5%)	30.5 (32.3)	28.9 (60.4)	0.18	29.1 (46.0)	28.7 (41.7)	0.65
No of valid alternating taps	742 (72.3%)	22.9 (30.0)	19.7 (56.8)	0.05	19.6 (43.8)	19.9 (40.7)	0.71
No of valid synchronous taps	785 (76.5%)	16.5 (18.3)	13.2 (27.9)	<0.0001	12.9 (21.9)	13.5 (20.5)	0.47
Memory [a c]							
Verbal-auditory							
Numbers (range, 1-19)							
Memory span (forward)	418 (85.1%)	9.9 (3.1)	8.7 (4.3)	<0.0001	9.0 (4.0)	8.5 (3.6)	0.18
Working memory (backward)	394 (80.2%)	10.3 (3.1)	9.5 (5.3)	0.01	9.7 (4.5)	9.3 (4.3)	0.24
Word pairs (proportion of correct responses)							
Learning	350 (71.2%)	0.5 (0.2)	0.4 (0.4)	<0.0001	0.4 (0.4)	0.4 (0.3)	0.67
Immediate memory	346 (70.5%)	0.4 (0.5)	0.4 (1.3)	0.07	0.4 (1.0)	0.4 (0.9)	0.55
Delayed memory	343 (69.9%)	0.4 (0.7)	0.4 (1.6)	0.12	0.4 (1.3)	0.4 (1.1)	0.43
Recognition	343 (69.9%)	0.9 (0.5)	0.9 (1.3)	0.15	0.9 (0.9)	0.9 (0.9)	0.46
Non-verbal, visual-spatial							
Pictures (proportion of correct responses)	404 (82.2%)	0.8 (0.1)	0.8 (0.2)	<0.0001	0.8 (0.2)	0.8 (0.2)	0.74
Dots (proportion of correct responses)							
Learning	370 (75.4%)	0.9 (0.2)	0.8 (0.4)	0.001	0.8 (0.4)	0.8 (0.3)	0.26
Immediate memory	367 (74.7%)	0.9 (0.3)	0.8 (0.7)	0.01	0.8 (0.5)	0.8 (0.5)	0.27
Delayed memory	361 (73.5%)	0.8 (0.4)	0.7 (1.1)	0.004	0.7 (0.8)	0.7 (0.8)	0.66

Learning index (range, 50-150)	341 (69.5%)	101.0 (22.6)	88.1 (33.2)	<0.0001	88.5 (27.4)	87.7 (25.8)	0.65

Results are presented in numbers with proportions (%) or mean (SD) from the 31 datasets combined generated by multiple data imputation by chained equations under a 'missing at random' assumption for the 684 post-PICU patients and 369 healthy control children. a For the clinical neurological evaluation score, higher scores reflect worse performance. For parent-reported executive functioning and emotional and behavioural problems, higher scores reflect worse performance. For intelligence and visual-motor integration, higher scores reflect better performance. For reaction time alertness and within-subject SD of repeated tests, higher scores reflect worse performance. For motor coordination, higher scores reflect better performance. For memory tests, higher scores reflect better performance. b Age- and gender-adjusted Z-scores, were calculated with the use of reference data from the World Health Organization Growth Charts: http://www.bcchildrens.ca/Services/SpecializedPediatrics/EndocrinologyDiabetesUnit/ForProfessionals/AnthropometricCalculators.htm. c For alertness, motor coordination, executive functions, emotional and behavioural problems and memory, applicable imputation was limited to relevant age-ranges. d For alertness, age adjusted Z-scores were calculated and imputed in the dataset BMI, body mass index; IQ, intelligence quotient; PICU, paediatric intensive care unit; PN, parenteral nutrition; SD, standard deviation.

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between late-PN and early-PN patient groups

Outcomes assessed at 4 years' follow-up[a]	No. (%) available data per outcome prior to imputation N=1053	Beta-estimate or odds ratio (95% CI) for the comparison patients vs. controls, adjusted for risk factors[d]	P-value	Beta-estimate or odds ratio (95% CI) for the comparison late PN vs. early PN, adjusted for risk factors[f]	P-value
Height – cm	1012 (96.1%)	-2.108 (-3.152 to -1.063)	<0.0001	-0.814 (-3.448 to 1.820)	0.54
Weight – kg	1004 (95.3%)	-0.091 (-0.966 to 0.785)	0.83	0.129 (-2.047 to 2.304)	0.91
Head circumference – cm	1008 (95.7%)	-0.421 (-0.665 to -0.176)	0.0007	-0.113 (-0.461 to 0.234)	0.52
Diagnosed with a somatic illness	840 (79.8%)	2.232 (1.635 to 3.047) [e]	<0.0001	0.974 (0.683 to 1.390) [e]	0.88
Diagnosed with a psychiatric illness	960 (91.2%)	2.465 (1.248 to 4.871) [e]	0.009	1.035 (0.562 to 1.905) [e]	0.91
Admitted to hospital for a medical or surgical reason	1011 (96.0%)	4.269 (3.120 to 5.842) [e]	<0.0001	0.715 (0.501 to 1.020) [e]	0.06
Clinical neurological evaluation score (range, 0-8)[a]	970 (92.1%)	0.237 (0.098 to 0.376)	0.0008	-0.098 (-0.275 to 0.079)	0.28
Executive functioning as reported by parents/caregivers - T-score [a b]					
Inhibition	918 (89.9%)	2.685 (1.059 to 4.310)	0.001	-1.665 (-3.643 to 0.313)	0.10
Flexibility	919 (90.0%)	2.706 (1.259 to 4.153)	0.0002	-1.487 (-3.283 to 0.309)	0.10

Emotional control	919 (90.0%)	2.061 (0.601 to 3.520)	0.005	-1.189 (-2.938 to 0.560)	0.18
Working memory	918 (89.9%)	3.695 (2.096 to 5.293)	<0.0001	-1.375 (-3.328 to 0.577)	0.17
Planning and organization	917 (89.8%)	2.866 (1.327 to 4.406)	0.0002	-0.380 (-2.270 to 1.511)	0.69
Meta-cognition index	916 (89.7%)	3.334 (1.714 to 4.954)	<0.0001	-0.610 (-2.580 to 1.359)	0.54
Total score	915 (89.6%)	3.566 (1.950 to 5.183)	<0.0001	-1.266 (-3.246 to 0.714)	0.21
Emotional and behavioural problems as reported by parents/caregivers – T-score [a b]					
Internalising problems	940 (92.1%)	2.730 (1.185 to 4.275)	0.0005	-1.880 (-3.690 to -0.071)	0.042
Externalising problems	940 (92.1%)	1.631 (0.185 to 3.076)	0.02	-1.731 (-3.433 to -0.028)	0.046
Total problems	940 (92.1%)	2.951 (1.443 to 4.459)	0.0001	-2.442 (-4.215 to -0.668)	0.007
Intelligence (range, 45-155) [a]					
Total IQ	937 (89.0%)	-7.349 (-9.311 to -5.387)	<0.0001	-1.100 (-3.399 to 1.198)	0.35
Verbal IQ	931 (88.4%)	-6.955 (-8.986 to -4.924)	<0.0001	-0.126 (-2.493 to 2.241)	0.92
Performance IQ	943 (89.6%)	-5.968 (-7.905 to -4.030)	<0.0001	-1.645 (-3.902 to 0.612)	0.15
Visual-motor integration (range, 0.9-20) [a]	1025 (97.3%)	-0.888 (-1.202 to -0.574)	<0.0001	-0.081 (-0.448 to 0.286)	0.66
Alertness and motor coordination [a b]					
Alertness [a b c]					
Reaction time right hand – Z-score	739 (72.0%)	0.668 (0.186 to 1.150)	0.007	0.077 (-0.334 to 0.489)	0.71
Within subject SD of repeated tests – Z-score	739 (72.0%)	0.663 (0.254 to 1.071)	0.001	0.020 (-0.393 to 0.434)	0.92
Reaction time left hand – Z-score	752 (73.3%)	0.498 (0.177 to 0.819)	0.002	0.141 (-0.221 to 0.502)	0.44
Within subject SD of repeated tests – Z-score	752 (73.3%)	0.476 (0.168 to 0.784)	0.002	0.173 (-0.166 to 0.512)	0.32
Motor coordination (No of taps in 10s) [a b]					
No of unimanual taps					
Right hand	816 (79.5%)	-1.762 (-3.448 to -0.076)	0.04	0.240 (-1.844 to 2.325)	0.82

Left hand	816 (79.5%)	-1.720 (-3.415 to -0.024)	0.04	0.094 (-1.893 to 2.081)	0.93
No of valid alternating taps	742 (72.3%)	-2.412 (-4.848 to 0.023)	0.05	0.503 (-2.202 to 3.209)	0.71
No of valid synchronous taps	785 (76.5%)	-2.066 (-3.348 to -0.783)	0.001	0.354 (-1.192 to 1.901)	0.65
Memory [a b]					
Verbal-auditory					
Numbers (range, 1-19)					
Memory span (forward)	418 (85.1%)	-0.644 (-1.270 to -0.019)	0.04	-0.601 (-1.371 to 0.168)	0.12
Working memory (backward)	394 (80.2%)	-0.165 (-0.781 to 0.450)	0.59	-0.323 (-1.047 to 0.400)	0.38
Word pairs (proportion of correct responses)					
Learning	350 (71.3%)	-0.081 (-0.122 to -0.040)	0.0001	-0.021 (-0.060 to 0.019)	0.30
Immediate memory	346 (70.5%)	-0.040 (-0.101 to 0.021)	0.19	-0.030 (-0.089 to 0.026)	0.31
Delayed memory	343 (70.0%)	-0.034 (-0.098 to 0.029)	0.28	-0.012 (-0.088 to 0.064)	0.76
Recognition	434 (70.0%)	-0.033 (-0.084 to 0.018)	0.20	-0.010 (-0.048 to 0.027)	0.58
Non-verbal, visual-spatial					
Pictures (proportion of correct responses)	404 (82.3%)	-0.029 (-0.056 to -0.003)	0.02	0.008 (-0.028 to 0.044)	0.68
Dots (proportion of correct responses)					
Learning	370 (75.4%)	-0.046 (-0.080 to -0.012)	0.007	0.007 (-0.040 to 0.054)	0.77
Immediate memory	367 (74.7%)	-0.053 (-0.102 to -0.003)	0.03	-0.012 (-0.073 to 0.050)	0.70
Delayed memory	361 (73.5%)	-0.078 (-0.148 to -0.007)	0.03	0.005 (-0.071 to 0.080)	0.90
Learning index (range, 50-150)	341 (70.0%)	-10.216 (-13.883 to -6.549)	<0.0001	-1.383 (-5.351 to 2.585)	0.49

Results are the combined beta-estimates and odds ratios from 31 datasets generated by multiple data imputation by chained equations under a 'missing at random' assumption for the 684 patients and 369 healthy control children. a For the clinical neurological evaluation score, higher scores reflect worse performance. For parent-reported executive functioning and emotional and behavioural problems, higher scores reflect worse performance. For

intelligence and visual-motor integration, higher scores reflect better performance. For reaction time alertness and within-subject SD of repeated tests, higher scores reflect worse performance. For motor coordination, higher scores reflect better performance. For memory tests, higher scores reflect better performance. b For alertness, motor coordination, executive functions, emotional and behavioural problems and memory, applicable imputation was limited to relevant age-ranges. c For alertness, age adjusted Z-scores were calculated and imputed in the dataset d Estimates and odds ratios were adjusted for the following risk factors: age, centre, race, gender, geographic origin, language, hand preference, history of malignancy, a predefined "syndrome", and the educational and occupational status of parents. e These values are odds ratios. f Estimates and odds ratios were adjusted for the following risk factors: age, centre, race, gender, geographic origin, language, hand preference, history of malignancy, a predefined "syndrome", the educational and occupational status of parents, PIM3 score and PeLOD score upon PICU admission, STRONGkids risk category, and parental smoking behaviour prior to PICU admission. IQ, intelligence quotient; PeLOD score, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3 score, paediatric index of mortality 3 score; PN, parenteral nutrition; SD, standard deviation; STRONGkids, Screening Tool Risk On Nutritional Status and Growth. Sensitivity analyses to the "missing at random' assumption and with imputing worst test-scores for the severely disabled and thus non-testable children, as specified in the Methods S2, further supported the robustness of these results.

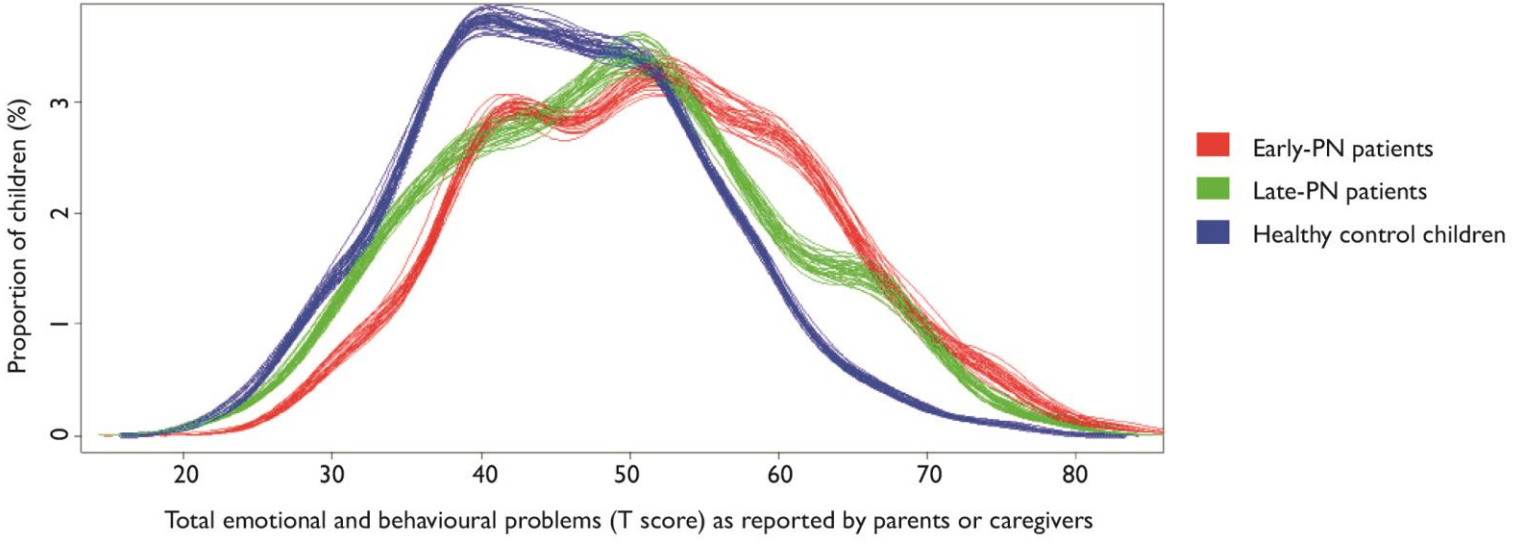


Figure 2. The effect of late-parenteral nutrition versus early parenteral nutrition on the development of long term emotional and behavioural problems**.** The figure represents the density estimates for total behavioural and emotional problems reported by parents or caregivers. Each line corresponds to an imputed dataset. Densities correspond to the proportions of children with a certain score (equivalent to a smoothed histogram). Higher scores indicate more total behavioural and emotional problems. PN: parenteral nutrition.

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APPENDIX

Methods S1. Detailed description of outcome measures

Medical assessment

Anthropometric data

At the beginning of the follow-up visit, height (in cm), body weight (in kg) and head circumference (in cm) were measured.

Health status

In an interview with the parents, the need for medical support of all kind during the past two years for healthy control children and during the 4 years following the index PICU admission for patients, was recorded. The hospital admissions because of surgery or a medical reason, and the occurrence of a psychiatric diagnosis were documented.

Clinical neurological examination

In order to assess whether there were gross neurological abnormalities, during a structured clinical neurological examination, signs of major neurologic dysfunction were detected in the following domains: interaction/language skills, gross motor function, involuntary movements, reflexes, coordination and balance, fine motor function, cranial nerves, and special senses (sensory, visual, and auditory function). These were all scored normal or abnormal. An abnormal result for each of these domains was given 1 point and the sum was made of all the abnormal results, with a range of 0-8.

Neurocognitive testing

A broad range of neurocognitive functions, including general intellectual functioning, visual-motor integration, alertness, motor coordination, verbal and visual-spatial learning, and memory were evaluated, as previously reported.[1]

Patient/Parents-reported outcomes (PROs)

Executive functioning was assessed with the Behaviour Rating Inventory of Executive Function in children aged years 6 months - 5 years 11 months with BRIEF-P, and in children 6 years – 17 years 11 months with BRIEF, filled out by the parents/caregivers of the child. Overlapping scales and indices of both questionnaires (Inhibition, Flexibility, Emotional Control, Working Memory, Planning and Organization, Meta-cognition) and a Total Score were analysed (T-scores, with mean 50 and SD 10).[2,3] Emotional and behavioural problems were assessed by the parent/caregiver with the Child behaviour Checklist (CBCL 1.5-5 years or CBCL 6-18 years).[4,5] Internalising, externalising, and total problems were analysed (T-scores, with mean 50 and SD 10).[4,5]

Intelligence

General intellectual ability was assessed with use of age-appropriate versions of the Wechsler Intelligence Quotient (IQ) tests. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)[6] was used for children aged 3 years 6 months – 5 years 11 months (one version for age range 3 years 6 months – 3 years 11 months, and another version for age range 4 years – 5 years 11 months), the Wechsler Intelligence Scale for Children (WISC-III-NL)[7] was used for children aged 6 years – 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IVNL) [8] for adolescents who were 17 years or older. For all these tests Total IQ, Verbal IQ, and Performance IQ scores (standard scores, with mean 100, SD 15) were computed.

Visual-motor integration

We used the Beery Developmental Test of Visual-Motor Integration, 6th Edition (VMI) to assess the ability to integrate visual and motor functions (scaled score, with mean 10 and SD 3). This involves eye-hand coordination.[9]

Alertness and motor-coordination

To measure alertness and motor coordination, the validated Amsterdam Neuropsychological Tasks (ANT) program was used.[10] The ANT is a computerised assessment battery of reaction time (RT) tasks that allows for the systematic evaluation of information processing capacities. Children aged 4 years and older performed ANT-Baseline Speed (BS) and ANT-Tapping (TP). The ANT-BS evaluated alertness by measuring simple RT to visual stimuli (Z-scores of mean RT and SD of RT with mean 0 and SD 1 were obtained for the right and left hand separately). The ANT-TP assessed motor coordination for the right hand, left hand, bimanual alternating, and bimanual synchronous (number of taps,).

Memory

Auditory/verbal memory and Visual-spatial/non-verbal memory were assessed with use of four tests from the Children's Memory Scale (CMS) for children aged between 5 and 16 years 11 months.[11] As to verbal memory, CMS-Numbers assessed short-term verbal memory span (forward digit recall) and verbal working memory load (backward digit recall). The CMS-Word Pairs (recall a list of word pairs) assessed short-term and long-term verbal memory, and recognition. As to non-verbal memory, CMS-Picture Locations (remembering and recall of pictures in various locations) assessed short-term visual memory. CMS-Dot Locations (remembering and recall of the location of dots) assessed short-term and long-term visual memory. For CMS-Numbers, scaled scores (with mean 10 and SD 3) for verbal memory span, CMS-numbers forward, and verbal working memory load, CMS-numbers backward were reported. For CMS-Word Pairs, CMS-Picture Locations, and CMS-Dot Locations, proportional scores were analysed (proportion of correct responses ranging from 0 to 1, with higher scores reflecting better performance). The CMS-Learning index is a standardised score of the sum of the three learning trials of the CMS-Word Pairs and the

three learning trials of the CMS-Dot Locations subtests. The range of the score is 50-150, with a higher score representing a better learning ability.

Methods S2. Imputation

Missing data (excluding the deceased and the severely disabled whereby non-testable children) were handled by ***multiple data imputation with chained equations under a 'missing at random' assumption***. There were no missing data in the baseline variables. Predictors for missing values included all covariates listed below, and were retained in the predictor models with a minimum correlation of 0.1 with the prediction target. Predictive mean matching[12] was used for numeric variables except for factors with two levels (which were imputed based on logistic regression) and factors with more than two levels (for which polytomous (unordered) regression was used). A monotonous visiting scheme was used such that variables for imputation were visited in increasing order of the number of missing data. Imputation convergence was assessed visually and set at 100 iterations (Figure S2) 31 complete imputed datasets were used in the analyses,[13] and pooled results were obtained across datasets using Rubin's rules.[14]

Plausibility of the imputations was assessed visually via the densities of the observed data and that resulting from the imputed values (Figure S3). **Sensitivity of results to the 'missing at random' assumption** was assessed with use of pattern mixture models14-16 assuming the original imputed values were either too high by a factor of 0.07 or too low by a factor of 0.1 for the main result of total emotional and behavioural problems as reported by parents/caregivers. Under this assumption, the obtained beta-estimates and P-values for randomization to late-PN vs. early-PN for the multivariable linear regression analyses performed to determine significant and independent associations between risk factors and total emotional/behavioural problems as reported by the parents/caregivers at 4 years' follow-up within the tested patient population ranged from -1.98 (p=0.05) to -1.84 (p=0.04). The effect-sizes thus remained of the same order of magnitude, sign, and statistical significance as observed for the original imputed datasets, which suggested that the analyses were robust against the investigated 'missing at random' violation.

To further evaluate the robustness of the main findings, the analyses were repeated after imputing a penalised test result for all severely disabled and thus non-testable patients, defined as the worst result in the observed patients or controls, plus or minus one, as appropriate for each test. In this case, the obtained beta-estimates (P-values) for randomization to late-PN vs. early-PN for the multivariable linear regression analyses were respectively: A) -1.80 (p=0.05) for internalising emotional/behavioural problems as reported by the parents/caregivers B) -1.62 (p=0.06) for externalising emotional/behavioural problems as reported by the parents/caregivers and C) -2.36 (p=0.01) for total emotional/behavioural problems as reported by the parents/caregivers. These sensitivity analyses corresponded closely to the primary results as reported in Table 3 of the main

manuscript. All multiple data imputation analyses were performed with R version 3.5.3 and MICE versions 3.4.0 and 3.6.0.

List of variables used for multiple data imputation by chained equations

Demographics of patients and control children and patient characteristics upon PICU admission

Centre, randomization for late-PN or early-PN, patient vs. controls, race, gender, geographic origin, language, hand preference, history of malignancy, history of diabetes, a predefined "syndrome", educational and occupational status of parents, diagnosis, PIM3 and PeLOD scores upon PICU admission, risk of malnutrition (STRONGkids category), parental smoking before, during and after pregnancy, age at randomization, age group at randomization.

Acute effects of randomization and post-randomization treatments in PICU

Acquisition of new PICU infections, duration of PICU stay, duration of mechanical ventilatory support, hypoglycemia, duration of treatment with hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and alpha-2-agonists.

At 4-years' follow-up

Age, test location, height, weight, head circumference, composite endpoint "diagnosed with a somatic illness", composite endpoint "diagnosed with a psychiatric illness", composite endpoint "admitted to hospital for a medical or surgical reason", clinical neurological examination, verbal IQ, performance IQ, total IQ, visual motor integration, Z-score reaction time left hand, Z-score reaction time right hand, Z-score within subject SD of reaction time left hand, Z-score within subject SD of reaction time left hand, number of unimanual taps right hand, number of unimanual taps left hand, number of valid alternating taps, number of valid synchronous taps, numbers memory span forward, numbers working memory backward, word pairs learning, word pairs immediate memory, word pairs delayed memory, word pairs recognition, pictures, dots learning, dots immediate memory, dots delayed memory, learning index, executive functioning as reported by parents/caregivers (inhibition, flexibility, emotional control, working memory, planning and organization, meta-cognition index, and total score), emotional and behavioural problems as reported by parents/caregivers (internalising problems, externalising problems, and total problems).

Methods S3. Definition of "Syndrome"

A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive

development, and which is subdivided in the following categories:[17]

- Genetically confirmed syndrome or pathogenic chromosomal abnormality

- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown etiology
- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumor or tumor with intracranial metastatic disease
- Paediatric psychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity
- disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental
- performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré
- Resuscitation and/or need for extracorporeal membrane oxygenation prior to randomization
- Severe convulsions or stroke prior to randomization

Methods S4. Definition of educational and occupational level of parents

Educational level of parents[17]

The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level.

Occupational level of parents[17]

The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions.[18] In case one of the parents filled in two jobs in the questionnaire, the highest Isco code level was used. In case "unemployed", "disabled", "student", or "housewife/houseman" was filled in, an Isco code level of 1 was given to that parent. When the parents described their profession as "employee", "worker", "liberal profession", or "retired", they were given an Isco code level of 2.

Methods S5. Correlation of physical, neurocognitive and psychosocial outcomes

We computed a correlation matrix to investigate the univariate association between all pairwise combinations of the physical, neurocognitive and psychosocial outcomes evaluated at 4-year follow up. In all cases we used a Pearson correlation of pairwise complete

observations. This correlation matrix was then visualised directly with a colour-code indicating the sign and strength of the correlation. This analysis was performed with the "Corrr" package version 0.4.0. for R version 3.5.3.

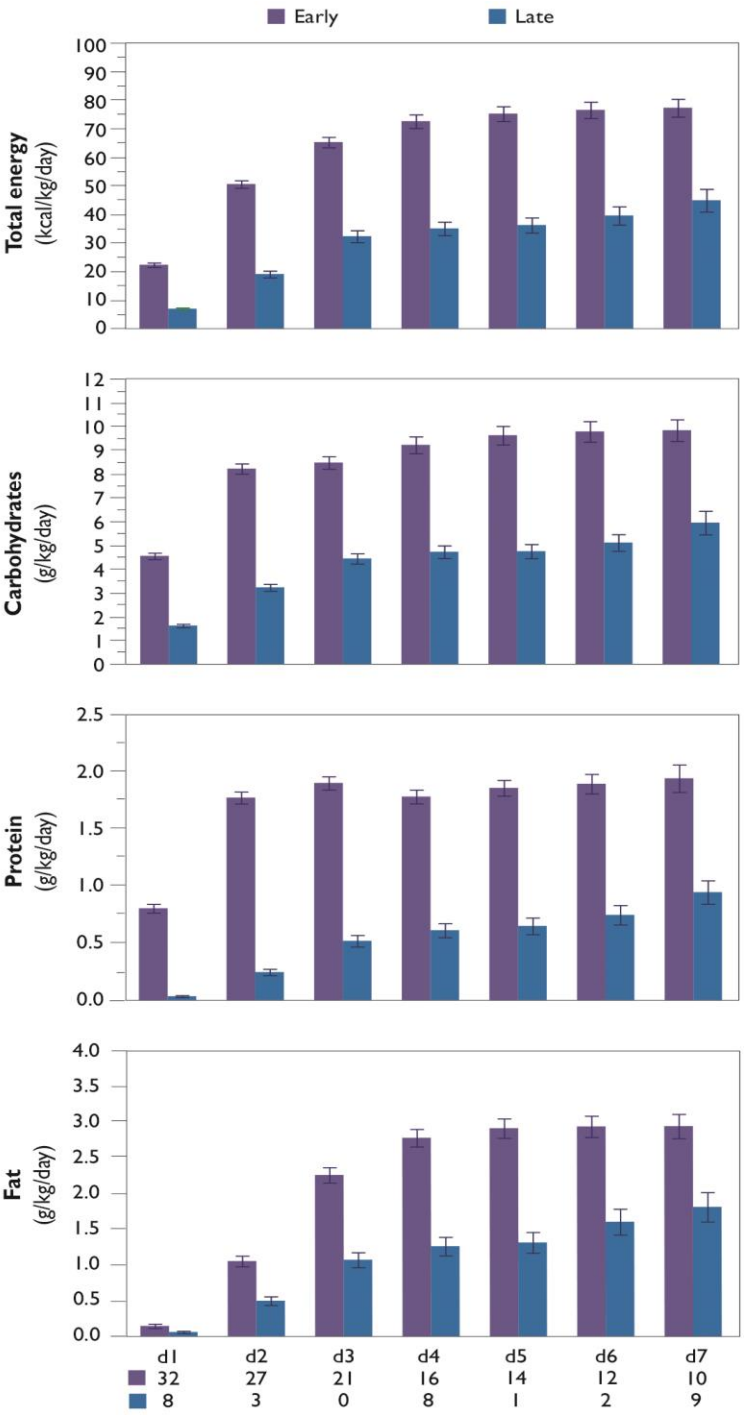

Figure S1. Macronutrient doses during the first week in PICU administered to the tested population

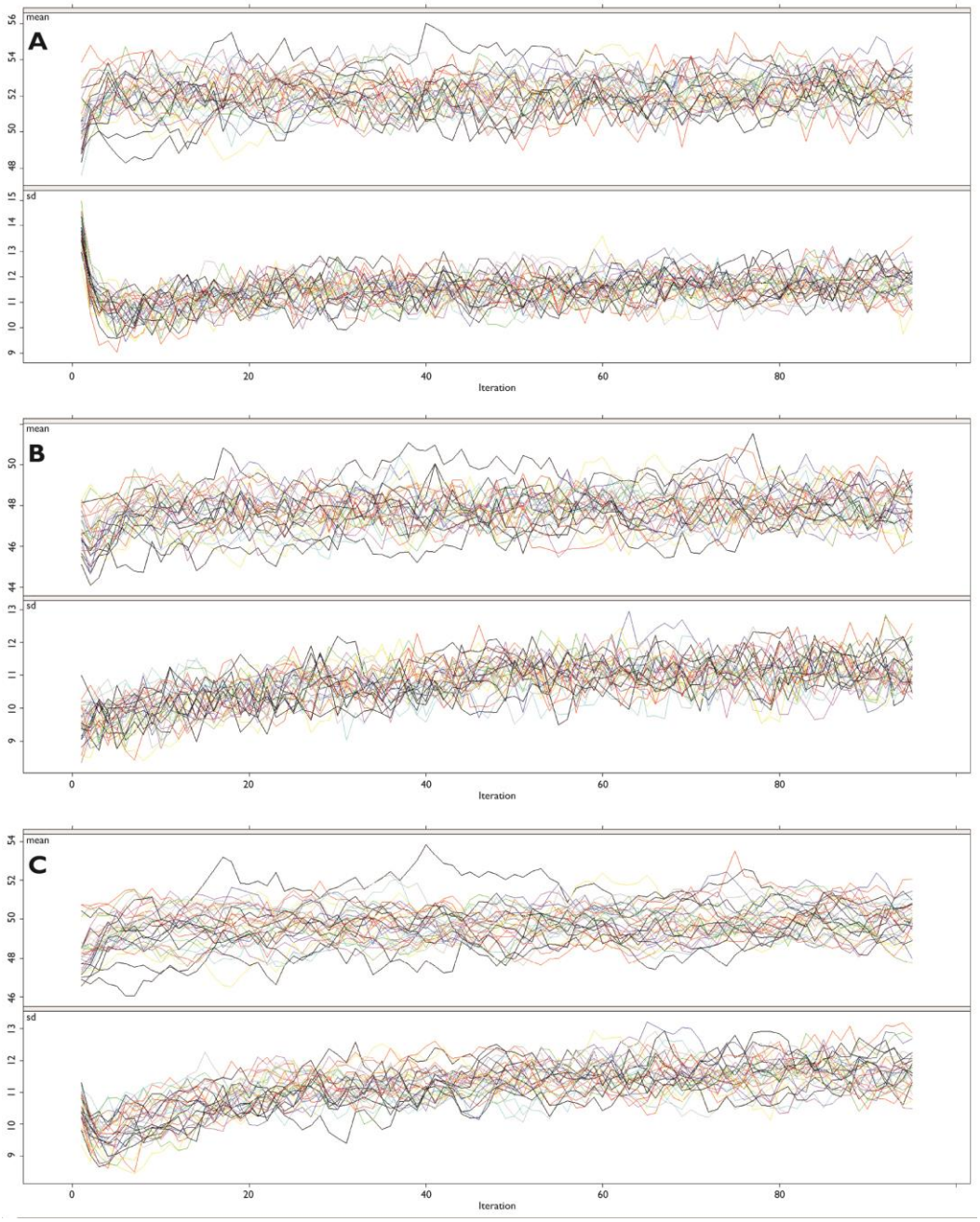

Figure S2. Imputation convergence for selected neurocognitive test results
Mean and standard deviation of imputed values in each of 31 datasets over 100 iterations for **A)** Emotional and behavioural problems as reported by parents/caregivers — T-score: Internalising problems **B)** Externalising problems **C)** Total problems.

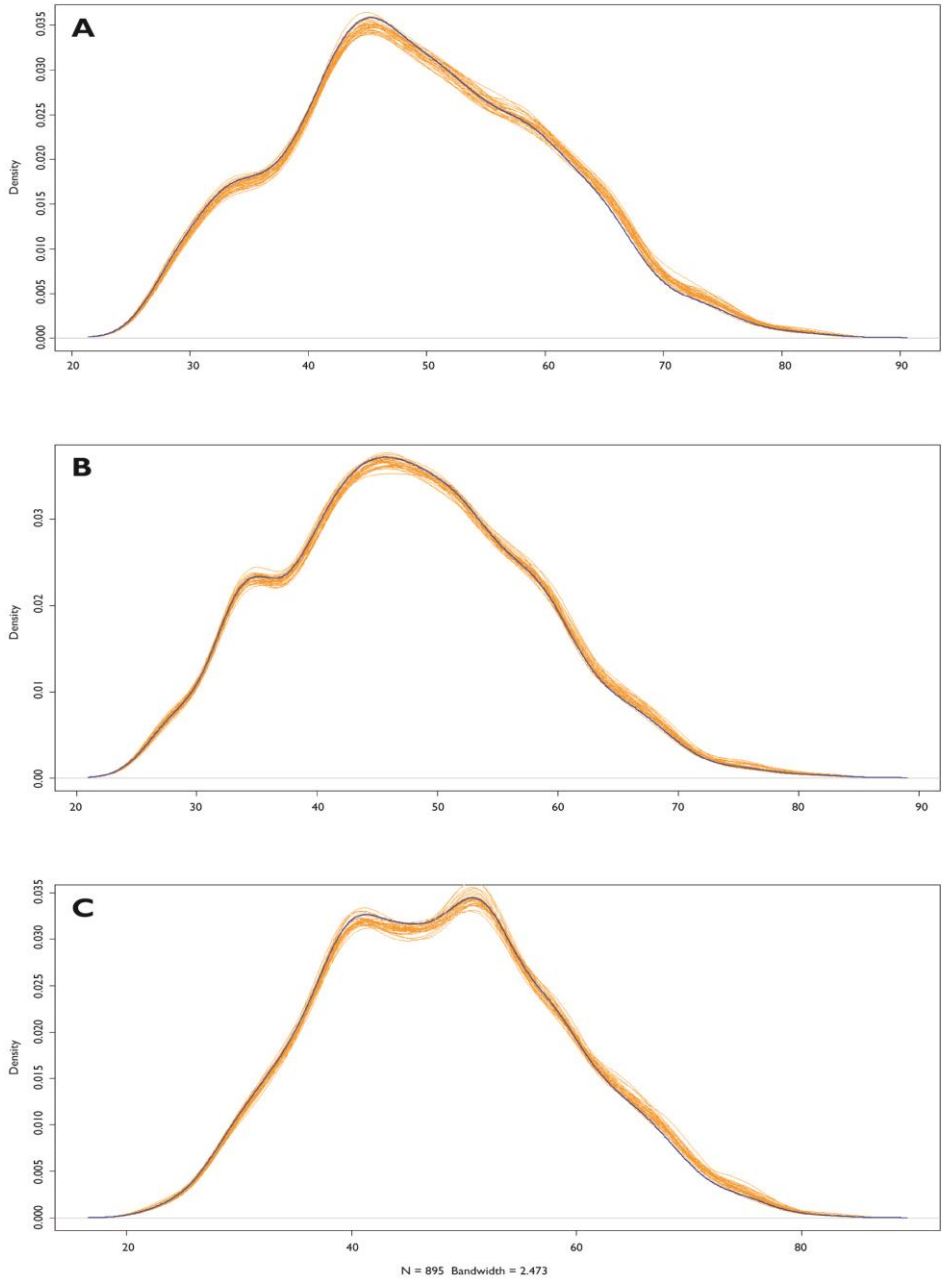

Figure S3. Density estimates of the observed and imputed values for selected neurocognitive test results Density estimated for observed values (in blue) and for each imputed dataset (in orange) for **A)** Emotional and behavioural problems as reported by parents/caregivers — T-score: Internalising problems **B)** Externalising problems **C)** Total problems.

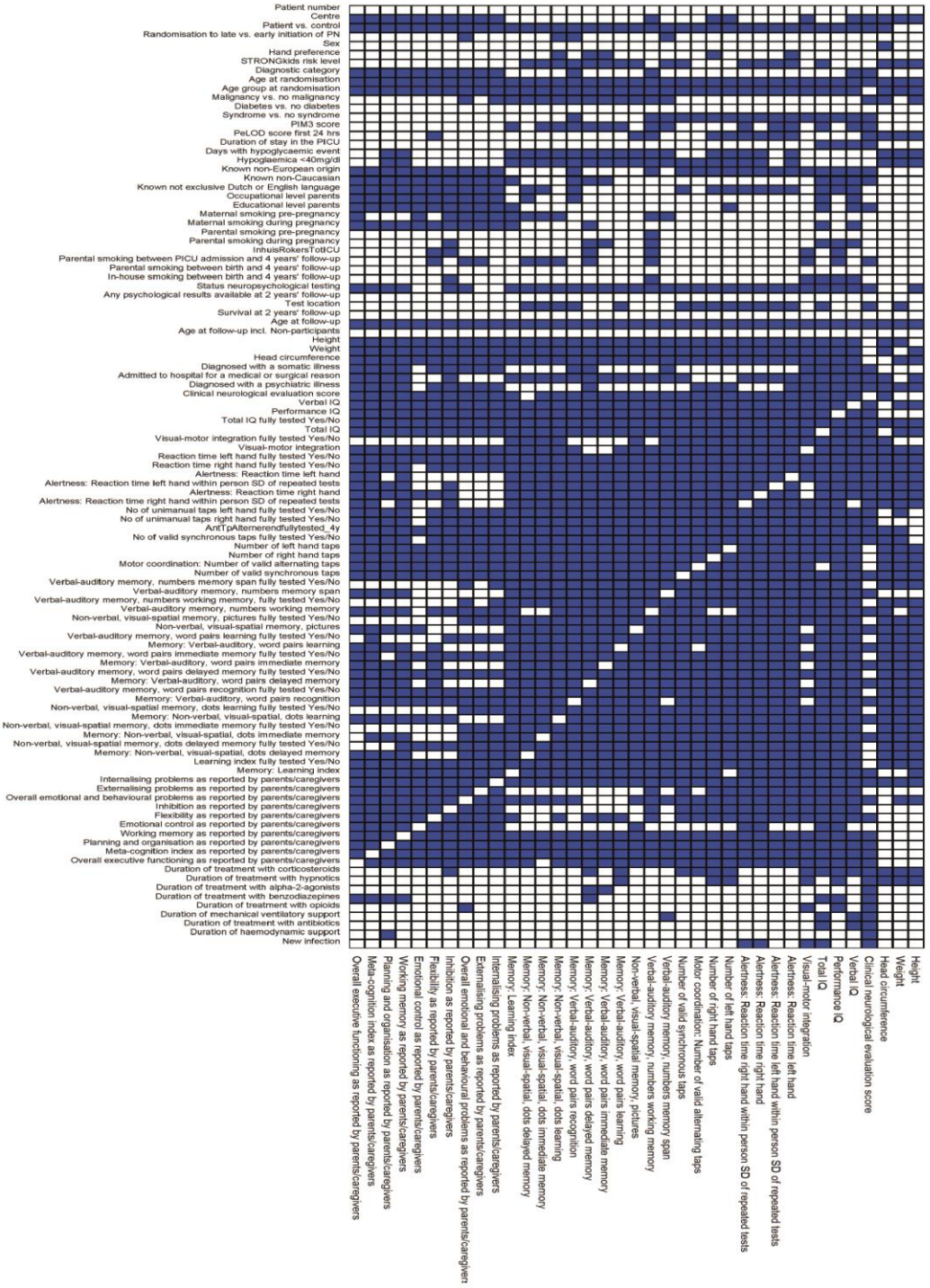

Figure S4. Multiple imputation predictor variables

Missing values for the variables in each row are imputed based on models that use as predictors only the column variables highlighted in blue. The predictor variables are selected as described in Methods S4

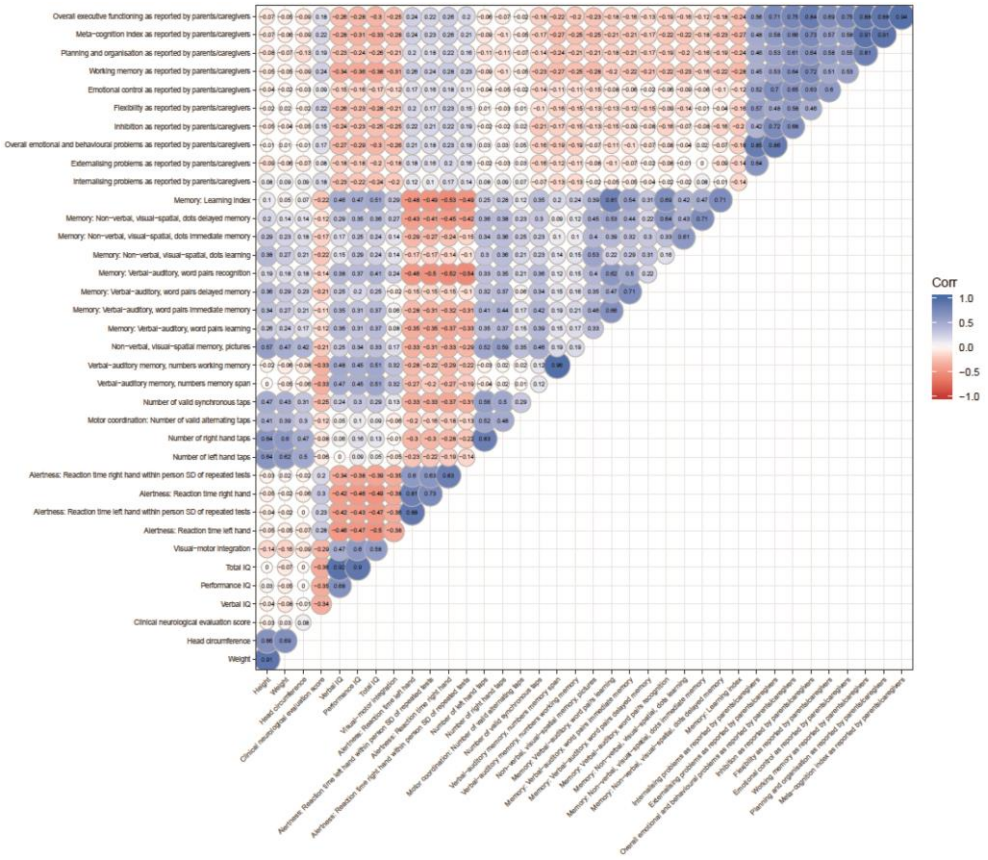

Figure S5. Correlation plot of physical, neurocognitive and psychosocial outcomes
The correlation matrix shows the correlation between all physical, neurocognitive and emotional/behavioural outcomes. Blue shades represent a positive correlation, red shades represent inverse correlations. Darker coloured shading represents a strongercorrelation. For the statistical methodology of this matrix, see Methods S5.

Table S1-1. Demographics and other patient characteristics upon PICU admission, acute outcomes and post-randomization treatments in the PICU of participating patients who were too disabled for neurocognitive testing and those who underwent neurocognitive testing

	Participating patients too disabled for neurocognitive testing N=84	**Neurocognitively tested patients N=684**	**P-value**
Demographics			
Age at 4-years' follow-up - yr	9.0 (5.6)	7.3 (4.3)	0.008
Sex			0.87
Male	49 (58.3%)	393 (57.5%)	
Female	35 (41.7%)	291 (42.5%)	
Known non-Caucasian race[a]	11 (13.1%)	53 (7.8%)	0.09
Known non-European origin[a]	20 (23.8%)	129 (18.9%)	0.27
Known not exclusive Dutch or English language	20 (23.8%)	158 (23.1%)	0.88
Socioeconomic status			
Educational level parents[b]			0.001
Educational level 1	9 (10.7%)	30 (4.4%)	
Educational level 1.5	4 (4.8%)	51 (7.5%)	
Educational level 2	21 (25.0%)	157 (23.0%)	
Educational level 2.5	11 (13.1%)	116 (17.0%)	
Educational level 3	10 (11.9%)	183 (26.8%)	
Educational level unknown	29 (34.5%)	147 (21.5%)	
Occupational level parents[c]			<0.0001
Occupational level 1	3 (3.6%)	7 (1.0%)	
Occupational level 1.5	6 (7.1%)	63 (9.2%)	
Occupational level 2	19 (22.6%)	108 (15.8%)	
Occupational level 2.5	5 (6.0%)	69 (10.1%)	
Occupational level 3	5 (6.0%)	118 (17.3%)	
Occupational level 3.5	0 (0.0%)	53 (7.8%)	
Occupational level 4	10 (11.9%)	102 (14.9%)	
Occupational level unknown	36 (42.9%)	164 (24.0%)	
Patient characteristics upon PICU admission			
Randomization			0.11
Early PN	48 (57.1%)	328 (48.0%)	
Late PN	36 (42.9%)	356 (52.1%)	
Infant (age<1y) at randomization	36 (42.9%)	331 (48.4%)	0.33

STRONGkids risk level[d]			0.15
Medium	71 (84.5%)	613 (89.6%)	
High	13 (15.5%)	71 (10.4%)	
PeLOD score, first 24h in PICU [e]	22.8 (12.4)	20.0 (11.6)	0.03
PIM3 score[f]	-3.0 (1.5)	-3.5 (1.4)	0.001
PIM3 probability of death - % [g]	9.1 (13.6)	6.6 (11.7)	0.001
Diagnostic category			<0.0001
Surgical			
Abdominal	1 (1.2%)	68 (9.9%)	
Burns	0 (0.0%)	3 (0.4%)	
Cardiac	28 (33.3%)	291 (42.5%)	
Neurosurgery-Traumatic brain injury	10 (11.9%)	58 (8.5%)	
Thoracic	1 (1.2%)	38 (5.6%)	
Transplantation	1 (1.2%)	11 (1.6%)	
Orthopedic surgery-Trauma	12 (14.3%)	19 (2.8%)	
Other	1 (1.2%)	25 (3.7%)	
Medical			
Cardiac	0 (0.0%)	23 (3.4%)	
Gastrointestinal-Hepatic	2 (2.4%)	2 (0.3%)	
Oncologic-Hematologic	0 (0.0%)	6 (0.9%)	
Neurologic	9 (10.7%)	42 (6.1%)	
Renal	0 (0.0%)	0 (0%)	
Respiratory	11 (13.1%)	70 (10.2%)	
Other	8 (9.5%)	28 (4.1%)	
Malignancy	3 (3.6%)	38 (5.6%)	0.44
Diabetes	0 (0.0%)	0 (0.0%)	>0.99
Syndrome[h]	48 (57.1%)	63 (9.2%)	<0.0001
Known parental smoking between birth and PICU admission	17 (20.2%)	151 (22.1%)	0.70
Acute effects of randomization and post-randomization treatments in PICU			
Duration of stay in the PICU – days	7.5 (14.6)	7.8 (16.0)	0.57
Patients who acquired a new infection in PICU	10 (11.9)	96 (14.0%)	0.59
Duration of mechanical ventilatory support – days	5.2 (10.8)	5.0 (11.7)	0.72
Number of days with hypoglycemia <40mg/dl – days	0.2 (0.8)	0.1 (0.5)	0.97
Duration of antibiotic treatment – days	4.9 (9.6)	5.4 (14.2)	0.81
Duration of hemodynamic support – days	1.9 (3.6)	2.7 (7.7)	0.71
Duration of treatment with opioids – days	3.2 (4.5)	5.0 (9.3)	0.01
Duration of treatment with benzodiazepines – days	4.2 (10.7)	4.4 (10.2)	0.35
Duration of treatment with hypnotics – days	1.0 (1.9)	1.5 (6.0)	0.79

Duration of treatment with alpha-2-agonists – days	0.9 (6.6)	1.1 (6.8)	0.22
Duration of treatment with corticosteroids - days	1.0 (1.9)	1.2 (3.9)	0.03

Data are n (%) or mean (SD). a Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance. b The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4). c The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4). d Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19] e Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20] f Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21] g Paediatric Index of Mortality 3 (PIM3) probability of death, ranging from 0% to 100%, with higher percentages indicating a higher probability of death in PICU.[21] h A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3). BMI, body mass index; PeLOD, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3, paediatric index of mortality 3 score; PN, parenteral nutrition; SEM, standard error of the mean.

Table S1-2. Physical development and parent-reported outcomes at 4 years' follow-up of participating patients who were too disabled for neurocognitive testing and those who underwent neurocognitive testing

	Participating patients too disabled for neurocognitive testing N=84		**Neurocognitively tested patients N=684**		**P-value**
	Number (%) of available data per outcome	**Outcome result**	**Number (%) of available data per outcome**	**Outcome result**	
Height - cm	77 (91.7%)	118.1 (24.2)	655 (95.8%)	120.9 (23.1)	0.04
Weight - kg	84 (100.0%)	25.6 (14.0)	647 (94.6%)	27.0 (17.1)	0.45
BMI - kg/m2	77 (91.7%)	17.4 (3.7)	646 (94.4%)	16.9 (3.4)	0.13
Head circumference - cm	83 (98.8%)	50.1 (3.7)	649 (94.9%)	51.9 (2.7)	<0.0001
Diagnosed with a somatic illness	42 (50.0%)	30 (71.4%)	523 (76.5%)	280 (53.5%)	0.02
Diagnosed with a psychiatric illness	76 (90.5%)	11 (14.5%)	609 (89.0%)	53 (8.7%)	0.10
Admitted to hospital for a medical or surgical reason	81 (96.4%)	73 (90.1%)	657 (96.1%)	435 (66.2%)	<0.0001
Clinical neurological evaluation score (range, 0-8)[a]	57 (67.9%)	4.3 (1.8)	616 (90.1%)	0.6 (1.3)	<0.0001
Executive functioning as reported by parents/caregivers - T-score[a]					
Inhibition	36 (42.9%)	61.8 (14.8)	556 (81.3%)	49.6 (11.8)	<0.0001
Flexibility	36 (42.9%)	59.0 (14.8)	557 (81.4%)	49.1 (10.6)	<0.0001
Emotional control	36 (42.9%)	56.1 (15.1)	557 (81.4%)	48.9 (10.5)	0.004

Working memory	35 (41.7%)	67.5 (12.4)	557 (81.4%)	51.5 (11.8)	<0.0001
Planning and organization	35 (41.7%)	62.0 (17.4)	557 (81.4%)	50.2 (11.2)	<0.0001
Meta-cognition index	35 (41.7%)	64.9 (15.7)	556 (81.3%)	50.3 (11.7)	<0.0001
Total score	35 (41.7%)	64.1 (16.8)	555 (81.1%)	49.7 (11.8)	<0.0001
Emotional and behavioural problems as reported by parents/caregivers - T-score[a]					
Internalising problems	44 (52.4%)	55.7 (10.4)	565 (82.6%)	50.4 (11.2)	0.006
Externalising problems	44 (52.4%)	53.4 (13.0)	565 (82.6%)	48.5 (10.3)	0.02
Total problems	44 (52.4%)	56.6 (12.2)	565 (82.6%)	49.7 (11.0)	0.0007

a Higher scores reflect worse performance. BMI, body mass index; IQ, intelligence quotient; PICU, paediatric intensive care unit; PN, parenteral nutrition; SD, standard deviation

Table S2. Demographics and other patient characteristics upon PICU admission, acute outcomes and post-randomization treatments in the PICU of patients who were tested and those patients who survived, but declined participation or could not be reached.

	Patients who survived, but declined participation or could not be reached N=469	**Neurocognitively tested patients N=684**	**P-value**
Patient characteristics upon PICU admission			
Randomization			0.11
Early PN	247 (52.7%)	328 (48.0%)	
Late PN	222 (47.3%)	356 (52.1%)	
Sex			0.97
Male	269 (57.4%)	393 (57.5%)	
Female	200 (42.6%)	291 (42.5%)	
Infant (age<1y) at randomization	193 (41.2%)	331 (48.4%)	0.01
STRONGkids risk level[a]			0.15
Medium	427 (91.0%)	613 (89.6%)	
High	42 (9.0%)	71 (10.4%)	
PeLOD score, first 24h in PICU [b]	17.4 (11.6)	20.0 (11.6)	0.0004
PIM3 score[c]	-3.5 (1.4)	-3.5 (1.4)	0.95
PIM3 probability of death - % [d]	6.5 (11.2)	6.6 (11.7)	0.95
Diagnostic category			0.12
Surgical			
Abdominal	40 (8.5%)	68 (9.9%)	
Burns	7 (1.5%)	3 (0.4%)	
Cardiac	173 (36.9%)	291 (42.5%)	
Neurosurgery-Traumatic brain injury	32 (6.8%)	58 (8.5%)	
Thoracic	19 (4.1%)	38 (5.6%)	
Transplantation	12 (2.6%)	11 (1.6%)	
Orthopedic surgery-Trauma	13 (2.8%)	19 (2.8%)	
Other	18 (3.8%)	25 (3.7%)	
Medical			
Cardiac	23 (4.9%)	23 (3.4%)	
Gastrointestinal-Hepatic	1 (0.2%)	2 (0.3%)	
Oncologic-Hematologic	4 (0.9%)	6 (0.9%)	
Neurologic	32 (6.8%)	42 (6.1%)	
Renal	1 (0.2%)	0 (0%)	
Respiratory	74 (15.8%)	70 (10.2%)	

Other	20 (4.3%)	28 (4.1%)	
Malignancy	17 (3.6%)	38 (5.6%)	0.15
Diabetes	2 (0.4%)	0 (0.0%)	0.16
Syndrome[e]	66 (14.1%)	63 (9.2%)	0.01
Acute effects of randomization and post-randomization treatments in PICU			
Duration of stay in the PICU – days	6.1 (8.2)	7.8 (16.0)	0.66
Patients who acquired a new infection in PICU	51 (10.9)	96 (14.0%)	0.11
Duration of mechanical ventilatory support – days	4.2 (7.1)	5.0 (11.7)	0.59
Number of days with hypoglycemia <40mg/dl – days	0.8 (0.3)	0.1 (0.5)	0.08
Duration of antibiotic treatment – days	4.4 (7.4)	5.4 (14.2)	0.70
Duration of hemodynamic support – days	1.8 (3.8)	2.7 (7.7)	0.13
Duration of treatment with opioids – days	4.1 (6.4)	5.0 (9.3)	0.19
Duration of treatment with benzodiazepines – days	3.5 (6.0)	4.4 (10.2)	0.49
Duration of treatment with hypnotics – days	1.3 (2.1)	1.5 (6.0)	0.001
Duration of treatment with alpha-2-agonists – days	0.5 (2.4)	1.1 (6.8)	0.19
Duration of treatment with corticosteroids - days	1.2 (3.4)	1.2 (3.9)	0.04

Data are n (%) or mean (SD). a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19] b Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20] c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21] d Paediatric Index of Mortality 3 (PIM3) probability of death, ranging from 0% to 100%, with higher percentages indicating a higher probability of death in PICU.[21] e A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3). BMI, body mass index; PeLOD, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3, paediatric index of mortality 3 score; PN, parenteral nutrition; SEM, standard error of the mean.

Table S3-1. Multivariable linear regression analyses determining significant and independent associations between risk factors and internalising problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		**Model further adjusted for acute effects of late-PN vs early-PN**		**Model further adjusted for post-randomization treatments**	
Variable	**β estimate (95% CI)**	**P-value**	**β estimate (95% CI)**	**P-value**	**β estimate (95% CI)**	**P-value**
Randomisation to late vs · early initiation of PN	*-1.880 (-3690; -0.071)*	*0.042*	*-1 ·702 (-3 ·541; 0 ·173)*	*0.070*	*-1.625 (-3.470; 0.219)*	*0.084*
Centre						
Leuven vs Edmonton	0.019 (-8.653; 8.691)	0.997	-0.024 (-8.717; 8.668)	0.996	0.082 (-8.725; 8.888)	0.985
Rotterdam vs Edmonton	0.627 (-7.840; 9.094)	0.884	0.424 (-8.050; 8.898)	0.922	0.292(-8.316; 8.899)	0.947
Male vs female sex	1.165 (-0.681; 3.011)	0.216	1.062 (-0.789; 2.913)	0.260	1.187(-0.674; 3.049)	0.211
Right vs left hand preference	-0.130 (-2.867; 2.608)	0.926	-0.230 (-2.981; 2.522)	0.870	-0.063 (-2.831; 2.706)	0.964
Medium vs high STRONGkids risk level[a]	-3.074 (-6.178; 0.031)	0.052	-2.727 (-5.867; 0.413)	0.089	-2.667 (-5.893; 0.559)	0.105
Diagnostic category (as compared with cardiac surgery)						
Surgical						
Abdominal	0.627 (-3.109; 4.363)	0.742	0.631 (-3.103; 4.365)	0.740	0.530 (-3.258; 4.317)	0.783
Burns	-2.005 (-14.952; 10.942)	0.761	-2.825 (-15.865; 10.215)	0.671	-2.919 (-16.09; 10.255)	0.664
Neurosurgery - traumatic brain injury	1.887 (-1.990; 5.764)	0.339	1.848 (-2.028; 5.725)	0.349	1.689 (-2.200; 5.577)	0.394
Thoracic	-1.197 (-5.380; 2.986)	0.574	-1.233 (-5.422; 2.955)	0.563	-0.961 (-5.192; 3.270)	0.655
Transplantation	-0.617 (-8.396; 7.162)	0.876	-1.493 (-9.446; 6.461)	0.712	-1.241 (-10.413; 7.930)	0.790
Orthopedic surgery-trauma	-0.573 (-6.724; 5.577)	0.855	-0.821 (-6.987; 5.346)	0.794	-0.917 (-7.153; 5.318)	0.772
Other	1.849 (-3.448; 7.147)	0.761	1.418 (-3.947; 6.783)	0.604	0.920 (-4.527; 6.368)	0.740
Medical						
Cardiac	-0.611 (-6.202; 4.980)	0.830	-1.314 (-6.929; 4.300)	0.646	-1.436 (-7.200; 4.328)	0.625

Gastrointestinal-hepatic	-4.742 (-25.519; 16.035)	0.652	-4.641 (-25.442; 16.160)	0.659	-4.818 (-25.658; 16.022)	0.648
Hematologic-oncologic	-2.598 (-12.953; 7.758)	0.622	-2.529 (-12.915; 7.857)	0.633	-2.829 (-13.968; 8.309)	0.618
Neurologic	-2.208 (-6.747; 2.331)	0.339	-2.106 (-6.655; 2.444)	0.363	-2.322 (-7.005; 2.361)	0.330
Respiratory	-1.383 (-4.996; 2.230)	0.452	-1.414 (-5.059; 2.231)	0.446	-1.294 (-5.025; 2.437)	0.496
Other	-0.106 (-4.796; 4.585)	0.965	-0.255 (-4.953; 4.443)	0.915	0.177 (-4.795; 5.148)	0.944
Infant (age<1y) vs child at randomization	-4.643 (-6.591; -2.694)	<0.0001	-4.610 (-6.602; -2.618)	<0.0001	-4.874 (-6.911; -2.836)	<0.0001
Malignancy vs no malignancy	2.107 (-2.272; 6.486)	0.345	2.061 (-2.328; 6.450)	0.357	2.049 (-2.421; 6.519)	0.368
Syndrome vs no syndrome[b]	1.699 (-1.521; 4.919)	0.300	1.520 (-1.732; 4.772)	0.359	1.906 (-1.400; 5.211)	0.258
PIM3 score (per point added)[c]	0.526 (-0.364; 1.416)	0.246	0.401 (-0.529; 1.330)	0.397	0.326 (-0.607; 1.260)	0.492
PeLOD score first 24 hrs (per point added)[d]	0.000 (-0.117; 0.117)	0.995	-0.007 (-0.125; 0.110)	0.906	-0.014 (-0.133; 0.105)	0.822
Known non-European origin vs other[e]	0.166 (-3.549; 3.881)	0.930	0.073 (-3.652; 3.798)	0.969	0.024 (-3.707; 3.755)	0.990
Known non-Caucasian vs other[e]	-2.306 (-7.355; 2.743)	0.368	-2.178 (-7.227; 2.872)	0.396	-2.025 (-7.097; 3.047)	0.431
Known not exclusive Dutch or English language vs other	1.709 (-1.020; 4.438)	0.219	1.922 (-0.830; 4.673)	0.171	1.794 (-0.968; 4.555)	0.202
Socioeconomic status						
Educational level parents (as compared with level 1)[f]						
Educational level 1.5	-2.778 (-8.831; 3.274)	0.367	-2.491 (-8.585; 3.603)	0.422	-2.240 (-8.415; 3.935)	0.476
Educational level 2	-1.811 (-7.261; 3.639)	0.514	-1.374 (-6.880; 4.133)	0.624	-1.536 (-7.121; 4.049)	0.589
Educational level 2.5	-4.396 (-10.040; 1.248)	0.126	-4.025 (-9.707; 1.657)	0.164	-3.934 (-9.700; 1.803)	0.178
Educational level 3	-4.973 (-10.619; 0.672)	0.084	-4.540 (-10.228; 1.149)	0.117	-4.629 (-10.387; 1.128)	0.115
Educational level unknown	-2.630 (-8.386; 3.125)	0.369	-2.324 (-8.109; 3.462)	0.429	-2.354 (-8.182; 3.474)	0.427
Occupational level parents (as compared with level 1)[g]						

Occupational level 1.5	1.679 (-7.871; 11.229)	0.730	1.529 (-8.054; 11.113)	0.754	1.092 (-8.523; 10.706)	0.824
Occupational level 2	0.238 (-9.230; 9.706)	0.961	0.149 (-9.361; 9.659)	0.975	-0.395 (-9.928; 9.138)	0.935
Occupational level 2.5	-2.341 (-12.174; 7.492)	0.640	-2.473 (-12.346; 7.400)	0.623	-2.704 (-12.618; 7.209)	0.592
Occupational level 3	-0.226 (-9.745; 7.492)	0.963	-0.300 (-9.840; 9.239)	0.951	-0.660 (-10.210; 8.890)	0.892
Occupational level 3.5	1.781 (-8.264; 11.826)	0.728	1.651 (-8.423; 11.725)	0.747	1.442 (-8.654; 11.538)	0.779
Occupational level 4	-1.396 (-11.172; 8.379)	0.779	-1.547 (-11.359; 8.265)	0.757	-2.074 (-11.907; 7.759)	0.679
Occupational level unknown	1.793 (-7.686; 11.273)	0.710	1.682 (-7.850; 11.214)	0.729	1.478 (-8.060; 11.017)	0.761
Parental smoking between birth and PICU admission vs no smoking	0.827 (-1.321; 2.974)	0.450	0.863 (-1.290; 3.016)	0.431	0.950 (-1.203; 3.103)	0.386
New infection vs no new infection			1.333 (-1.910; 4.576)	0.420	0.436 (0.802; -2.972)	3.844
Duration of stay in the PICU (per day added)			0.083 (-0.055; 0.220)	0.237	0.164 (0.279; -0.134)	0.461
Days with hypoglycemic event (per day added)			-0.049 (-1.813; 1.714)	0.956	-0.369 (0.708; -2.298)	1.561
Duration of mechanical ventilatory support (per day added)			-0.094 (-0.276; 0.088)	0.310	-0.095 (0.340; -0.291)	0.101
Duration of treatment with antibiotics (per day added)					-0.127 (0.375; -0.407)	0.154
Duration of hemodynamic support (per day added)					-0.013 (0.898; -0.215)	0.188
Duration of treatment with corticosteroids (per day added)					0.020 (0.905; -0.316)	0.357
Duration of treatment with opioids (per day added)					-0.001 (0.996; -0.284)	0.282
Duration of treatment with benzodiazepines (per day added)					0.173 (0.227; -0.108)	0.454
Duration of treatment with hypnotics (per day added)					-0.012 (0.931; -0.286)	0.262
Duration of treatment with alpha-2-agonists (per day added)					-0.183 (0.153; -0.434)	0.068

For internalising problems as reported by parents, higher scores reflect more problems. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19] b A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3) c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21] d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20] e Paarticipants were classified according to

race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[22,36] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4).[18] PeLOD, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3, paediatric index of mortality 3 score; PN, parenteral nutrition.

Table S3-2. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalising problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		**Model further adjusted for acute effects of late-PN vs early-PN**		**Model further adjusted for post-randomization treatments**	
Variable	**β estimate (95% CI)**	**P-value**	**β estimate (95% CI)**	**P-value**	**β estimate (95% CI)**	**P-value**
Randomization to late vs. early initiation of PN	*-1.731 (-3.433; -0.028)*	*0.046*	*-1.645 (-3.379; 0.090)*	*0.063*	*-1.51 (-3.242; 0.219)*	*0.086*
Centre						
Leuven vs Edmonton	-3.194 (-11.275; 4.886)	0.438	-3.337 (-11.463; 4.790)	0.420	-2.708 (-10.865; 5.449)	0.51
Rotterdam vs Edmonton	-4.080 (-11.970; 3.811)	0.310	-4.365 (-12.279; 3.549)	0.279	-4.168 (-12.145; 3.809)	0.30
Male vs female sex	1.987 (0.306; 3.667)	0.021	1.922 (0.235; 3.609)	0.026	2.058 (0.362; 3.754)	0.017
Right vs left hand preference	0.299 (-2.443; 3.041)	0.830	0.284 (-2.452; 3.020)	0.838	0.526 (-2.236; 3.287)	0.70
Medium vs high STRONGkids risk level[a]	-1.276 (-4.212; 1.660)	0.394	-1.211 (-4.189; 1.766)	0.424	-1.380 (-4.461; 1.700)	0.37
Diagnostic category (as compared with cardiac surgery)						
Surgical						
Abdominal	-1.137 (-4.542; 2.268)	0.512	-1.150 (-4.562; 2.263)	0.508	-1.192 (-4.630; 4.711)	0.496
Burns	2.862 (-4.331; 5.632)	0.643	2.764 (9.451; 14.978)	0.657	1.044 (-11.235; 13.322)	0.867
Neurosurgery - traumatic brain injury	-0.836 (-9.256; 14.980)	0.653	-0.807 (-4.459; 2.846)	0.665	-1.174 (-4.826; 2.477)	0.527
Thoracic	-0.543 (-4.486; 2.813)	0.786	-0.545 (-4.479; 3.390)	0.786	-0.359 (-4.292; 3.575)	0.857
Transplantation	-4.324 (-4.465; 3.379)	0.241	-4.343 (-11.742; 3.056)	0.249	-6.763 (-15.230; 1.770)	0.119
Orthopedic surgery-trauma	-2.478 (-11.568; 2.921)	0.385	-2.524 (-8.144; 3.096)	0.378	-2.685 (-8.333; -2.964)	0.350
Other	0.650 (-4.331; 5.632)	0.798	0.453 (-4.575to 5.480)	0.860	-0.359 (-5.428; 4.711)	0.889

Medical							
Cardiac	0.085 (-5.026; 5.195)	0.974	-0.210 (-5.378; 4.957)	0.936	-0.280 (-5.636; 5.075)	0.918
Gastrointestinal-hepatic	-6.568 (-24.963; 11.828)	0.482	-6.447 (-24.862; 11.968)	0.490	-6.618 (-24.971; 11.734)	0.477
Hematologic-oncologic	-5.302 (-14.848; 4.245)	0.276	-5.263 (-14.876; 4.350)	0.283	-7.950 (-18.288; 2.388)	0.131
Neurologic	-3.142 (-7.219; 0.934)	0.130	-3.122 (-7.217; 0.973)	0.135	-3.883 (-8.063; 0.297)	0.068
Respiratory	-1.308 (-4.669; 2.052)	0.445	-1.575 (-4.970; 1.820)	0.362	-1.416 (-4.878; 2.045)	0.421
Other	-2.207 (-6.608; 2.195)	0.325	-2.468 (-6.881; 1.946)	0.273	-2.788 (-7.433; 1.858)	0.238
Infant (age<1y) vs child at randomization	0.085 (-3.814; -0.112)	0.038	-1.929 (-3.820; -0.039)	0.046	-1.930 (-3.864; 0.003)	0.050
Malignancy vs no malignancy	-1.963 (-1.993; 6.212)	0.313	2.077 (-2.034; 6.188)	0.321	1.233 (-2.948; 5.414)	0.562
Syndrome vs no syndrome[b]	1.045 (-0.206; 1.471)	0.139	0.861 (-2.032; 3.754)	0.559	1.754 (-1.173; 4.682)	0.239
PIM3 score (per point added)[c]	0.632 (-0.118; 0.098)	0.851	0.567 (-0.303; 1.438)	0.201	0.497 (-0.373; 1.367)	0.262
PeLOD score first 24 hrs (per point added)[d]	-0.010 (-5.192; 1.861)	0.353	-0.010 (-0.119; 0.099)	0.854	-0.028 (-0.234; 0.114)	0.498
Known non-European origin vs other[e]	-1.665 (-4.125; 5.649)	0.758	-1.591 (5.129; 1.946)	0.377	-3.444 (-8.677; 1.789)	0.196
Known non-Caucasian vs other[e]	0.762 (-0.483; 4.868)	0.108	0.824 (-4.064; 5.713)	0.739	0.165 (-6.148; 6.479)	0.958
Known not exclusive Dutch or English language vs other	2.192 (-3.814; -0.112)	0.038	2.243 (-0.441; 4.926)	0.101	-2.959 (-6.951; 1.033)	0.146
Socioeconomic status						
Educational level parents (as compared with level 1)[f]						
Educational level 1.5	-0.738 (-6.223; 4.747)	0.792	-0.787 (-6.313; 4.739)	0.780	0.169 (-5.412; 5.751)	0.952
Educational level 2	0.941 (-3.973; 5.855)	0.707	1.121 (-3.845; 6.087)	0.657	1.720 (-3.280; 6.719)	0.499
Educational level 2.5	-2.784 (-7.912; 2.345)	0.286	-2.608 (-7.774; 2.557)	0.321	-2.013 (-7.196; 3.171)	0.445
Educational level 3	-4.599 (-9.875; 0.678)	0.087	-4.448 (-9.759; 0.862)	0.100	-3.841 (-9.179; 1.497)	0.157
Educational level unknown	-1.506 (-6.824; 3.813)	0.578	-1.378 (-6.726; 3.970)	0.612	-0.718 (-6.076; 4.640)	0.792

Occupational level parents (as compared with level 1)[g]						
Occupational level 1.5	-2.079 (-10.773; 6.615)	0.639	-2.325 (-11.046; 6.397)	0.601	-3.048 (-11.746; 5.650)	0.492
Occupational level 2	0.088 (-8.613; 8.789)	0.984	-0.177 (-8.922; 8.568)	0.968	-0.847 (-9.576; 7.883)	0.848
Occupational level 2.5	-2.387 (-11.413; 6.639)	0.604	-2.712 (-11.774; 6.351)	0.557	-3.471 (-12.537; 5.595)	0.452
Occupational level 3	0.527 (-8.275; 9.329)	0.906	0.344 (-8.483; 9.171)	0.939	-0.141 (-8.941; 8.660)	0.974
Occupational level 3.5	-0.920 (-10.204; 8.365)	0.846	-1.190 (-10.505; 8.125)	0.802	-1.568 (-10.882; 7.746)	0.740
Occupational level 4	-1.592 (-10.639; 7.454)	0.730	-1.904 (-10.989; 7.181)	0.681	-2.735 (-11.812; 6.341)	0.554
Occupational level unknown	-0.963 (-9.764; 7.838)	0.830	-1.260 (-10.107; 7.587)	0.780	-1.575 (-10.400; 7.251)	0.726
Parental smoking between birth and PICU admission vs. no smoking	1.797(-0.309; 3.903)	0.094	1.781 (-0.332; 3.893)	0.098	1.895 (-0.203; 3.993)	0.076
New infection vs no new infection			-0.648 (-3.674; 2.378)	0.674	-2.044 (-5.248; 1.160)	0.210
Duration of stay in the PICU (per day added)			0.046 (-0.077; 0.170)	0.461	0.086 (-0.187; 0.359)	0.536
Days with hypoglycemic event (per day added)			-0.231 (-1.904; 1.441)	0.786	-0.449 (-2.265; 1.367)	0.627
Duration of mechanical ventilatory support (per day added)			-0.008 (-0.174; 0.158)	0.924	-0.057 (-0.237; 0.122)	0.527
Duration of treatment with antibiotics (per day added)					-0.096 (-0.355; 0.163)	0.466
Duration of hemodynamic support (per day added)					0.017 (-0.168; 0.202)	0.859
Duration of treatment with corticosteroids (per day added)					0.244 (-0.077; 0.566)	0.135
Duration of treatment with opioids (per day added)					-0.015 (-0.266; 0.236)	0.906
Duration of treatment with benzodiazepines (per day added)					0.176 (-0.073; 0.425)	0.646
Duration of treatment with hypnotics (per day added)					0.214 (-0.038; 0.466)	0.095
Duration of treatment with alpha-2-agonists (per day added)					-0.273 (-0.504; -0.043)	0.020

For internalising problems as reported by parents, higher scores reflect more problems. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19] b A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3) c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21] d Paediatric Logistic

Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20] e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[22] f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4). g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4).[18] PeLOD, paediatric logistic organ dysfunction score; PICU, paediatric intensive care unit; PIM3, paediatric index of mortality 3 score; PN, parenteral nutrition.

Table S3-3. Multivariable linear regression analyses determining significant and independent associations between risk factors and total emotional and behavioural problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		**Model further adjusted for acute effects of late-PN vs early-PN**		**Model further adjusted for post-randomization treatment effects**	
Variable	**β estimate (95% CI)**	**P-value**	**β estimate (95% CI)**	**P-value**	**β estimate (95% CI)**	**P-value**
Randomization to late vs early initiation of PN	*-2.442 (-3.433; -0.028)*	*0.046*	*-2.242 (*-4.043; -0.4043)	*0.015*	*-2.163 (-3.960; -0.365)*	*0.019*
Centre						
Leuven vs Edmonton	-2.834 (-11.275; 4.886)	0.438	-2.687 (-11.115; 5.742)	0.531	-2.172 (-10.667 6.324)	0.616
Rotterdam vs Edmonton	-2.360 (-11.970; 3.811)	0.310	-2.476 (-10.732; 5.742)	0.556	-2.506 (-10.848; 5.837)	0.555
Male vs female sex	1.483 (0.306; 3.667)	0.021	1.411 (-0.360; 3.183)	0.118	1.558 (-0.224; 3.339)	0.086
Right vs left hand preference	0.019 (-2.443; 3.041)	0.830	-0.067 (-2.865; 2.731)	0.962	0.190 (-2.625; 3.004)	0.894
Medium vs high STRONGkids risk level[a]	-2.630 (-4.212; 1.660)	0.394	-2.369 (-5.452; 0.713)	0.132	-2.445 (-5.610; 0.721)	0.130
Diagnostic category (as compared with cardiac surgery)						
Surgical						
Abdominal	-0.652 (-4.542; 2.268)	0.512	-0.679 (-4.249; 2.891)	0.709	-0.703 (-4.301; 2.895)	0.701
Burns	1.540 (-9.256; 14.980)	0.643	0.682 (-12.001; 13.365)	0.916	-0.229 (-12.993; 12.536)	0.972
Neurosurgery - traumatic brain injury	0.503 (-4.486; 2.813)	0.653	0.433 (-3.290; 4.157)	0.819	0.086 (-3.633; 3.805)	0.964
Thoracic	-1.323 (-4.465; 3.379)	0.786	-1.354 (-5.435; 2.727)	0.515	-1.091 (-5.197; 3.015)	0.602
Transplantation	-2.856 (-11.568; 2.921)	0.241	-3.506 (-11.188; 4.176)	0.370	-4.678 (-13.497; 4.141)	0.298
Orthopedic surgery-trauma	-0.542 (-8.086; 3.129)	0.385	-0.778 (-6.692; 5.137)	0.796	-0.892 (-6.840; 5.056)	0.768
Other	0.705 (-4.331; 5.632)	0.798	0.379 (-4.881; 5.640)	0.887	-0.426 (-5.742; 4.891)	0.875
Medical						

Cardiac	-1.239 (-5.026; 5.195)	0.974	-1.771 (-7.124; 3.582)	0.516	-1.964 (-7.501 ; 3.573)	0.486
Gastrointestinal-hepatic	-5.844 (-24.963; 11.828)	0.482	-5.716 (-24.994; 13.563)	0.559	-5.919 (-25.143; 13.305)	0.544
Hematologic-oncologic	-5.495 (-14.848; 4.245)	0.276	-5.668 (-15.844; 4.507)	0.274	-7.908 (-18.814; 2.998)	0.155
Neurologic	-4.072 (-7.219; 0.934)	0.130	-3.963 (-8.229; 0.303)	0.069	-4.661 (-9.032; -0.289)	0.037
Respiratory	-2.226 (-4.669; 2.052)	0.445	-2.311 (-5.835; 1.214)	0.198	-2.282 (-5.887; 1.323)	0.214
Other	-2.103 (-6.608; 2.195)	0.325	-2.285 (-6.863; 2.293)	0.327	-2.352 (-7.170; 2.466)	0.338
Infant (age<1y) vs child at randomization	-4.487 (-3.814; -0.112)	0.038	-4.406 (-6.347; -2.464)	<0.001	-4.536 (-6.517; -2.553)	<0.001
Malignancy vs no malignancy	3.260 (-1.993; 6.212)	0.313	3.273 (-0.978; 7.524)	0.131	2.827 (-1.492; 7.145)	0.199
Syndrome vs no syndrome[b]	2.110 (-1.819; 3.909)	0.474	1.892 (-1.198; 4.983)	0.229	2.610 (-0.519; 5.738)	0.102
PIM3 score (per point added)[c]	0.582 (-0.206; 1.471)	0.139	0.450 (-0.451; 1.351)	0.327	0.375 (-0.527; 1.276)	0.414
PeLOD score first 24 hrs (per point added)[d]	-0.007 (-0.118; 0.098)	0.851	-0.014 (-0.128; 0.100)	0.807	-0.029 (-0.144; 0.086)	0.615
Known non-European origin vs other[e]	-0.459 (-5.192; 1.861)	0.353	-0.513 (-4.143; 3.118)	0.781	-0.575 (-4.201; 3.050)	0.755
Known non-Caucasian vs other[e]	-0.943 (-4.125; 5.649)	0.758	-0.850 (-5.866; 4.166)	0.738	-0.582 (-5.609; 4.445)	0.819
Known not exclusive Dutch or English language vs other	1.987 (-0.483; 4.868)	0.108	2.172 (-0.532; 4.876)	0.115	2.133 (-0.572; 4.837)	0.122
Socioeconomic status						
Educational level parents (as compared with level 1)[f]						
Educational level 1.5	-1.687 (-6.223; 4.747)	0.792	-1.543 (-7.337; 4.252)	0.601	-0.819 (-6.677; 5.040)	0.784
Educational level 2	-0.445 (-3.973; 5.855)	0.707	-0.095 (-5.296; 5.106)	0.971	0.126 (-5.125; 5.377)	0.962
Educational level 2.5	-4.285 (-7.912; 2.345)	0.286	-3.979 (-9.365; 1.407)	0.147	-3.577 (-9.000; 1.846)	0.195
Educational level 3	-5.469 (-9.875; 0.678)	0.087	-5.138 (-10.638; 0.362)	0.067	-4.864 (-10.405; 0.677)	0.085
Educational level unknown	-2.716 (-6.824; 3.813)	0.578	-2.467 (-8.024; 3.091)	0.383	-2.127 (-7.708; 3.453)	0.453
Occupational level parents (as compared with level 1)[g]						

Occupational level 1.5	1.882 (-10.773; 6.615)	0.639	1.757 (-7.374; 10.888)	0.706	1.105 (-8.007; 10.217)	0.812
Occupational level 2	1.570 (-8.613; 8.789)	0.984	1.513 (-7.619; 10.644)	0.745	0.781 (-8.335; 9.897)	0.866
Occupational level 2.5	-0.537 (-11.413; 6.639)	0.604	-0.636 (-10.101; 8.829)	0.895	-1.220 (-10.689; 8.248)	0.800
Occupational level 3	1.799 (-8.275; 9.329)	0.906	1.736 (-7.453; 10.925)	0.711	1.242 (-7.921; 10.405)	0.790
Occupational level 3.5	1.154 (-10.204; 8.365)	0.846	1.011 (-8.701; 10.723)	0.838	0.678 (-9.025; 10.381)	0.891
Occupational level 4	0.701 (-10.639; 7.454)	0.730	0.546 (-8.937; 10.028)	0.910	-0.254 (-9.721; 9.214)	0.958
Occupational level unknown	1.571 (-9.764; 7.838)	0.830	1.481 (-7.699; 10.661)	0.751	1.142 (-8.012; 10.296)	0.806
Parental smoking between birth and PICU admission vs. no smoking	1.450 (-0.309; 3.904)	0.094	1.451 (-0.677; 3.579)	0.181	1.571 (-0.547; 3.689)	0.146
New infection vs no new infection			1.215 (-1.941; 4.370)	0.450	-0.185 (-3.501; 3.131)	0.913
Duration of stay in the PICU (per day added)			0.057 (-0.071; 0.186)	0.380	0.105 (-0.180; 0.389)	0.471
Days with hypoglycemic event (per day added)			-0.343 (-2.051; 1.366)	0.694	-0.517 (-2.380; 1.346)	0.586
Duration of mechanical ventilatory support (per day added)			-0.046 (-0.218; 0.127)	0.601	-0.080 (-0.266; 0.107)	0.401
Duration of treatment with antibiotics (per day added)					-0.115 (-0.386; 0.155)	0.402
Duration of hemodynamic support (per day added)					-0.017 (-0.209; 0.174)	0.858
Duration of treatment with corticosteroids (per day added)					0.166 (-0.161; 0.493)	0.320
Duration of treatment with opioids (per day added)					-0.054 (-0.317; 0.210)	0.690
Duration of treatment with benzodiazepines (per day added)					0.277 (0.011; 0.543)	0.041
Duration of treatment with hypnotics (per day added)					0.134 (-0.129; 0.398)	0.316
Duration of treatment with alpha-2-agonists (per day added)					-0.281 (-0.523; -0.039)	0.023

For total emotional and behavioural problems as reported by parents, higher scores reflect more problems. a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19] b A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3) c Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21] d Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20] e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[22] f The education level is the average of the paternal and maternal

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Table S4. Comparison of patients randomised to late-PN during PICU stay with healthy control children for the tests significantly affected by the randomised intervention

Neurocognitive testing	**P-value**
Internalising problems as reported by parents/caregivers	0.103
Externalising problems as reported by parents/caregivers	0.313
Total behavioural and emotional problems as reported by parents/caregivers	0.085

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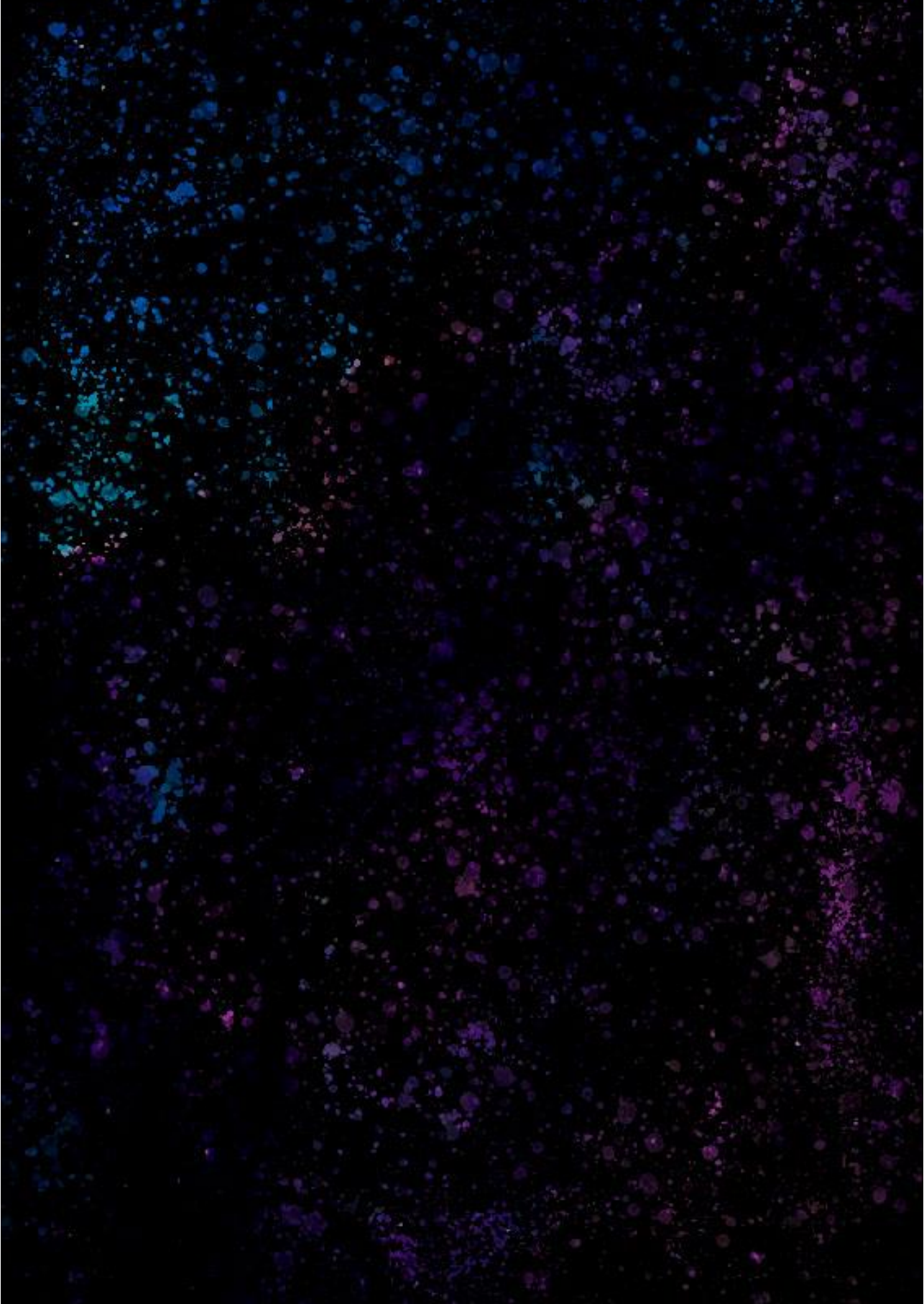
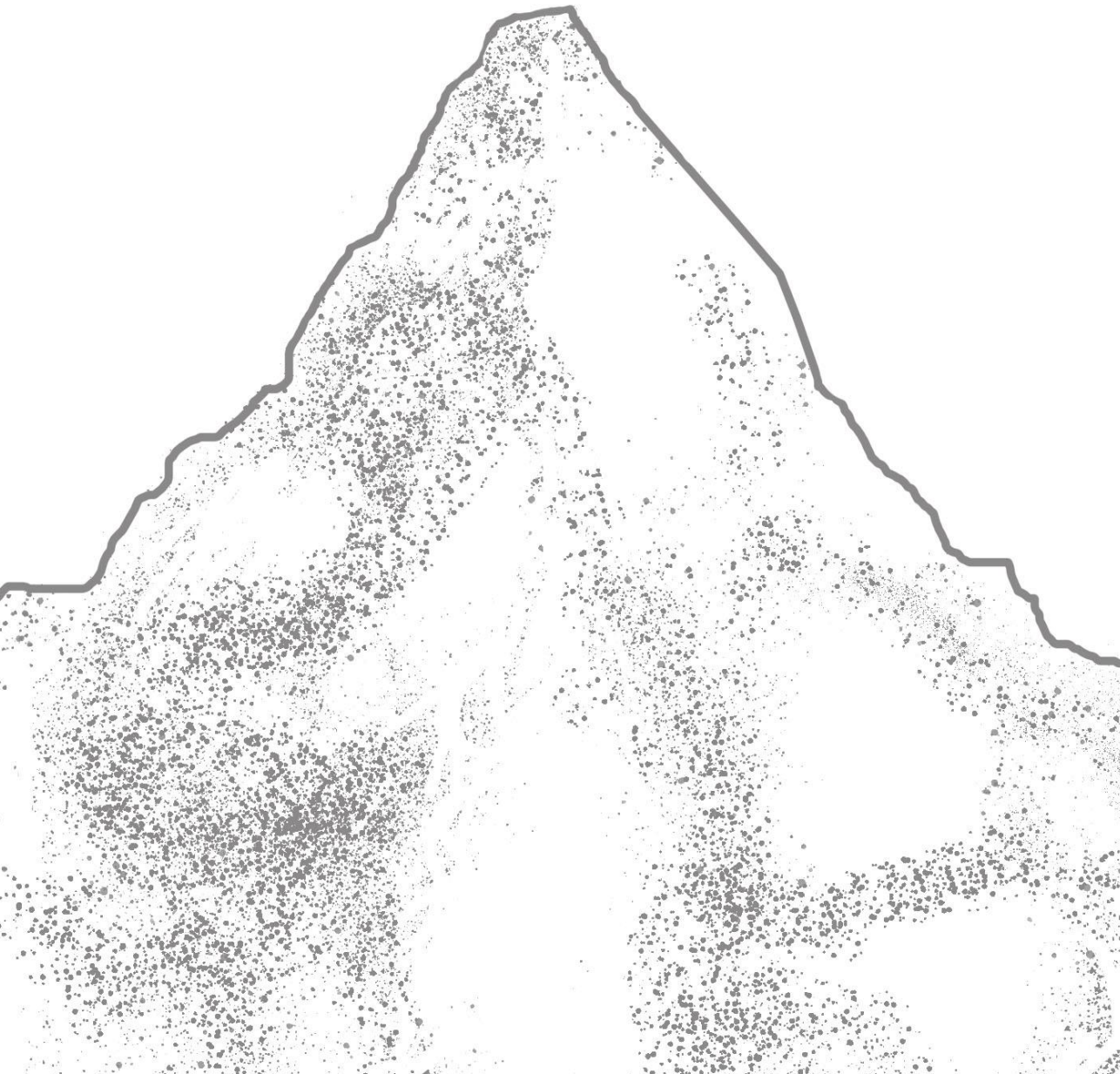


PART V

CHAPTER 13
GENERAL DISCUSSION



INTRODUCTION

Optimal nutritional support in critical illness remains controversial and this thesis highlighted several important considerations in the ongoing debate; what is optimal nutrition in critically ill children? The primary focus was to provide more insight in nutritional therapy for critically ill children concerning the route, timing and amount during acute, stable and recovery phase, with a special focus on a conceptual insight of the barriers to provide such optimal nutrition. Major barriers who were thought to inhibit enteral intake achievement during the different phases of illness, and management of these barriers, were investigated i.e. feeding intolerance, fluid restriction and non-invasive ventilator support.[1]

Then, if we are able to overcome these barriers, the question concerning the optimal amount during the different phases arises. The knowledge of the neuro-endocrine stress response is critical for the nutritional recommendations. During the acute phase (parenteral) nutrient restriction appears beneficial for short-term and long-term outcome, while during stable and recovery phase inclining nutrient intake should be considered.

Identification of barriers on the PICU

To allow an early identification of barriers for enteral nutrition (EN) during PICU admission, a paediatric quality improvement survey tool was developed. We executed a survey among 920 physicians, nurses and dieticians across 57 countries which showed that many perceived barriers to enteral feeding are still an important concern in PICUs worldwide (Chapter 2). This survey tool did not only focus on the patient related factors, but included possible barriers in the organisation and infrastructure. The main perceived barriers for EN delivery in PICU were related to feeding interruptions around procedures, lack of dietician coverage, inadequate training and education on multiple levels. These appear to be caused by a general lack of prioritization of nutrition during paediatric critical illness. More education in recognizing and resolving PICU related barriers and training of staff abilities are key, whereby the individual role of the physician, nurse and dietician should be determined. Hence, future education and interventions to improve nutritional support must involve all three health care professions as well as an active role in addressing these barriers. With improved education, prioritizing and infrastructure we will finally be able to address difficult barriers and misconceptions around longstanding perceived barriers such as feeding intolerance, fluid restriction and non-invasive ventilator support; and strategies to overcome these barriers.

Feeding intolerance

Feeding intolerance with a median prevalence of 19% is a highly relevant problem in achieving enteral intake, and is presumed to have a considerable impact on morbidity and mortality during critical illness (Chapter 4). Still, feeding intolerance is perceived differently from health care professional to health care professional, and assessment of feeding intolerance is in clinical practise largely based upon the amount of gastro residual volume

(GRV), despite the lack of evidence supporting this bed-side decision making process.[2,3] A GRV below cut-off thresholds or a single presentation of vomiting often results in withholding EN, whereas it is questionable if this is justified. Studies comparing PICU sites with and without routine GRV measurements did not find differences in aspiration or complications, while it did result in lower EN intake.[4,5]

Our systematic review revealed numerous definitions of feeding intolerance in the literature all using different parameters. The inconsistent use of signs and symptoms to define feeding intolerance limits the ability to find causes and identify strategies to overcome feeding intolerance. Based upon this systematic review, we proposed a definition to be used in future research, which includes the presence of vomiting, diarrhoea, large GRV and abdominal distention/ischemia together with the inability to enhance enteral feeding (Chapter 4). A uniform evaluation is key to not only identify whether feeding intolerances truly exist, moreover, it is a tool to start to unravel this descriptive term.

Feeding intolerance may be considered a symptom of yet another organ failing during critical illness. The gastrointestinal tract comprises of more than its nutrient absorption and digestion function and plays an important role in the first line immunologic defence and gut-brain-microbiome axis. The underlying question here is what feeding intolerance comprises. As most research is focussed on nutrient absorption, we fail to incorporate these other essential functions, which both presumably have a considerable impact on the patient, into one overall organ dysfunction. By focussing on only one mechanism we remain incapable to comprehend the complete pathophysiological mechanisms.[6]

Also, whether gastrointestinal failure independent of enteral nutrition intake determines clinical outcomes remains in interesting question. Hence, more detailed knowledge on the short-term and long-term health consequences of these major gastrointestinal functions is required. Moreover, an early identification and management is key in optimizing EN support.

Mechanism behind feeding intolerance

Both the gastrointestinal morphology and function can be altered leading to feeding intolerance.[7] Having a better understanding of the pathophysiology of feeding intolerance during the different phases of critical illness may lead towards novel diagnostic and therapeutic management.

Motility

Important pathophysiologic parameters of feeding tolerance are delayed gastrointestinal motility, intestinal inflammation and decreased enterocyte function. In health, gastric emptying is regulated by a network of neural and humoral (circulating or hormonal) mechanisms which modulate the intrinsic myogenic activity. The motility is evoked by depolarisation initiated by a network of interstitial cells embedded in the GI tract.[8] The activity of the gut is different between fasting and fed state. During fasting state the gut

enters in several phases migrating the nutrients along the gastrointestinal tract.[9,10] The vagus nerve plays an important extrinsic influence and can increase the motility via parasympathetic pathway. Furthermore, numerous hormones are related to the gut motility i.e. ghrelin, motilin, secretin, neurotensin, gastrin, gastrin-releasing peptide, cholecystokinin, peptide YY and glucagon like peptide-1. Dysfunction of these gastrointestinal hormones, identified by altered plasma levels, have been associated with feeding intolerance in non-critically ill populations. There are also indications that these hormones are altered during paediatric critical illness,[11-16] however, our systematic review showed that studies relating these hormone profiles with feeding intolerance are sparse and highly needed (Chapter 4).

In critical ill patients presenting with delayed gastric emptying, the upper gastrointestinal tract is frequently impaired in both the fasting and fed state.[9,10,17] Abnormal functions seen during the fed state are often contributed to the somatic function i.e. delayed fundal relaxation, reduced antral motility and increased isolated pyloric activity. These abnormalities are already pronounced when minimal amounts of nutrients are provided.[18] The duodenal function often remains, however this may be disorganised and even showing retrograde peristaltic contractions.

Gut integrity

Other mechanisms affecting feeding intolerance are the intestinal enterocyte function or inflammation. Besides the absorption of nutrients the gut plays in important role in the body's first line immunologic defence. There are reports that during critical illness the gut integrity is disrupted with hyperpermeability and increased epithelial apoptosis, with decreased epithelial proliferation and mucus integrity.[19,20] Furthermore, there is a direct correlation between thinning of the mucus layer and reduction of villus height, making the intestinal epithelium more exposed to injury from digestive enzymes.[21]

Several hypothesis have been formed on how the association between disrupted gut integrity and sepsis and organ failure exist. The general hypothesis is via direct translocation of intact bacteria into the systemic circulation, however, the evidence surrounding this hypothesis is mainly from preclinical models.[22,23] A new theory hypothesised that the effect on organ failure occurs from toxic mediators migrating from the gut travel via the mesenteric lymphatics into the system causing among others severe long damage.[24,25]

Several markers have been identified in association with impaired gastrointestinal function and inflammation in non-critically ill children such as citrulline, Intestinal fatty-acid binding protein (I-FABP), Clauding-3 and faecal calprotectin or faecal interleukin (IL)-8. As discussed in Chapter 4, abnormal concentrations of these gastrointestinal hormones have been found in critically ill children,[11,15] especially presenting with feeding intolerance, indicating the importance of these hormones as a possible mediator.

Microbiome

The gut microbiome plays an important role in the synthesis and absorption of macro- and micronutrient and production of short-chain fatty acids. Studies show that the microbiome is severely altered during illness due to the use of antibiotics, intestinal ischemia, fasting or altered EN, infections and abnormal intestinal motility, into a virulent pathobiome, inhibiting its normally health promoting function.[19,26,27] Faecal samples from critically adults patients collected at admission and discharge showed fast deterioration of the health-promoting organisms with overgrowth of pathogens as compared with healthy subjects, which makes patients vulnerable for new acquired infections, sepsis, and organ failure.[28,29]

Gut-brain-microbiome axis

Though still unrecognised during critical illness, there seems to be a bidirectional pathway between the central and enteric nervous system affecting the emotional and cognitive centres of the brain (figure 1). Recent evidence suggest that the gut microbiome plays in central role in this interaction and it is known to influence anxiety, depression, cognition and visceral pain recognition.[30,31] Because of its many functions, i.e. nutrient absorption, immune system and microbiome, the gut has been hypothesised to be the "motor" of the systemic inflammatory response in critical illness.[19,20,32,33]

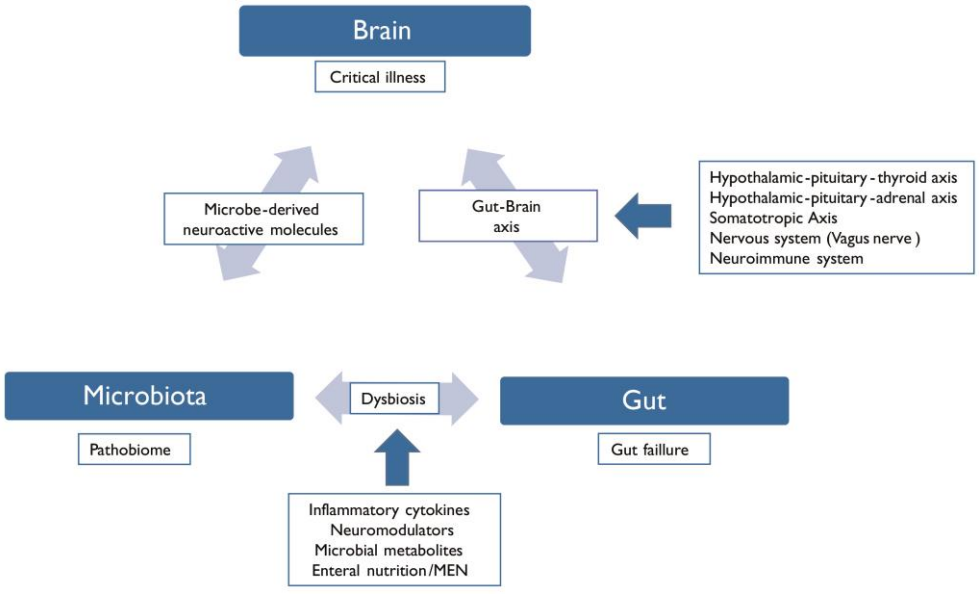


Figure 1. The brain-gut-microbiome axis

Bidirectional interactions between the brain, gut and microbiome. Interactions entail the central nervous system, gastrointestinal system, endocrine system and immune systems combined. MEN, minimal enteral nutrition

Preservation of the gastrointestinal functions

Enteral nutrition is considered safer, more physiological and protective for gastrointestinal mucosal integrity and motility as compared with parenteral nutrition (PN).[34,35] Maintenance of gut integrity is presumable an important indicator for the beneficial effect of EN. Prolonged enteral fasting leads to negative consequences on intestinal morphology and microbial diversity possible leading to feeding intolerance.[36] Even short-term fasting may impact the function of Paneth cells, allowing to an increase in bacterial translocation and following its infectious consequences.[37] Paneth cells are located in the small intestine and are important in the production of antimicrobial proteins in the gut. EN generally consisted of processed liquid formulas with limit microbial diversity. These formulas are often absorbed in the proximal part of the gastrointestinal tract leaving the distal tract open for the severe consequences of fasting. Therefore, EN is less effective in comparison to an oral diet. Nonetheless, even trophic feeding, the practice of feeding small volumes of enteral feed termed as minimal enteral nutrition (MEN), is thought to already stimulate normal enzyme activity, hormone release, blood flow, motility and microbial flora, and the development of the immature gastrointestinal tract in infants. Unfortunately, there is currently no evidence indicating the minimum or maximum amount of EN needed to maintain gastrointestinal integrity, Paneth cell function and minimise the risk of harm and positively affect outcomes.

Identification of dysbiosis during illness in faecal samples may lead to novel treatment options. Adding antioxidants or probiotics to EN could hypothetically limit the development of a pathobiome, however, thus far it has not led to an altered feeding intolerance symptomology in critically ill children (Chapter 4). Researchers have called this strategy rather naïve, as the complex microbiome cannot be saved by adding only a few commensal probiotic organisms.[38] Although the *Firmicutes* and *Bacteroidetes* microorganism have the largest impact on gut integrity and might be a promising place to start. Furthermore, faeces microbiota transplantations are increasingly used in the non-critically ill population to adapt the microbiome. In critically ill patients only 4 case reports were published, making it impossible to form any premature conclusions.[39]

Fluid restriction

Fluid restriction due to renal, hepatic, or cardiac failure often precludes the use of large fluid volumes and the ability to achieve feeding goals either enteral or parenteral. Our survey showed that 29% of the respondents classified severe fluid restriction as an important barrier for EN (Chapter 2) ranking this barrier 6 out of 25 possible barriers.

During stable and recovery phase protein and energy-dense formula may be considered to support achievement of nutritional requirements to allow normal development, growth and preservation of lean body mass (Chapter 6). This formula allowed for a lower fluid intake deriving from EN, while maintaining target caloric and macronutrient intake. In Chapter 7 we examined 70 critically ill infants receiving protein and energy-dense formula for at least

14 days and found that realising the target of approximately 2 times of resting energy expenditure (REE) was possible. This resulted in normal growth as comparable with healthy subjects and even a significant weight-for-age z-score of +0.48 enabling catch-up growth in the majority of infants. These findings have yet to be extrapolated to older children.

There are some signs that dense formulas affect nutrients absorption by delaying gastric emptying.[40] However, previous observational studies in critically ill children have seen similar tolerance when compared to standard polymeric feeding.[41,42] In our study (Chapter 7), limited gastrointestinal symptoms occurred, comprising of large GRV, vomiting, diarrhoea and obstipation while using protein and energy-dense formula. However, comparison with standard formula regarding these gastrointestinal symptoms were not made in this particular study.

There is still a paucity of evidence favouring specific feeding formulas in critically ill children. In general, nutritional studies focus on the first period after admission. This is unfortunate as much harm can be caused by prolonged underfeeding of overfeeding during stable and recovery phase. Thus, when strict fluid restriction or feeding intolerance inhibits full enteral feeding in children, protein and energy dense-formula should be considered.

Non-invasive ventilation

Non-invasive ventilator support (e.g. high-flow nasal cannula, bilevel positive airway pressure and continuous positive airway pressure) is often perceived as a barrier to start or incline EN by clinicians due to the suggested increased risk for pulmonary aspiration and potential need for intubation. Our multicentre retrospective cohort study showed that, although there was a large centre difference in ventilatory support and feeding protocol, children admitted to the PICU tolerated feeding well, with relatively limited feeding related complications or presence of gastrointestinal symptoms (Chapter 3). Especially the occurrence of respiratory aspiration was rare, however, further prospective trials are needed to determine both the optimal timing and feeding method in critically ill children receiving non-invasive ventilatory support.

Medication

Several medications are known to influence gastrointestinal motility, including sedatives, analgesics, antibiotics and vasoactive drugs administered to critically ill patients, can potentially affect gastrointestinal motility. Analgesics (opioids) impact gastric emptying and upper gastrointestinal tract through the central and peripheral opioid receptors, whereas sedatives delay gastric emptying, increase gastrointestinal transit time, and affect the gastrointestinal motility. Subsequently, gastrointestinal symptoms such as vomiting may also be a sign of factors not related to the gastrointestinal function such as sedation withdrawal with subsequent agitation, rather than a direct results of sedative on feeding intolerance and delayed gastric emptying.[43] Our study showed that children who received antibiotics had an overall lower enteral intake (Chapter 5). Antibiotics play a role in many aspects of critically

illness, apart from the relationship with inflammation, it can have both a pro-kinetic function and results in negative effects such as diarrhoea. Moreover, the effect on the impoverishment of the microbiome has been established in multiple studies all contribution to worse outcomes.[27,44,45] The "motor" of the gut is also controlled by the adrenergic and dopaminergic nerve system, thereby catecholamines can lead to feeding intolerance. Often these drugs are prescribed simultaneously and are associated with the degree of illness. After correction for confounders, the provision of inotropic agents as compared with antibiotics, sedatives and analgesics was found to influence EN intake the most (Chapter 5).

Management of barriers

Numerous factors contribute to the pathogenesis of feeding intolerance, meaning that approaches to its prevention and management are most likely multifaceted.

Medication

In addition to medication causing feeding intolerance, they also serve a role in its therapeutic management. Dopamine receptor antagonists (metoclopramide and domperidone), motilin agonists (erythromycin) and 5-HT4 receptor agonists (prucalopride) promote gastrointestinal motility.[46] Although not uncommonly used in critically ill children, current RCTs in paediatric critical care are lacking to support the use of drugs to reduce feeding intolerance. Moreover, these drugs may have serious side effects in young children. Novel prokinetic agents such as opiate receptor antagonists, CCK receptor antagonist and Ghrelin agonist have (hypothetical) promising effects, however, the efficacy of in the management of feeding intolerance has not been formally assessed during critical illness.[47]

Post-pyloric feeding

There is ongoing debate on the optimal feeding route in critically ill children. Enteral nutrition, via nasogastric tube, is often perceived to lead to large GRV and pulmonary aspiration in children who are intolerant to feeding, increasing the risk of nosocomial pneumonia. These risks may be decreased when using a post-pyloric feeding tube. However, the difficulty of inserting a post-pyloric feeding tube may cause a delayed start with subsequent inability to achieve nutritional targets.[48,49]

Based on the lack of evidence favouring a specific route and the difficulties of inserting a post-pyloric tube, recent guidelines did not indicate that post-pyloric feeding is superior to gastric feeding.[50-53] Nevertheless, in centres with sufficient expertise and training, post-pyloric feeding was associated with a higher achievement of nutritional goals as compared with gastric feeding (Chapter 5). Although this finding was corrected for confounders, this conclusion still pertains to observational research and could be subjected to bias. However, strengths of this study were the multicentre nature and the large cohort size (n=690). The higher achievement of EN via post-pyloric route in Chapter 5 is pertained to the acute phase of illness, whether this therapy is also more successful in the stable and recovery phase remains speculative.

It is remarkable that there is currently only one RCT investigating feeding intolerance in gastric versus post-pyloric feeding in 74 critically ill children. In contradiction to observational studies, this RCT found no significant differences for aspiration, vomiting, diarrhoea or abdominal distention, which could lie in the small number of participants. In children with a successful post-pyloric tube placement a higher achievement of caloric goals was possible, however, in 29% of the children tube placement was unsuccessful.[54] Additional training to health care professional is highly needed to improve the success of post-pyloric tube placement, which consequently could improve enteral intake.

Feeding formula

A possible strategy to overcome feeding intolerance is the changing the type of feeding. Adding fibre or switching to peptide feeding (Chapter 8) are relative easy and non-invasive strategies which have been explored in observational studies. Peptide feeding is frequently used in children suffering from cow's milk allergy, but also in medical conditions without evidence-based research supporting its use.[55] In our multicentre observational study, protein and energy-dense peptide feeding was feasible and safe in 50 critically ill infants, however, the study did not compare this formula with other types of formula (Chapter 8). A retrospective observational study in critically ill children investigating signs of feeding intolerance before and after implementation from peptide to polymeric diet identified no differences. Currently, expert consensus stated that polymeric feeding is first choice and peptide feeding should be considered to improve tolerance and advancement of enteral feeding in children who present with signs of intolerance to polymeric feeding.[51] In addition, diarrhoea can be treated or prevented by adding fibres to the feeding formula, with a gaining interest for specific fibre blends, including soluble fibres and prebiotics.[56]

Overcoming barriers

For decades it was believed that low enteral intake resulted in worse clinical outcomes, as many observation studies showed an association between these two factors.[57,58] Therefore, research has focussed on removing barriers to allow a higher intake. This viewpoint has been challenged in the current debate on the nutritional requirements during paediatric critical illness.

The investigated barriers might be related to different concepts and as such be addresses in a different way. Barriers such as non-invasive ventilation and delays in gaining small bowel excess are partially the results of inadequate education and knowledge and should be addresses as such.

Feeding intolerance and the inability to achieve enteral intake might be an adaptive response to stress. Interfering with this adaptive response to stress, by adding more nutrient content than the body can metabolise, could potentially even have harmful consequences. This leaves the question, if we can improve the management of barriers, should we?

What are optimal nutritional targets?

When discussing nutritional requirements during paediatric critical illness it is probably essential to take the phase of illness into account. Although arbitrarily, these phases of illness are divided into three phases; acute, stable and recovery. During the acute phase the body turns into a catabolic state altering its energy expenditure and use of energy substrates.[59] During stable and recovery phase the catabolic response adapts into an anabolic state restoring the protein balance.

The acute phase

This phase is characterised by protein wasting and loss of lean body mass, leading to increases impaired morbidity and mortality. Nutritional support was thought to partially ameliorate protein wasting during the catabolic response and historically artificial nutrition, including EN and PN, was recommended to be provided as early as possible and as high as possible.

Enteral nutrition

The guidelines and recommendations have changed substantial over the past years, however, they still pertain to observational research. The new guidelines recommend to achieve 67%-100% of REE via EN by the end of the first week.[50,51,53,60]. Moreover, there is a strong consensus to start artificial nutrition via enteral route with an early initiation (< 24-48 hours) i.e. for the maintenance of gut integrity. This advice is primarily based upon low grade evidence were an earlier and higher achievement of nutritional targets is associated with improved outcome in observational designs, without incorporating the heterogeneity of the PICU population and variances in the severity of illness.[57,58,61-63] Furthermore, the beneficial effect of early and higher EN has been found in animal models and laboratory studies using surrogate outcome markers.[42,64-71] However, the conclusions made from these observational and laboratory studies need to be carefully interpreted due to unmeasured confounders.

The observational designs on which the guidelines are based need careful interpretation, as association does not imply proof for causation. Additionally, when many variables need to be taken in to account in the analyses, spurious associations may occur. The magnitude of illness deterioration is associated to the amount of feeding intolerance,[17,72] as critically ill children who are able to achieve higher feeding goals, might have an overall lesser amount of organ failure and thereby inherently have an improved outcome. To avoid premature conclusions between EN intake and improved outcome, confounding variables contributing to enteral adequacy such as age, diagnosis, malnutrition, type and method of feeding, medication, systemic laboratory inflammation markers and illness severity scores should be encountered (Chapter 5). Previous observational paediatric studies fail to correct for these important confounders and there are currently no RCT's published addressing different macronutrient contents or artificial nutrition targets to improve outcome in children.

Chapter 5 shows that during the acute phase, higher achievement of nutritional targets via EN was no longer beneficial after multivariable correction for these important confounders. This provides a new hypothesis whereby achieving high caloric goals early during critical illness does not automatically result in favourable outcomes; and even that the use of trophic feeding and permissive underfeeding may be beneficial. This hypothesis is supported by a small retrospective study showing improved outcomes with underfeeding as compared with overfeeding.[73] This might be partially related to the adverse outcomes of the inability to use the exogenous substrates. Thereby, in the acute phase, energy intake provided to critically ill children should not exceed the metabolic abilities of the patients. Unfortunately, causal evidence on the optimal EN target in critically ill children is lacking.

Systemic inflammation

In Chapter 5 we showed that the degree of illness severity assessed by validated scores and systemic inflammation markers were associated with the amount of enteral intake. This finding supports previous studies associating illness severity with enteral intake or with the presence of gastrointestinal symptoms.[17,58,72] Whether this reflects a causal link or merely adaptation to the underlying illness remains a topic of debate.

An induced epithelial apoptosis is found in patients with sepsis together with a decrease in crypt proliferation, which reduces the nutrient absorption function of the gut, but also the first line defence mechanism allowing systemic inflammation.[20,32,33] This alteration was also found in patients with non-infectious inflammation such as trauma, burns, and haemorrhage. Hence, systemic inflammation should be seen as more than a just simple confounder.

As systemic inflammation could be one of the indicators for gastrointestinal organ failure, this may be incorporated into the bed-side decision around feeding practices. However, a more complete picture including biomarkers for gut motility and integrity is needed to allow individual targeted nutritional support.

Specific populations

The PICU population is quite heterogeneous, whereby specific populations may respond differently to nutritional interventions. For instance, patients admitted after traumatic brain injury often experience large GRV and vomiting due to the increased intracranial pressure to delay gastric motility via the autonomic nervous system.[74] In our study we found that admission for neurology or neurosurgery led to normal or higher intake (Chapter 5). Children admitted due to gastrointestinal surgery were the only subgroup which significant lower EN intake, which is likely influenced by the clinician or surgeon deeming the gut unsuitable or contraindicated for feeding rather than actual feeding intolerance.

Based upon low grade evidence, guidelines currently only recommend to postpone or withhold early EN in hemodynamically instable patients with a high risk of impaired splanchnic perfusion and subsequent bacterial translocation or gut ischemia.[50-53] Conversely,

delaying EN in instable patients may lead to undernutrition and reduction of this gastrointestinal barrier function. Both sides have been associated with poorer clinical outcomes. Hence, whether early initiation in hemodynamically instable patients causes beneficial or deleterious effects remains controversial. However, no evidence suggests that EN should not be attempted in stable patients, including children receiving extra corporal membrane oxygenation, and may even be attempted in instable patients under certain precautions. The presence of uncontrollable shock, hypoxaemia, acidosis or severe signs of 'feeding intolerance' including GI bleeding, exceedingly large gastric residue, bowel ischemia or obstruction are strong signs to delay EN. However, MEN may play a role in these patients due to the many favourable effects and small burden on the gut. Overall, early initiation of EN seems valuable in the majority of critically ill children.

What can we learn from adults ICU studies?

Recently, the TARGET study showed that approximately 100% (±1900 kcal/d) compared with 70% (±1300 kcal/d) of recommended caloric intake did not result in improved short-term clinical outcomes, or quality of life and functional outcomes six months after ICU admission in 3957 mechanically ventilated adults.[75,76] During this trials the amount of protein was comparable between the two groups resulting in a differences between carbohydrate and lipid amounts. The EDEN RCT compared trophic feeding (± 400kcal/d) with full enteral feeding (±1300kcal/d) for the first six days in 1000 patients within 48 hours of developing acute lung injury and found no differences.[77] Also, the PermiT RCT showed that receiving 800 kcal/d versus 1300 kcal/d for the first 14 days of admission did not affect outcome.[78] Furthermore, secondary analyses from the EPaNIC study involving 4640 adults found that the group of patients who received <30% of recommended target was associated with improved recovery, regardless of the administration route, and higher amounts of amino acids primarily explained the harm.[79] Thus, the historic believe that higher enteral achievement would benefit the patient has not been confirmed by a RCT.

Parenteral nutrition

The landmark PEPaNIC RCT[80] had a large impact on the paediatric guidelines, which now recommend to withhold parenteral nutrition during the first week of admission while continue to provide micronutrients[50-53]. Subjects included in the PEPaNIC trial were all critically ill children with an expected admission duration >24 hours and a medium or high nutritional risk score assessed by the STRONGkids score. The critically ill population is heterogeneous, whereby some subpopulations are thought to be more at risk for macronutrient restriction, such as children who are undernourished upon admission or neonates. Though, these subgroups showed similar beneficial effects.[81,82]

Macronutrients

Secondary analyses of the PEPaNIC RCT confirmed the adult result, whereby higher doses of amino acid administration were associated with worse outcome, while the effect of lipids and carbohydrates were neutral of even beneficial.[83] Higher glucose administration did not

negatively affect outcome, however, a higher blood glucose concentration is known to cause worse short-term and long-term outcomes.[84,85]

Recommended minimum amino acid amount in critically ill children is 1.0 g/kg/d (children) up to 1.5 g/kg/d (term infants) according to the European guidelines[86] and a minimum of 1.5 g/kg/d according to the American guidelines which might be even higher in young infants and children[50]. These advices are the results of the threshold needed to acquire a positive nitrogen balance in children, which has been associated with improved outcomes. The PEPaNIC study showed that the harm from amino acids was already present at amounts starting at 40–50% of reference doses for age and weight, which increased with higher doses of amino acids. The maximum risk of harm was already established when amino acid amounts of 0.75 kg/g/d in older children and 1.15 kg/g/d in children <10kg was provided, which is considerably lower than recommended.

Hence, the negative impact of amino acids was identified even at low macronutrient amounts, whereby the impact was primarily investigated per dose, rather than feeding route.[79,83] In two recent large RCTs involving adult ICU patients feeding provided via enteral route did not reduce mortality or the risk of new acquired infections compared to parenteral provided feeding. However, there was a greater risk of gastrointestinal complications in the EN group. Importantly, in both studies feeding was provided at isocaloric doses and similar between the two randomisation groups.[87,88] Hypothesis generating, the amount of nutrients provided, and thereby allowing overfeeding rather than permissive underfeeding, could be more important than the feeding route nutrients are provided.

Mechanism behind beneficial caloric and macronutrient restriction

The leading hypothesis behind the counter-intuitive findings is the consequence of nutritional intake to suppress the fasting response, which induces ketosis and activates autophagy.[89-92] Autophagy is an evolutionary conserved intracellular degradation process and it is crucial for maintaining cellular integrity and function, which of course becomes even more essential during acute stress. Starvation-induced autophagy is an important evolutionary response during acute illness against intracellular pathogens and improves survival.

Mice studies dating back to 1979 already found that force-fed mice had worse survival compared to mice who were allowed to feed ad libitum or underwent a 72 starvation period when infected with bacteria.[93,94] Remarkably, survival rates were highest in mice who lost the most weight, while achieving weight gain is still a surrogate outcome measure of benefit. More recent, animal models have shown that providing artificial nutrients, in particular amino acids, are a strong suppressor of autophagy. While revolutionary steps are performed in laboratory research, in vivo human studies are complicated by the inability to measure

autophagy. In the absence of a "golden standard", secondary parameters, such as the presence of ketone bodies, are currently used.

Micronutrients

Reintroduction of feeding potentially results in a shift of micronutrients. Micronutrient depletions are often seen in critically ill children which is associated with impaired morbidity and mortality. Although no trials showed an advantageous effect of micronutrient supplementation, it seems logical to provide micronutrients during all phases of critical illness. However, due to a lack of evidence, current recommendations are based upon expert opinion and dietary reference nutrient intake for healthy children without incorporation of the phase of the disease. In Chapter 10 we showed the lack of clinical evidence supporting supplementation and the inability to provide all recommended amounts with the current commercial products hampers the implementation of current guideline recommendations.[95-98] Although the ESPGHAN/ESPEN/ESPR/CSPEN guidelines advise to use commercial products due to the lower risk for microbial contamination and compounding errors[99,100], the ESPGHAN/ESPEN/ESPR/CSPEN and ASPEN guidelines both acknowledge the recommended intakes can only be accomplished using individualised micronutrient products in critically ill children.[99,101] It would greatly improve the healthcare system if pharmaceutical companies are able to provide micronutrient products in adherence to the guidelines, and in adherence to the paediatric critically ill population.

The difficulties in assessment and interpretation of micronutrient status and management of depletions lies in the different methods used to determine depletions. Most often serum levels are used, however other methods entail clinical signs of deficiencies, dietary assessment or intracellular depletion measurements. All methods have their pitfalls, as clinical signs are often not differentiated from critical illness itself and for serum and intracellular measurements paediatric reference standards are lacking.[102] Furthermore, cautions interpretation of thresholds is needed during the acute inflammatory response, as levels are significantly lowered during inflammation.[103]

Stable and recovery phase

Taking into consideration that biomarkers determining the timing of transition from acute to stable to recovery phase are lacking, currently the transition towards the anabolic phase is arbitrarily assumed to be by the end of the first week.[60] Unquestionably, this is highly dependent on the individual acute stress response to critical illness, and more knowledge is needed on how to determine these transition points. Besides the clinical status of the child, additional information on inflammation status, metabolic markers and neuro-endocrine stress response hormones may help to differentiate these phases on an individual level in the future, and guide the nutritional requirements according to these phases.

During the stable and recovery phase the bodies' acute response to prioritise the delivery of energy substrates to vital tissues from endogenous production has faded, and resynthesis

of lost tissue follows. The body is more capable to digest and process exogenous nutrients and energy requirements increase. The provided intake should incorporate physical activity, rehabilitation and (catch-up) growth (Chapter 6). In specific diagnoses the requirement may rise up to twice the recommended daily intake for healthy children. There is an increased risk of undernutrition which is detrimental for short-term and long-term outcome. We know that worldwide prolonged undernutrition places a large long-term burden on children with approximately 113.4 million children being undernourished and 3.1 million children dying from undernutrition each year mostly in low-income and middle-income countries.[104,105] Long-term adverse effects in these children consist of poor learning ability and school performances which influence the societal perspectives.[106] The Minnesota Starvation Experiment (1944-1945) showed that a semi-starvation period of six months reducing the daily intake with 50% in healthy adults led to neurocognitive and psychiatric problems only after a few weeks of starvation.[107] Therefore, a transition in nutrient regime is needed to counteract the detrimental consequences of (long-term) macronutrient deficits.

Hence, the stepwise manner to increase EN intake should be guided by the metabolic stress response and patients tolerance, which could mean modification to a protein and energy-dense formula or other management of barriers. When patients remain unable to achieve macronutrient goals adequately due to many barriers identified on the PICU, supplemental PN start to play an important role. As these recommendations are withdrawn from observational evidence, it is important to allow individual circumstances and patient characteristics to take precedence over the guidelines advised nutritional targets.

Long-term developmental outcomes

The development of feeding intolerance as well as nutritional support is suspected to have prolonged impact after discharge from the PICU, as both undernutrition and overfeeding during childhood are associated with impaired neurocognitive and behavioural development.[108,109] The impact of caloric adequacy during PICU admission on long-term development is currently unknown. The adult ICU TARGET study was one of the first to assess recommended enteral intake (100%) versus lower than recommended intake (70%) during the acute phase and could not identify any differences in survival, functional outcomes or altered quality of life at six month follow-up.[75,76]

Nonetheless, studies have indicated that even short-term metabolic intervention during PICU admission has an impact on physical and neurocognitive development.[85] Therefore, the children who participated in the PEPaNIC RCT were assessed for long-term physical, neurocognitive, and emotional and behavioural development two and four year after admission to investigate the impact of parenteral nutrition provided during the acute phase. On both time points, an important physical, neurocognitive, and emotional and behavioural burden was reported in comparison with matched healthy control children (Chapter 11 and 12).

Two points specifically warranted careful and extensive investigation of long-term neurocognitive and psychical development in this vulnerable patient group. First, during the PEPaNIC RCT, a large proportion of children allocated to the late PN group had no or minimal enteral intake, resulting in substantial lower macronutrient intakes than recommended by the former guidelines.[110] Despite the short-term clinical benefits of omitting PN during the first week of illness, concerns were raised about potential adverse long-term consequences of below recommended macronutrient intake for the patients' anthropometric, health status, neurocognitive and psychosocial development. Second, the occurrence of hypoglycaemia (glucose level <40 mg/dl or <2.2 mmol/L) was higher in the late PN group (9.1% late PN versus 4.8% early PN), however, this had no effect the short-term outcomes of providing late PN. Indeed, severe or recurrent hypoglycaemia, especially in neonates and infants, have been associated with worse long-term neurocognitive outcomes.[111,112] However, a short and transitory hypoglycaemic occurrence during critical illness did not cause harm on long-term neurocognitive development two to four years after PICU admission in neonates and children who participated in the PEPaNIC RCT or three years after a tight glucose control RCT.[85]

The omission of PN did not harm any of the physical and neurocognitive developmental domains and protected the ability for normal development on several (executive) domains 2 years after (Chapter 11) and neurobiological pathways that coordinate emotions and behaviour 4 years after PICU admission (Chapter 12), which were no longer over represented in patients in the late PN group compared with healthy controls. These data support de-implementation of the use of parenteral nutrition early during critical illness in infants and children. The findings also open perspectives for future identification of other modifiable risk factors related to intensive care management.[113]

Epigenetics

Unravelling the mechanism behind this beneficial long-term effect is needed to comprehend this complex adaptation and provide new insights in possible therapeutic options. Epigenetics is the genetic control, other than the individual's DNA sequence, that alters and may switch genes "on" or "off" and subsequently determine which proteins are and are not transcribed. Examples of epigenetic control are DNA methylation, histone modification and noncoding RNAs, all of have been shown to alter by metabolic or lifestyle interventions.[114] Epigenetic regulation may have a substantial impact on the outcomes long after critical illness. Specifically, DNA Methylation or demethylation which is a chemical process that alters gene expression and thereby alters the biological processes, could alter the development of physical and neurocognitive functioning.[115]

Epigenetic analyses from the PEPaNIC study showed that a total of 159 functionally relevant de novo alterations in DNA methylation partially explained the long-term harm, and 37 of these were related to early-PN. The DNA methylations occurred in genes know to be involved in brain development and signalling as well as in growth and metabolism. The harm

was most prominently elucidated by early administration of amino acids, rather than carbohydrates or lipids.[116] Furthermore, these alteration were already present within the first 3 days of PICU admission and maintained or deteriorated during the course of admission.[117] Therefore, it seems sensible for future studies to aim at intervention starting early during PICU admission.

Epigenetics is modifiable in response to stimuli and a longer follow-up is warranted to examine if these alteration are permanent. Furthermore, the DNA methylation alterations within the PEPaNIC RCT were investigated in leucocytes, whether this is mirrored in other cells needs to be investigated. A special concern should be placed on the reproductive organs cells, as this could potentially have consequences continuing for generations.

Identification of subgroups

While in the heterogenetic PEPaNIC population based-level no harm was identified, a similar beneficial effect of this interventional in children who are thought to be more at risk for metabolic insults e.g. neonates, malnourished children upon admission and children who develop hypoglycaemia has to be further investigated regarding long-term consequences. Furthermore, specific diagnostic or age groups could respond differently to the omission of PN. This hypothesis was confirmed by a secondary analyses form the PEPaNIC RCT identifying that children between 1 and 11 months old were most vulnerable for the development of long-term consequences of early PN.[118]

Furthermore, in view of the potential benefits of fasting-induced responses for removal of cell damage and prevention of neurodegeneration, withholding PN early during the course of critical illness in children brings beneficial effects in the short-term and long-term, in particular for neurocognitive development. Maturation of the brain takes place in different stages of life. During the first 5 years the brain rapidly develops and alters, which continues into adulthood. These first years lay the foundation for future learning, health and life successes. It is currently unknown if and how omitting PN affects their future societal perspectives for which a longer follow-up period is warranted.

FUTURE PERSPECTIVES

The PEPaNIC study shows that improvements made in national support have a substantial impact on daily life years after PICU admission. Unfortunately, recommendations for nutritional support in critically ill children is still largely driven by low-grade evidence i.e. observational studies and expert opinions. To allow further optimization this thesis asks and answers some important considerations leading to future research perspectives in the following fields:

- Unravel the mechanism behind feeding intolerance to allow early assessment and management
- Assessment of nutritional requirements for optimal short-term and long-term outcome during acute, stable and recovery phase; and the role of amino acids herein.
- Explore the impact of micronutrient deficiencies and supplementation
- Building a model towards individual tailored nutritional support by further exploring specific populations

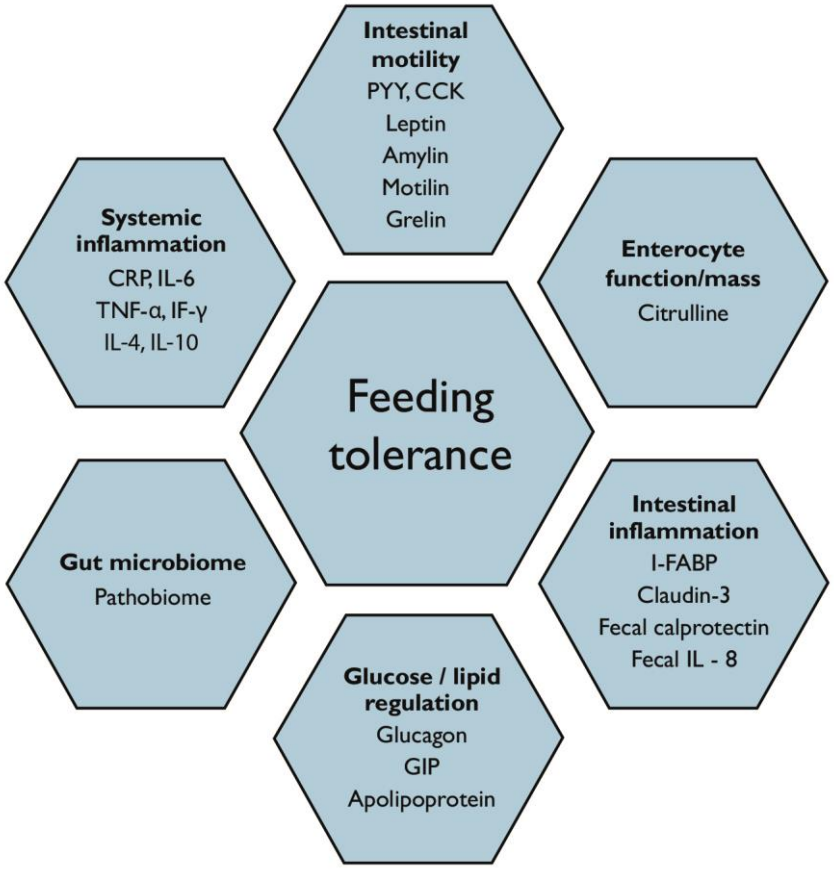
Feeding intolerance

The proposed uniform definition to screen for feeding intolerance needs to be validated in clinical practice. This definition currently fails to incorporate several essential factors affecting patients' tolerance, such as prescribed medication, pre-existing nutritional impairments and electrolyte imbalances impairing gastrointestinal motility e.g. hyperglycaemia, hypokalaemia and hypomagnesaemia or the use of hyperosmolar diluent.[119] With a validated definition clinicians and researcher will be able to identify the causes and consequences of feeding intolerance to one benchmark; and allow comparison of different feeding intolerance managements.

Gastrointestinal biomarkers

Studies exploring the mechanism behind feeding intolerance are warranted, not only in regards to improve body composition or short-term outcomes, but also its impact for long-term health. In addition to clinical screening of GI symptoms and EN enhancement, laboratory markers could help to identify patients at risk for feeding intolerance. There is currently no marker to identify critically ill children who are tolerant to feeding, however, several makers have been identified in association with altered gastrointestinal function in other (paediatric) populations. Additionally, (systemic) inflammation markers and the microbiota could help to guide nutritional practices and individualise nutritional support in critically ill children. Figure 2 highlights some of the markers that have been associated with gastrointestinal dysfunction and could potentially lead to an early screening of feeding intolerance during critical illness, or indicate when the gastrointestinal tract is able to recover its normal functions.

Figure 2. Factors affecting feeding tolerance to enteral feeding and possible markers for determining these factors during critical illness.
CCK, Cholecystokinin; CRP, C-reactive protein; GIP, Gastric Inhibitory Polypeptide; I-FABP; Intesntial Fatty Acid-Binding Protein IL, interleukin; PYY, Peptide YY; TNF, Tumor necrosis factor



Nutritional requirements

Several large and sufficiently powered RCTs did not support evidence for high enteral caloric goals to affect patients' outcomes. This should heighten our awareness of the lack of high quality evidence addressing the question of amino acid requirements in critical illness. Optimal amino acid requirements remain controversial during the acute phase. Guidelines recommendations are mainly based on maintaining muscle mass and avoid a negative nitrogen balance, both common in the critically ill, and associated with increased morbidity and mortality. New insights have shown that amino acids were the primary substrate explaining harm. In addition, parenteral nutrients restriction has led to a more efficient activation of autophagic quality control of myofibres and reduced muscle weakness.[89]

Therefor, determination of low vs normal or high amino acid intake, timing and the combination with early mobilisations are currently in the highest scoring research priorities.[78,120]

Besides finding optimal macronutrient targets, more research is needed to investigate the range within feeding can be provided with a special interest towards minimal enteral nutrition. Hence, what amount of feeding is required to maintain gut function?

In addition, the variation in illness severity, heterogeneity of the population and PICU confounders make it difficult to comprehend the metabolic processes to nutritional interventions.[121,122] The diversity in metabolic, genetic, epigenetic response have been investigated on population-bases level, but the lack of biomarkers inhibits the investigation of individualised patient-level approach. The need to better understand de individual malnutrition risk and metabolic heterogeneity has led to several biomarkers in nutrition. Screening for malnutrition upon admission i.e. STRONGkids malnutrition score, illness severity scores (PIM, PELOD, PRISM) and systemic inflammatory have been well recognised in paediatric research as important patient-level biomarkers, still observational studies often fail to incorporate these in their conclusions. Furthermore, established biomarkers for nutrient absorption and metabolic response are the whole body protein balance measured via calculation of the nitrogen balance, metabolic substrates such as albumin, retinal binding protein, transthyretin and transferrin and measurement of body composition. These biomarkers could help the translation towards patient-level, however, little is known to what extent these surrogate outcomes markers affect clinical outcomes.[121]

Lastly, strategies to enhance caloric intake, such as post-pyloric feeding tube, dense formula or medication, should be critically reviewed during the acute phase, as this hypothetically could result in unfavourable consequences.

Macronutrients

Not all macronutrients have an equal effect on body's immunologic and metabolic stress response. As most harm was identified from amino acids substrates, future studies may have to rethink the amount of supplementation provided. Doses as low as 40-50% of currently recommended amounts resulted in harm during the acute phase, thereby studies comparing of the effect of different protein contents via enteral or parenteral route are highly needed. Contrariwise, the provision of non-protein sources could protect critically ill children against harm, as higher glucose doses from admission onwards and lipids from day 4 onwards resulted in faster recovery. This sets a basis for research adapting macronutrient supplementation towards different time points, rather than recognising it as one sustenance.

Micronutrients

While substantial improvements have been made for macronutrient supplementation, research for optimal micronutrient provision is lacking behind.[51] Current gaps of knowledge

are the interpretation of serum micronutrient levels in comparison with actual intracellular depletions, the prognostic value of electrolyte disturbances after reintroduction of feeding, such as refeeding hypophosphatemia, and the impact of micronutrient supplementation on short-term and long-term outcomes. The advancements in micronutrient research is complicated by the difficulties of multiple assessment methods. In the most optimal situation research should include a multiple approach model including all forms of assessment i.e. clinical, dietary intake and laboratory serum and intracellular makers.

Other feeding patterns

While autophagy as a result of macronutrient restriction is thought to determine the beneficial effect of late PN, prolongation of this period of starvation seems detrimental. A possible solution to allow autophagy while also providing full amounts of nutrients is to mimic the fasting response in an intermittent or cyclic feeding pattern. No human naturally eats continuously for 24 hrs a day and the gastrointestinal tract is designed for intermittent ingestion of nutrients a few times a day including intermitted hormonal release. Indeed, the normal gastrointestinal hormonal response to feeding almost disappeared when continuous tube feeding is provided.[123,124] Cyclic feeding has been used for many years in children with bowel diseases, however this has never been investigated in critically ill children. Animal models have shown that cyclic feeding, and thereby allowing autophagy, was beneficial for age-related diseases and resulted in an older age. A recent trial showed that a fasting period of 12 hours was sufficient to develop a metabolic fasting response in adult critically ill patients.[92]

The next step in research lies in determination of the optimal duration of fasting to allow autophagy and improve clinical outcome, while limit the risk of feeding intolerant complication due to high feeding provision during the feeding window and monitor hyperglycaemic and hypoglycaemic insults. While cyclic/intermitted feeding begins to mirror the gastrointestinal digestion process in health, it could hypothetically also result in a normalisation of the circadian rhythm. Due to a lack of studies invested in this topic, this feeding methods is currently not advices in acutely ill children, hence, cyclic feeding allowing autophagy is still a controversy to overcome.

Epigenetics

Epigenetics might help to unravel the biological basis behind the impact of metabolic interventions to affect the outcome after critical illness. Alterations in the DNA methylation associated with long-term disturbances in physical and neurocognitive development can be induces by both internal en external factors and have been associated with undernutrition and overfeeding. Providing a biological basis will help to implement or de-implement certain intervention which might feel counterintuitive.

A total of 37 of the 159 methylation alterations in the PEPaNIC RCT were related to the early-PN randomisation, resulting in 122 DNA methylation alterations unaccounted for. It

would be interesting to investigate if these alterations are the result of critical illness itself or potential other modifiable factors. Hence, the identification of DNA methylation as an important mediator for long-term development affected by the early provision of PN opens perspectives for other factors contributing to the legacy of critical illness to be investigated.

Identification of subgroups

A (metabolic) insult may not have a similar effect on physical, neurocognitive and emotional and behavioural development in all critically ill children. Identification of subgroups at risk to experience difficulties in specific developmental domains might help to individualise therapy or treatment for deficits before that are experienced in daily life. Hence, a predictive individualise model is needed, to allow early identification and targeted treatment, to reduce impairments following critical illness.

Finally, future research should focus on building models which help to individualise nutritional support. This model should include clinical characteristics such as different age groups and diagnosis, (bio) markers for neuro-endocrine, immunologic and inflammatory stress response and gastrointestinal function. This model should help to guide: 1) the amount of EN the gut can appropriately tolerate and is desirable; and 2) when the endogenous energy supply alters and safe starvation is no longer preferred. In order to build a nutritional guidance model, the nutritional research field needs to incorporate results from a system biology approach (e.g. genomics/transcriptomics, proteomics and metabolomics) creating more extensive knowledge on the individual response to a nutritional therapy.[125] Ultimately, you would like to deliver the child the most optimal nutritional therapy with the lowest impact possible from critical illness in order to provide the best future.

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CHAPTER 14

SUMMARY

Chapter 1 describes the important role of nutritional therapy in critically ill children in accelerating recovery and maintaining normal physical and neurocognitive development. The awareness of the changes in metabolism during the different phases of critical illness is essential in determining metabolic and nutritional support. As both underfeeding and overfeeding are known to affect outcome during the complete course of admission.

Furthermore, chapter 1 focuses on the gastrointestinal tract as the preferred route for nutritional support. Enteral nutrition (EN) is considered safe, cost-effective and more physiologic compared to parenteral nutrition (PN). However, recommended caloric and protein targets are often not achieved via enteral feeding, and discrepancies between the amount prescribed and the amount delivered range up to 60%. Numerous studies have been carried out to investigate these discrepancies, with (perceived) feeding intolerance as a result of gut failure, fluid restriction, fasting around extubation and (bedside) procedures, and ventilatory support most frequently reported.

The chapter ends with the aims of this thesis, which is to provide insight into optimal nutritional therapy for critically ill children concerning the route, timing, and amount during acute, stable and recovery phase, with special attention to a conceptual insight into the barriers that restrict such optimal nutrition.

The Acute phase

In Chapter 2, we developed a survey tool to allow clinicians (i.e. physicians, nurses and dieticians) to assess and address the barriers for EN in their Paediatric Intensive Care Unit (PICU). This resulted in a large worldwide survey to identify perceived barriers that hamper the delivery of EN in PICUs. The prominent barriers identified, related to fasting for procedures, dietician coverage, inadequate education, care priorities and delays in gaining small bowel access. Hence, most of the primary perceived barriers for EN were related to

an overall lack of prioritising nutrition during paediatric critical illness. This further warrant education as a tool to improve awareness of the existing evidence regarding these perceived barriers.

In Chapter 3, we retrospectively explored EN practices in critically ill children receiving non-invasive respiratory support in four centres across Europe. Due to concerns about the potential need for escalation of treatment, subsequent intubation, and of the risk of aspiration, non-invasive respiratory support was thought to be one of the major factors for delaying EN. In this observational study, children received a median of 56% of their energy goals compared to a benchmark target of 85% of the recommended dietary allowance, whereby feeding was well tolerated, with relatively few gastrointestinal complications. Despite the variations found between the four centres in terms of non-invasive respiratory support use, nutrition targets and delivery practices, our study supports that enteral nutrition is possible at an early stage during non-invasive respiratory support. However, prospective trials are required to determine the optimal timing and feeding method for these children.

In Chapter 4, a systematic literature search was performed to evaluate the definitions of feeding intolerance used in critically ill children and to investigate the prevalence, predictors and outcomes of feeding intolerance. Our literature search revealed a median prevalence of 20%. Moreover, feeding intolerance was inconsistently defined throughout the literature overview, and no causes, therapies or consequences could be identified. Due to the lack of a standardised definition, we proposed a definition for feeding intolerance for future research, entailing the inability to achieve enteral nutrition target intakes in combination with the presence of gastrointestinal symptoms indicating gastrointestinal dysfunction. Such a standardised definition is needed for both clinical and research purposes to determine the consequences of feeding intolerance and to identify therapeutic options in relation to short-term and long-term consequences.

For decades, it is believed that low enteral intake results in increased morbidity and mortality, as many observation studies show an association between these two factors. The observational design of these studies calls for cautiousness in assuming a relationship between higher EN achievement and improved outcomes, as children who tolerate EN might become less critically ill and inherently have a better outcome. Chapter 5 presents data involving 690 critically ill children, and it was found that enteral nutrition was low in the majority of critically ill children, whereby only 32% achieved their energy goals compared to a benchmark target of 100% of resting energy expenditure during the first seven days of admission. Gastrointestinal surgery diagnosis, gastric feeding tubes, treatment with inotropic agents and large gastric residual volumes were negatively associated with successfully achieving EN using multivariable mixed models. Univariable analyses supports the frequently reported association between higher achievement of enteral intake and improved clinical outcome during the acute phase. However, after multivariable adjustment, these

associations were no longer present, suggesting that the impact on clinical outcome reported in previous studies reflects insufficient adjustment for confounders such as illness severity. These data substantiate the requirement of sound multivariable adjustment in observational nutritional support research and the necessity for randomised controlled trials (RCTs) investigating optimal EN.

The stable and recovery phase

Chapter 6 provides an overview of the literature on strategies and considerations for nutritional support during the recovery phase. Although (parenteral) nutrient restriction during the acute phase appears to be beneficial, persisting this course of nutrient restriction after the metabolic stress response resolves has detrimental short-term and long-term consequences. The caloric requirements increase markedly during the stable and recovery phase towards at least twice the resting energy expenditure to enable recovery, preservation of lean body mass, and (catch-up) development and growth in children. Such large amounts of intake demand for an alternate approach, especially when feeding intolerance or fluid restriction constitute a barrier for full enteral feeding. This approach includes a protein and energy-dense and / or hydrolysed formula. In addition, mobilisation and exercise are essential to achieve catch-up growth with an optimal body composition.

Chapter 7 highlights the use of polymeric protein and energy-dense feeding formula in infants with a prolonged admission duration (>2 weeks). On average, 100% of their energy target was accomplished during admission, and the majority of the 70 infants receiving this formula showed (catch-up) weight gain (median +0.48 weight-for-age z-score). This was most prominent in infants with a low weight-for-age Z-score at admission to the PICU. Furthermore, the polymeric protein and energy-dense feeding formula was well tolerated based on the limited gastrointestinal symptoms observed.

Expert consensus recommends hydrolysed feeding when establishing enteral feeding fails, or in children who do not tolerate polymeric protein. Chapter 8 describes the use of hydrolysed protein and energy-energy dense enteral feeding in critically ill infants in two different PICUs, taking into consideration feasibility, tolerance and nutritional targets. The 53 infants met their nutritional targets, enabling weight gain and minimal feeding interruptions arising from feeding intolerance were observed. Therefore, this formula may further improve nutritional intake and minimise feeding interruptions as a result of gastrointestinal symptoms.

Parenteral nutrition: macronutrients and micronutrient supplementation

Chapter 9 presents an overview of the current role of PN in paediatric critical care. Despite the strategies to improve enteral intake, EN often remains insufficient in critically ill children which might result in a need for parenteral nutrition. The paediatric early versus late parenteral nutrition in critical illness (PEPaNIC) multicentre RCT showed that omitting supplemental PN during the first week of PICU admission as compared with early initiation

of PN (<24 hours) reduced new infections and accelerated recovery in term neonates, infants and children, independent of their nutritional status during admission. The leading explanation behind the counter-intuitive findings is the consequence of nutritional intake, especially amino acids, to suppress the fasting response, which induces ketosis and activates autophagy. These findings of the landmark PEPaNIC RCT had a considerable impact on the new guidelines. Although parenteral macronutrient restriction during the acute phase has been found beneficial for critically ill children, further research is required to determine the optimal timing, dose and composition of parenteral nutrition during stable and recovery phase as well as the determination of the role of parenteral micronutrients.

Following the results of the PEPaNIC RCT, the new nutritional guidelines recommend considering withholding parenteral macronutrients for one week, while providing micronutrients, in critically ill children if enteral nutrition is insufficient.

Chapter 10 provides an overview of the current practice of micronutrient administration and practical considerations in the three participating centres of the PEPaNIC RCT, and compares these therapies with the recommendations in the new guidelines. It was found that the lack of hard clinical evidence and the inability to administer all recommended amounts with the currently available commercial products hampered the implementation of these new recommendations.

Long-term developmental outcome of parenteral nutrition

Despite the short-term clinical benefits of withholding PN during the first week of paediatric critical illness, concerns have been raised about potential adverse long-term consequences of low caloric and macronutrient intake for the patients' bodyweight, length, head circumference, health status, neurocognitive, emotional and behavioural development. Any adverse patient-centred long-term consequences would discourage withholding PN early in the course of paediatric critical illness. In Chapter 11, the two-year long-term developmental outcomes of the PEPaNIC RCT were investigated. The study showed that patients who were admitted to the PICU early in life compared to healthy control children had worse outcomes on all developmental domains e.g. anthropometrics, health status and neurocognitive development. Withholding supplemental PN for one week in the PICU did not negatively affect survival, anthropometrics, health status and neurocognitive development two years later, and protected the children against problems with their inhibitory control.

Several neurocognitive domains can only be fully investigated from age 4 onwards. Because the PEPaNIC RCT involved a large proportion of young infants, a longer assessment period was needed in addition to the two-year follow-up. Chapter 12 presents the four-year follow-up study. Again, the burden of critical illness was clearly seen when comparing the critically ill children to healthy control children. Omitting PN in critically ill children did not adversely affect long-term outcomes four years after randomisation and even decreased parent-

reported internalising, externalising and total emotional and behavioural problems. These problems could arise from difficulties with inhibitory control found at the two-year follow-up. Therefore, the two- and four-year long-term follow-up data supports the de-implementation of PN during the first week of admission.

Chapter 13 discusses the key findings of this thesis in light of current knowledge. In general, our findings underline the necessity of a uniform assessment of barriers inhibiting enteral feeding and the increased need to individualise nutritional support during the different phases of the acute stress response. The need to better understand the metabolic heterogeneity of the PICU population and pathophysiology of gastrointestinal failure during critical illness has led to the following future research perspectives:

- Unravel the mechanism behind feeding intolerance to allow early assessment and management
- Assessment of nutritional requirements for optimal short-term and long-term outcomes during acute, stable and recovery phase and the role of amino acids.
- Explore the impact of micronutrient deficiencies and supplementation
- Build a model towards tailored nutritional support by further exploring specific populations

HOOFDSTUK 14

SAMENVATTING

Kinderen die worden opgenomen op de intensive care (IC) afdeling zijn kritiek ziek en kunnen daardoor meestal niet zelfstandig eten of drinken. Optimale voeding is belangrijk voor het herstel van de kinderen, maar ook voor het in stand houden van normale groei en ontwikkeling. Daarom wordt al vroeg tijdens de opname kunstmatige voeding gestart. Voeding kan via een sonde in de maag worden gegeven (enterale voeding) of via een infuus direct in de bloedbaan (parenterale voeding).

In Hoofdstuk 1, de inleiding van dit proefschrift, wordt het belang van optimale voeding benadrukt. Hoeveel voeding een kritiek ziek kind nodig heeft is afhankelijk van veel factoren, zoals diagnose, leeftijd en ernst van ziekzijn. Nadat een kind ernstig ziek is geworden, ondergaat het lichaam meerdere fases naar herstel. Deze fases zijn onderverdeeld in een acute-, een stabiele- en een herstelfase, maar zowel de duur als de ernst van de fase verschilt per kind. Tijdens elke fase zijn de optimale voeding strategieën verschillend. In dit proefschrift willen we per fase onderzoeken wat de beste voedingsstrategie is, waarbij we met name geïnteresseerd zijn in wanneer we enterale en parenterale voeding moeten starten en in welke hoeveelheid. Het is belangrijk om in elke fase niet te veel of te weinig voeding geven, want zowel overvoeding als ondervoeding zijn nadelig voor het kind.

Enterale voeding via het maagdarmkanaal wordt gezien als de betere manier van voeding geven, omdat het veilig, kosteneffectief en meer fysiologisch dan parenterale voeding is. De aanbevolen calorie- en eiwitdoelstellingen worden echter vaak niet via de enterale route bereikt. Er wordt tot wel 60% minder toegediend dan door de arts wordt voorgeschreven. Er zijn talloze onderzoeken geweest die de redenen voor dit verschil beschrijven, waarbij (vermeende) voedingsintolerantie als gevolg van falen van het maagdarmkanaal, vochtbeperking, vasten rond extubatie, procedures en niet-invasieve beademingsondersteuning het vaakst worden gemeld. Om deze redenen zal in sommige gevallen toch gekozen worden parenterale voeding te geven.

De acute fase

In Hoofdstuk 2 hebben we een vragenlijst ontwikkeld waarmee clinici (o.a. artsen, verpleegkundigen en diëtisten) de belemmeringen voor enterale voeding op hun kinder-IC kunnen beoordelen en aanpakken. Om een goed beeld te krijgen van de wereldwijde belemmeringen hebben we deze vragenlijst tevens rondgestuurd. In totaal hebben 920 clinici uit 57 landen deze vragenlijst ingevuld. De barrières die het meest voorkwamen waren vasten rondom behandeling, afwezigheid van diëtisten, onvoldoende opleiding en training, lage zorgprioriteiten en problemen bij het plaatsen van een voedingssonde in de dunne darm. Hierbij zou de lage prioritering van voedingszorg een rol kunnen spelen. Dit is opmerkelijk gezien voeding erg belangrijk is voor het herstel van zieke kinderen.

Vanwege bezorgdheid over de mogelijke noodzaak van intensivering van de behandeling en daaropvolgende intubatie én vanwege het risico op overgeven en aspiratie, werd aangenomen dat niet-invasieve ademhalingsondersteuning één van de belangrijkste factoren was voor het uitstellen van enterale voeding. In Hoofdstuk 3 hebben we retrospectief in vier centra in Europa onderzocht of kinderen goed enterale voeding konden verdragen terwijl ze niet-invasieve ademhalingsondersteuning ontvingen. De kinderen bereikten gemiddeld 56% van hun calorische doelstelling. Deze hoeveelheid voeding werd goed verdragen met relatief weinig gastro-intestinale symptomen. Omdat de voedingsprotocollen en manieren van niet-invasieve ademhalingsondersteuning erg verschilden tussen de vier centra, was het lastig om een eenduidige conclusie te vormen. Ons onderzoek toonde wel aan dat het meestal mogelijk is om spoedig enterale voeding te starten tijdens niet-invasieve ademhalingsondersteuning. Er zijn echter prospectieve onderzoeken nodig om de optimale timing en voedingsmethode voor deze kinderen te bepalen.

Eén van de grootste barrières tijdens het geven van enterale voeding is het ontstaan van voedingsintolerantie. Omdat bijna elke clinicus of onderzoeker een ander beeld heeft bij wat voedingsintolerantie is, maakt dit onderzoek doen naar dit begrip lastig. In Hoofdstuk 4 hebben we een systematisch literatuuronderzoek uitgevoerd om de definities van voedingsintolerantie die gebruikt werden bij kritiek zieke kinderen te evalueren en om de prevalentie, oorzaken en gevolgen van voedingsintolerantie te onderzoeken. In de literatuur was voedingsintolerantie inconsistent gedefinieerd en er konden geen oorzaken, behandelingen of gevolgen worden geïdentificeerd. Wel werd het vaak geobserveerd (mediane prevalentie van 20%). Vanwege het ontbreken van een gestandaardiseerde definitie in de literatuur én om geen appels met peren te blijven vergelijken, hebben we een definitie voor voedingsintolerantie voorgesteld, welke gebruikt kan worden in toekomstig onderzoek. De voorgestelde definitie omvat twee factoren. Allereerst moeten de kinderen minder dan 2/3 van hun voedingsdoel kunnen bereiken. Ten tweede moeten er gastro-intestinale symptomen zoals overgeven, buikpijn en vertraagde maagontlediging aanwezig zijn, die de verlaagde enterale inname verklaren. Voor zowel klinisch- als onderzoeksperspectief is een dergelijke gestandaardiseerde definitie nodig om de gevolgen van voedingsintolerantie te bepalen én om therapeutische opties te identificeren.

Decennia lang werd aangenomen dat een lage voedingsinname leidt tot een slechter herstel in de acute fase van ziekzijn, aangezien veel observationele studies een verband tussen deze twee factoren lieten zien. De observationele methode van deze onderzoeken vraagt om voorzichtigheid bij het aannemen van een verband tussen hogere voedingsinname en beter herstel, omdat kinderen die voeding beter tolereren mogelijk minder ernstig ziek zijn en alleen daarom al een beter herstel hebben. Om deze reden hebben we in Hoofstuk 5 in 690 kritiek zieke kinderen onderzocht of het verband tussen voeding en herstel nog steeds aanwezig is als je corrigeert voor aanvullende factoren zoals de ernst van ziekzijn. Het viel ons op dat gemiddeld slechts 32% van het calorische voedingsdoel gehaald werd gedurende de eerste 7 dagen van opname. Een significant lagere voedingsinname werd gezien bij kinderen die opgenomen werden na gastro-intestinale chirurgie, voeding kregen via een sonde in de maag in vergelijking met dunne darm, bloeddrukverhogingen middelen (inotropica) ontvingen of een te grote maagresidu hadden. In onze studie zagen ook wij het bekende verband tussen meer voedingsinname en verbeterd herstel, echter was dit verband niet meer aanwezig na correctie van aanvullende factoren die van invloed zijn op herstel zoals de ernst van ziekzijn. Dit ondersteunt de noodzaak van een gedegen correctie in observationeel voedingsonderzoek en de noodzaak van gerandomiseerde gecontroleerde studies (RCT) die optimale caloriedoelen onderzoeken.

De stabiele en herstel fase

Hoofdstuk 6 is een literatuuroverzicht over de optimale voeding strategieën en overwegingen tijdens de herstelfase van kritiek ziek zijn. Hoewel (parenterale) voeding restrictie tijdens de acute fase gunstig lijkt te zijn, kan het aanhouden van deze restrictie nadat de acute metabole stressrespons is verdwenen, nadelige gevolgen hebben op zowel korte als lange termijn. De benodigde hoeveelheid calorieën kan zelfs oplopen tot twee keer meer dan normaal voor een gezond kind. Deze hoeveelheid is nodig om herstel, behoud van vetvrije massa en (inhaal) ontwikkeling en groei bij kinderen mogelijk te maken. Ook in deze fase is het behalen van de relatief hoge doelen lastig door onder andere voedingsintolerantie en vochtbeperking. Het geven van eiwit- en energierijke voeding en / of intensief gehydrolyseerde voeding (verknipte eiwitten zodat deze makkelijk te verteren zijn) kan mogelijk helpen. Daarnaast zijn mobilisatie en beweging essentieel om bij een optimale lichaamssamenstelling een inhaalgroei te realiseren.

Hoofdstuk 7 belicht het gebruik van eiwit- en energierijke zuigelingenvoeding bij kritiek zieke zuigelingen tijdens de herstelfase (opnameduur > 2 weken). Gemiddeld werd 100% van de energiedoelstelling behaald tijdens de opname en de meerderheid van de 70 patiënten die deze zuigelingenvoeding kreeg vertoonde gewichtstoename (mediaan gewicht-voor-leeftijd SD-score +0,48). De gewichtstoename was het meest prominent aanwezig bij zuigelingen met een lage SD-score bij opname op de kinder-IC. Bovendien werd de zuigelingenvoeding goed verdragen en waren er weinig gastro-intestinale symptomen aanwezig.

De Europese richtlijnen raden aan om intensief gehydrolyseerde voeding te geven indien standaard enterale voeding niet goed verdragen wordt, echter was deze voeding type nog niet onderzocht bij kritiek zieke kinderen. Hoofdstuk 8 beschrijft het gebruik van intensief gehydrolyseerde zuigelingenvoeding die tevens verrijkt is met eiwitten en energie tijdens de herstelfase op twee verschillende kinder-IC afdelingen. De 53 zuigelingen die observationeel werden onderzocht, bereikten hun voedingsdoelen en vertoonden gewichtstoename. Ook zagen we minimale voedingsonderbrekingen als gevolg van voedingsintolerantie. Deze resultaten tonen voorzichtig aan dat deze zuigelingenvoeding resulteert in een goede voedingsopname en dat voedingsonderbrekingen als gevolg van gastro-intestinale symptomen tot een minimum worden beperkt in kritiek zieke kinderen.

Parenterale voeding: macronutriënten en micronutriënten

Hoofdstuk 9 geeft een literatuuroverzicht van de huidige rol van parenterale voeding op de kinder-IC. Ondanks de behandelingen om de opname van enterale voeding te verbeteren, blijft dit vaak onvoldoende bij kritiek zieke kinderen, waardoor parenterale voeding gestart moet worden. Kinderen die geen parenterale voeding ontvangen hebben anders een beperkte inname van voedingsstoffen. Omdat meerdere observationele studies hebben aangetoond dat ondervoeding schadelijk is, werd van oudsher vroeg gestart met het geven van parenterale voeding. De pediatrische vroege versus late parenterale voeding bij kritieke ziekte (PEPaNIC) multicentre RCT toonde echter aan dat het weglaten van parenterale voeding tijdens de eerste week van opname in vergelijking met de vroege start van parenterale voeding (<24 uur) zorgde voor minder nieuwe infecties en sneller ontslag van de kinder-IC. Wachten met parenterale voeding is dus beter op de kinder-IC. Dit lijkt tegenstrijdig, maar de verklaring ligt in het natuurlijke opruimsysteem van de cellen. Kritieke ziekte veroorzaakt schade aan de cellen van alle belangrijke orgaansystemen. Beschadigde delen van cellen worden opgeruimd door een proces dat autofagie heet. Dit opruimsysteem wordt geactiveerd door vasten en simultaan onderdrukt door voedingsstoffen. Met name het geven van eiwitten leek de boosdoener te zijn in dit proces. Hoewel deze restrictie van parenterale voeding (suiker, eiwitten en vetten) tijdens de acute fase gunstig is bevonden voor kritiek zieke kinderen, is verder onderzoek nodig om de optimale timing, dosering en samenstelling van parenterale voeding tijdens de stabiele en herstelfase te weten te komen.

De bevindingen van de PEPaNIC RCT hebben een aanzienlijke impact op de nieuwe parenterale voeding richtlijnen gehad. Deze adviseren nu om macronutriënten (suiker, eiwitten en vetten) gedurende 1 week achterwege te laten, terwijl micronutriënten (elektrolyten, vitamines en mineralen) wel voldoende gegeven dienen te worden bij kritiek zieke kinderen die te weinig enterale voeding ontvangen. Hoofdstuk 10 geeft een overzicht van de huidige klinische praktijk en beperkingen in het geven van elektrolyten, vitamines en mineralen in de drie deelnemende centra van de PEPaNIC RCT. De lokale protocollen werden met elkaar en met de aanbevelingen in de nieuwe parenterale voedingsrichtlijn vergeleken. We ontdekten dat het gebrek aan hard klinisch bewijs en het onvermogen om

alle aanbevolen hoeveelheden toe te dienen met de momenteel beschikbare commerciële producten, de uitvoering van deze nieuwe aanbevelingen belemmerden in alle drie de centra.

Lange termijn resultaten van parenterale voeding

Ondanks het gunstige effect van het onthouden van parenterale voeding op de korte termijn, is het belangrijk om na te gaan hoe deze kinderen op de lange termijn presteren. In theorie kan het geven van minder voedingsbouwstoffen een nadelig effect hebben op de groei, de gezondheidstoestand, de neurocognitieve ontwikkeling en de emotionele- en gedragsontwikkeling van patiënten. Indien dit het geval is, zouden we opnieuw kritisch naar deze behandeling moeten kijken.

In Hoofdstuk 11 werden de ontwikkelingsresultaten 2 jaar na deelname aan de PEPaNIC RCT onderzocht. De lange termijn studie toonde aan dat kinderen die werden opgenomen op de kinder-IC in vergelijking met gezonde kinderen een slechtere ontwikkeling hadden op alle vlakken. Het onthouden van parenterale voeding gedurende 1 week in de kinder-IC had geen negatieve invloed op overleving, groei, gezondheidstoestand en neurocognitieve ontwikkeling 2 jaar later, en beschermde de kinderen tegen problemen met hun impulscontrole.

Verschillende ontwikkelingsaspecten kunnen pas volledig worden onderzocht vanaf de leeftijd van 4 jaar. Omdat bij de PEPaNIC RCT een groot deel van de kinderen jonger dan 1 jaar was bij opname, was naast de follow-up van 2 jaar een langere beoordelingsperiode nodig om een goed beeld te krijgen van de kinderen. Hoofdstuk 12 presenteert de essentiële 4-jaar vervolgstudie. Opnieuw werd het nadelige effect van kritieke ziekte duidelijk in vergelijking met gezonde kinderen. Het weglaten van parenterale voeding bij kritiek zieke kinderen had geen nadelige invloed op de langetermijnresultaten 4 jaar na deelname aan de studie. Daarbij had deze behandeling een positief effect op de emotionele- en gedragsproblemen die vaak gezien worden na IC opname. Emotionele- en gedragsproblemen kunnen het gevolg zijn van problemen met impulscontrole die werden gevonden bij het 2 jaar vervolgonderzoek.

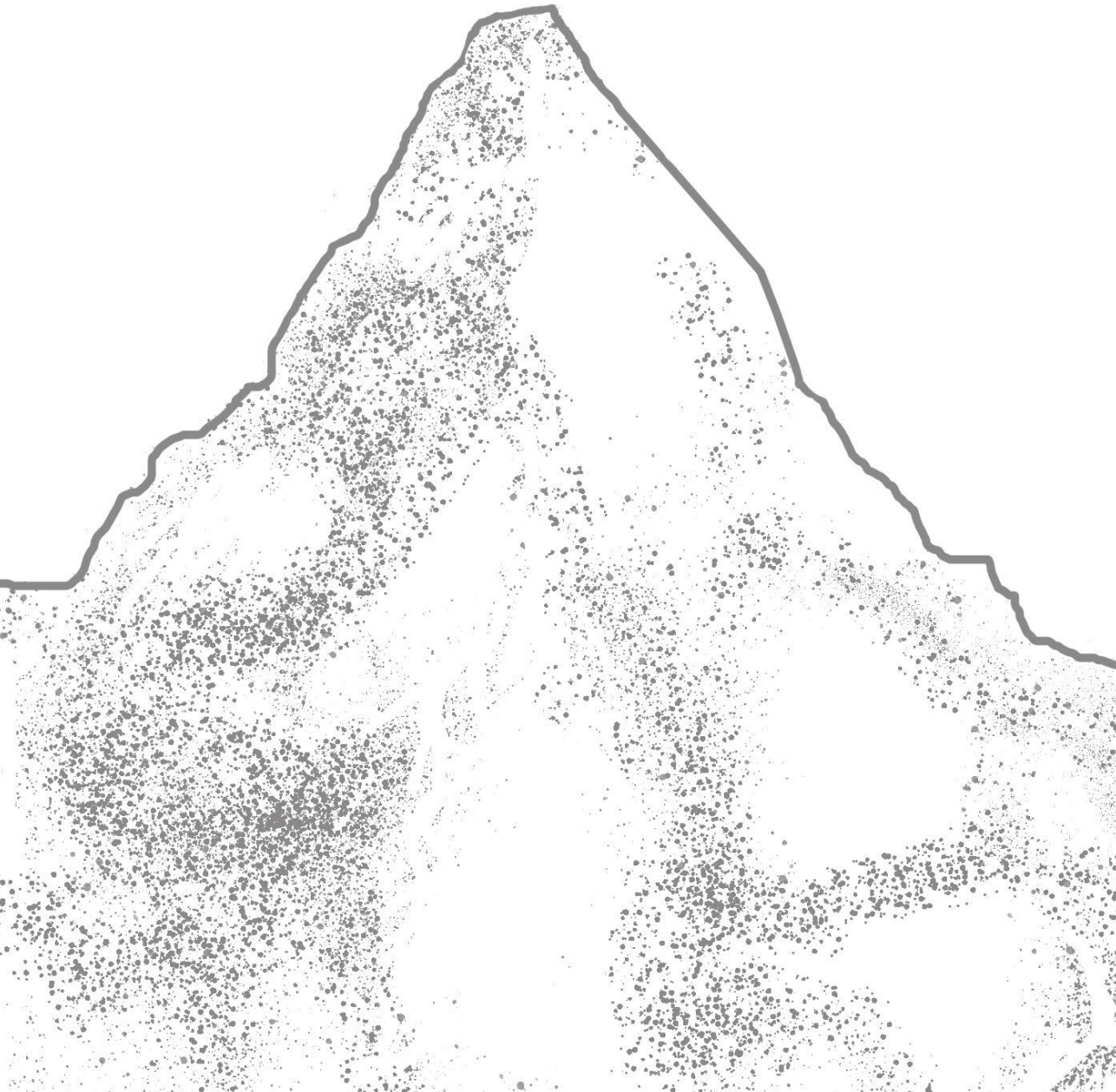
Samenvattend ondersteunen de 2 en 4 jaar lange termijn vervolgstudies de nadelige impact van een opname op de kinder-IC én bevestigt dit de noodzaak tot het niet geven van parenterale voeding tijdens de eerste week van opname.

Hoofdstuk 13 bediscussieert de belangrijkste bevindingen van dit proefschrift. Onze bevindingen benadrukken het belang van optimale voeding tijdens de verschillende fases van ziekzijn voor het herstel en de ontwikkeling van het kind tot 4 jaar na opname. Voor optimale voeding is het belangrijk om alle barrières die enterale voeding tegengaan te herkennen, een beter begrip van voedingsintolerantie te krijgen en zorgen voor restrictie van (parenterale) tijdens de acute fase.

Dit proefschrift stelt voor dat toekomstig onderzoek zich richt op de volgende essentiële onderwerpen:

- Ontrafelen van het mechanisme achter voedingsintolerantie om vroege beoordeling en behandeling mogelijk te maken.
- Vaststellen van de voedingsbehoeften tijdens de acute-, stabiele- en herstelfase voor een optimaal herstel op korte en lange termijn.
- Onderzoeken van de rol van individuele macronutriënten tijdens kritieke ziekte (suiker, eiwitten en vetten).
- Onderzoeken van de rol van micronutriënten tijdens kritieke ziekte (elektrolyten, vitamines en mineralen).
- Een model bouwen voor individuele voedingsondersteuning met inachtneming van de grote diversiteit van de kinder-IC populatie.

CHAPTER 15
APPENDICES



AUTHOR AFFILIATIONS

Greet van den Berghe	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Britney Bernard	Department of Paediatrics, Intensive Care Unit, University Alberta, Stollery Children's Hospital, Edmonton, Canada.
Jeroen van Brakel	Department of Paediatrics and Paediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam
Michael P. Casaer	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Hanna van Cleemput	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Katrien Cosaert	Department of Pharmacy, University Hospitals KU Leuven, Leuven, Belgiu
Desley K. Dekker-van den Dungen	Department of Paediatrics and Paediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam
Lars Desmet	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Karolijn Dulfer	Department of Paediatrics and Paediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam
Astrid Durt	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Marianne Fricaudet	Université Claude Bernard Lyon 1, Villeurbanne, France
Georgia Harrison	Department of Paediatrics, University of the West of England, Bristol, United Kingdom

Lidwien M. Hanff	Department of Pharmacy, Princess Maxima Centre for Paediatric Oncology, Utrecht, The Netherlands
José A. Hordijk	Department of Paediatrics and Paediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam
Jessie M. Hulst	Paediatric Gastroenterology, Department of Paediatrics, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands; Division of Paediatric Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, Toronto, Canada
An Jacobs	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Fabian Güiza	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Mireia Garcia Garcia Cusco	Paediatric Intensive Care Unit, Bristol Royal Hospital for Children, University Hospitals Bristol NHS Trust, Bristol, United Kingdom
Gonzalo Garcia Guerra	Department of Paediatrics, Intensive Care Unit, University Alberta, Stollery Children's Hospital, Edmonton, Canada.
Koen F.M. Joosten	Department of Paediatrics and Paediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam
Barbara A.E. de Koning	Paediatric Gastroenterology, Department of Paediatrics, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands
Sofie Maebe	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium.
Louise V. Marino	Department of Dietetics and Speech & Language Therapy, University of Southampton, Southampton, United Kingdom; NIHR Biomedical Research Centre Southampton, University Hospital Southampton NHS Foundation Trust, University of Southampton,

	Southampton, United Kingdom; Faculty of Health Sciences, University of Southampton, Southampton, United Kingdom
Juan Mayordomo-Colunga	Paediatric Intensive Care Department, Hospital Universitario Central de Asturias, Oviedo, Spain; Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain; Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain
Katy Morton	Faculty of Health Sciences, University of Southampton, Southampton, United Kingdom; Paediatric Intensive Care, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
Jos M. Latour	School of Nursing and Midwifery, Faculty of Health and Human Sciences, University of Plymouth, Plymouth, United Kingdom
Lynne Latten	Department of Nutrition and Dietetics, Alder Hey Children's Hospital, Liverpool, United Kingdom
Jorge López	Paediatric Intensive Care Department, Gregorio Marañón General University Hospital, Gregorio Marañón Health Research Institute, Mother-Child Health and Development Network (RedSAMID) of Carlos III Health Institute, Complutense University of Madrid, Madrid, Spain
Sandra Leys	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Liese Mebis	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Esther van Puffelen	Department of Paediatrics and Paediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands

Dimitris Rizopoulos	Department of Biostatistics, Erasmus MC, Rotterdam, the Netherlands
Clare Smith	Paediatric Intensive Care Unit, Bristol Royal Hospital for Children, University Hospitals Bristol NHS Trust, Bristol, United Kingdom
Lyvonne N. Tume	Department of Child Health (Critical Care Nursing), School of Health & Society, University of Salford, Manchester, United Kingdom
Frédéric V. Valla	Department of Paediatric Intensive care unit, Hôpital Femme Mère Enfant, Carmen inserm umr 1060, Hospices Civils de Lyon, Lyon-Bron, France.
Ilse Vanhorebeek	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Ines Verlinden	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Sascha C.A.T. Verbruggen	Department of Paediatrics and Paediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam
Sören Verstraete	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Dirk Vlasselaers	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium
Bregje C.M. Witjes	Department of Clinical Pharmacology and pharmacy, Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, The Netherlands
Pieter J. Wouters	Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, University Hospitals KU Leuven, Leuven, Belgium

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*Contributed equally

PHD PORTOFOLIO

Name PhD student: Renate Desiree Eveleens
Erasmus MC Department: Intensive Care Unit, Department of Paediatric and Paediatric surgery
PhD Period: February 2017 – December 2020
Promotors: Prof. K.F.M. Joosten
Prof. M. de Hoog
Co promotor: Dr. S.C.A.T. Verbruggen

	Year	Workload (ECTS)
General academic skills		
Pubmed, Endnote and Searching in other databases	2017	1.0
BROK Erasmus University	2017	1.5
CPO course Erasmus MC	2017	0.3
Integrity in Scientific research	2017	0.3
Teach the Teacher I cursus	2019	0.6
Open Clinica Training	2019	0.3
Workshop coaching bachelor students	2018	0.2
Workshop individual counselling	2019	0.2
Research skills		
Biostatistical methods I: Basic principles – NIHES	2017	5.7
Using R for Statistics in Medical research - NIHES	2018	1.4
Repeated Measurements - NIHES	2018	1.4
Joint Models for longitudinal and survival data - NIHES	2018	0.7
Missing Value - NIHES	2019	1.4
Symposia / national conferences		
Erasmus PhD day	2017	0.3
Healthy Food Congress, The Netherlands	2017	0.3
Symposium "Sectie Intensive Care Kinderen (SICK)"	2017	0.3
Symposium "Voeding voor zieke kinderen"	2017	0.3
Tulips Young Research day	2017	0.3
Theme Sophia Research Day – *organiser*	2018	0.3
Theme Sophia Research Day – *organiser*	2019	0.3
Masterclass Gut and Beyond	2019	0.2
Refereer avond ICK – *oral*	2019	1.0
Symposium "Uitdaging of Kans?"	2020	0.3
International conferences		
39th ESPEN congress The Netherlands – *oral*	2017	2.0
51st ESPGHAN annual meeting, Switzerland – *poster*	2018	1.0
7th EAPS congress, France – *poster*	2018	1.0
52st ESPGHAN annual meeting, United Kingdom – *oral and poster*	2019	1.0
41th ESPEN Congress, Poland – *oral and poster*	2019	1.0
42th ESPEN Virtual Congress – *2x oral – best clinical abstract*	2020	1.0
8th EAPS Virtual congress – *oral*	2020	1.0

Local Research meetings		
Metabolism, endocrinology and nutrition (monthly) - *organiser*	2017-2019	0.5
Research work meetings KJPP (biweekly)	2017-2019	0.5
Research meetings PICU (weekly)	2018-2020	0.5
Teaching		
Master Thesis Supervision – M. Kooij – J. van Brakel J. Schuijs – M. Veen	2017-2020	2.0
Coaching bachelor students	2018-2020	1.0
Professional societies		
Member Theme Sophia Research Day 2018 committee	2017-2018	1.0
Member Theme Sophia Research Day 2019 committee	2018-2019	1.0
Member Erasmus Tour committee	2019-2020	0.5
Member SOV educational committee	2019-2020	0.5
Board member Sophia Research Representation (SOV)	2019-2020	1.0
Other		
Peer reviewer international scientific journals (e.g. Clin Nutr, Critical Care, JPEN)	2017-2020	0.5
Winner ESPEN Research Fellowship Grant	2019	
Nomination SICK Junior Researcher award	2020	
Winner best clinical abstract ESPEN congress	2020	
Nomination ESPNIC Young Investigators award	2020	
Total		39.4

CURRICULUM VITAE

Renate Desiree Eveleens was born on January 7th 1990 in Amstelveen, the Netherlands and grew up in Aalsmeer.

She completed her high school at the Alkwin Kollege in Uithoorn in 2008 and started her medical training at the Vrije Universiteit Amsterdam in the same year. During her first year in medical school she started volunteering in the Ronald McDonald children's city above the VUmc in Amsterdam which she continued for over 10 years. This city is designed for children and their relatives to forget their illness for a moment. She has been passionate on giving back to the community as she also volunteered in a poverty house building project in the Philippines when she was just 16 and worked in an elderly home.

During her master she did a general surgery internship at the Muhammadiya Hospital in Indonesia after which she traveled through Asia for five months. After finishing het senior clinical internship at the ear-nose-throat department at Amsterdam Medical Centre, where she worked together with the anatomy & embryology department on a 3D developmental atlas project of the inner ear, she obtained her master's degree in 2015.

In August 2015 she started working as a cardio-thoracic surgery resident (ANIOS) in the St. Antonius Hospital in Nieuwegein. Under supervision of Prof. dr. K.F.M. Joosten, Prof. dr. M. de Hoog and Dr. S.C.A.T. Verbuggen she started with her dissertation focusing on optimising barriers in enteral and parenteral nutrition in critically ill children at the paediatric intensive care unit at the Erasmuc MC-Sophia's Childrens Hospital in February 2017. During this period she was a board member of the Sophia Researchers Association and organised the Theme Sophia Research Days in 2018 and 2019. In January 2021 she started her anaesthesiology residency (AIOS) at Amsterdam UMC, location AMC. She is keen on combining her broad clinical interest and scientific aspirations in her future career.

DANKWOORD

Bij het schrijven van dit dankwoord realiseer ik me hoe leuk, bijzonder, intensief, mooi, gezellig en vooral leerzaam de afgelopen 4 jaar zijn geweest. Omdat je promoveren niet alleen kan doen, wil ik een aantal mensen in het bijzonder bedanken voor hun steun en begeleiding om de figuurlijke top van de promotieberg te bereiken.

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Om vanuit 020 promotieonderzoek te verrichten in 010 vindt plaats onder de nodige gevate opmerkingen en voetbaltermen. Waarvan één in het bijzonder een rode draad in mijn promotie heeft gevormd: the Champions League. Ik ben blij en vereerd dat ik heb mogen samenwerken met veel inspirerende, scherpe en kritische begeleiders.

Prof. Dr. Joosten, beste Koen. Niemand is beter geschikt om de rol als coach binnen de champions league te vervullen. Je weet op de juiste plek te stimuleren, de juiste mensen bij elkaar te zetten en blijft gevoel houden voor de persoon. Je betrokkenheid, efficiëntie (het was uitzonderlijk als ik niet binnen 48 uur een volledig geredigeerd manuscript terugkreeg) en kritische blik zorgde ervoor dat ik mij als wetenschapper optimaal heb kunnen ontplooien. Niet alleen binnen het ziekenhuis, maar ook daarbuiten maak je je hard voor optimale voedingszorg. Deze gedrevenheid hoop ik ook over te mogen dragen.

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Dr. Verbruggen, beste Sascha, coach, trainer, aanvoerder, welke rol had je eigenlijk niet? De hoeveelheid ballen die jij hooghoudt is benoemenswaardig, maar desondanks stond jij vooraan bij elke inclusie of probleem. Als ik vastliep, wanneer dit ook maar was, mocht ik

altijd even aankloppen. De hoeveelheid energie en nieuwe ideeën waarmee ik dan weer naar buiten liep heeft me enorm veel geholpen.

Prof. Dr. Van den Berghe, beste Greet, uw compassie voor wetenschap is ongeëvenaard. De samenwerking met het labo in Leuven was inpirerend en het is uiterst indrukwekkend hoeveel onderzoek u onder uw hoede heeft. Bedankt voor uw scherpe en gemotiveerde blik. Tevens bedankt voor uw deelname aan de grote commissie.

Prof. Dr. Utens, beste Lisbeth, uw enthousiasme en motivatie voor onderzoek is aanstekelijk, daarbij is uw expertise voor de pediatrische psychologie bewonderingswaardig. Daarmee wil ik u bedanken voor de bereidheid om plaats te nemen in de grote commissie.

Prof. Dr. Rings, Prof. Dr. Van Woensel en Prof. Dr. Van Zanten, bedankt voor het beoordelen van dit proefschrift en ik vind het een eer dat u allen bereid bent om deel te nemen in de commissie.

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Karolijn, jouw waarde voor het PEPaNIC FU project is onbeschrijfelijk. Niet alleen inhoudelijk of door het zien van de vele patiënten, vooral vanwege je empathie en de fijne mentale ondersteuning die je soms nodig hebt bij het doen van onderzoek.

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Sharon en Jolanda, wat fijn dat jullie als onderzoeksassistente vele uren hebben gebeld en patiënten hebben gezien. En dan vergeet ik nog al het harde werk rondom het sluiten van de datasets. Maar ook de psychologische en medische stagiairs enorm bedankt voor jullie inzet. Bedankt Charlotte (eigenlijk heb jij mij ingewerkt), Jeroen (wanneer gaan we nu klimmen?), Marissa (wat leuk dat we nu weer samen werken), Eline, Floortje, Lotte, Fien en Laura.

Het is bewonderenswaardig hoeveel werk verzet kan worden in één kwartaal. Bedankt Pieter, Ilse, Fabian, Sören, An, Ines, Liese, Sandra, Hanna, Astrid, Cettina en Shakira voor de fijne samenwerking en gastvrijheid. Elke trip naar Leuven zorgde voor een boost aan inspiratie.

Na het afronden van de PEPaNIC follow up, stond het volgende grote project op het programma: ContInNuPIC. Arnout en Karlien, in slechts een paar maanden hebben jullie het hele project op poten weten te zetten en ik ben heel benieuwd naar de komende tijd. Jullie maakte het laatste (corona) jaar een stuk gezelliger en laten we vooral snel weer een diner met wijn erbij houden. Ellen en Mirjam, het nut van verpleegkundige in een onderzoeksgroep is mij goed duidelijk geworden, jullie nemen ontzettend veel werk uit handen. Ook Maud (mis onze koffiemomentjes nu al) en Melissa bedankt voor jullie inzet en gezelligheid.

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Joke, jij hoort eigenlijk onder alle kopjes. Ontzettend bedankt voor al je hulp en het ad rem meedenken met alle problemen. Je bent een grote steun voor alle ICK onderzoekers.

Ik kan elke (medische) promovendus aanraden om in ieder geval een deel van de tijd te spenderen tussen psychologen. Naast psychosociale ondersteuning, is er op de KJPP afdeling geen gebrek aan statistische en wetenschappelijke kennis. De research lunches, borrels, kantoorcavia-gesprekken, theeleut-rondes en sportieve uitstapjes zoals de bruggenloop en bootcamp waren een fijne afwisseling. Suus, mijn enige eilandgenoot, wat heerlijk om naast jou te werken. Zonder jou was mijn promotie een stuk saaier geweest (en minder sportief), maar ik wil je vooral bedanken dat je altijd de moeite nam een antwoord op mijn vragen te vinden. Vanaf heden leid ik je in ieder geval niet meer op dagelijkse basis af.

Roomies, fijne collega's maken het werk pas echt leuk en bij ons was er geen gebrek aan gezelligheid. Wat ga ik onze koffierondes, escape room uitjes, kroketbuffets en do/vrijmibo's missen. Naast hard werken heb ik ook enorm met jullie gelachen, waarvan sommige mooie uitspraken nog steeds op de deur staan. Ik zal ze hier maar niet herhalen.

Wyts, al die lekkere (natuur)wijntjes hebben uiteindelijk geleidt tot de inspiratie voor de design van dit boekje. Op naar vele meer, afgewisseld met een sportief lesje.

Lieve, Heidi, Jeroen, Marjolijn, Ivar, Masha, Jimmy, Gusta en Martijn, en de uitbreiding Xam, Keo, Pux en Mika. Hoe lang zijn we nu al vrienden? Ik raak elke keer de tel kwijt, maar het voelt alsof jullie er altijd al waren. In het begin nog voorzichtig Sinterklaas-spelletjes spelen, lekker puberen in de kroegen van Noordwijk. Inmiddels hebben we allemaal een ander pad genomen. We zijn zo verschillend, maar matchen zo goed. Bedankt voor jullie steun en dat julie er altijd voor mij zijn, of de situatie nu om ijs, thee of wat sterkers vraagt.

Vanaf dag één op de VU was het raak en wat is het fijn dat we nog steeds zulke goede vriendinnen zijn. Wat heerlijk om te zien dat idereen een andere kant op is gegaan en een prachtige baan heeft weten te bemachtigen. Lieve, Violet, Truc My, Jessica en Emma, jullie begrijpen als geen ander hoe het is om te promoveren, maar vooral ook hoe je van het leven moet genieten. Ik kijk uit naar de feestjes, bruiloten, vele etentjes en (ski)vakanties die nog zullen volgen.

Lieve Eske, onze vriendschap begon op de long en geriatrie afdeling in het UZ Leuven. Met als traditie nog steeds onze jaarlijkste stedentripjes samen met Emma waarbij we meestal terug naar Leuven gaan. Weekendjes Rottedam/Zeeland, bbq's, festivalletjes met Mara. Dit dankwoord zou niet compleet zijn zonder jullie nadrukkelijk te bedanken voor jullie steun rond alle hoogte- en dieptepunten (lees Maleisië). Ik gun iedereen zo'n hechte vriendschap zoals ik met jullie heb!

Lieve Masha, wat fijn dat jij als paranimf aan mijn zijde staat. Vanaf moment één was je super enthousiast over het doen van onderzoek. Je hebt mij dan ook door alle momenten heen gesteund. De promotieoutfit was al besteld alvorens je uberhaupt de datum wist. Ik heb bewondering voor hoe jij in het leven staat en wat voor goede moeder je bent.

In slechts enkele jaren zijn wij gegroeid van collega's bij de CTC naar ontzettend goede vriendinnen en mogen wij vlak na elkaar aan elkaars zijde staan als paranimf. Wie o wie zal het eerst zijn? Maakt niet uit, zoalg de gepersonaliseerde Jimmy's maar binnen zijn. Bedankt voor je steun, het sparren en de gezamelijke schrijfsessies onder het genot van een kaasplankje en wijn. Ik heb onwijs genoten van de afgelopen jaren. Indonesië, Ibiza en Zuid-Afrika waren toch wel hele mooie hoogtepunten.

Wat is het een genot om af te dalen naar de Brabantse gezelligheid voor de schoonfamilie. Mijn tweede date was niet voor niets op de bank van "os" ma. Lekker curry eten, proper English tea drinken en vooral heel veel geklets en gezelligheid. Annette, haal dat schoon maar weg voor familie. Je ontvangt iedereen met open armen en geen verzoek is te gek. Wat fijn dat jij ons altijd uit de brand helpt en Murphy altijd welkom is. Dad, ik hou ervan

dat we samen kunnen genieten van koken, maar vooral van het daarna opeten. Brad, hoe vaak heb jij wel niet op onze bank geslapen? Gamen tot in de late uurtjes en onze favoriet burrito's eten. De traditie van spelletjes spelen zullen we nog lang volhouden nu Marjolein en Bram erbij zijn.

In een totaal niet medische familie blijft promoveren toch een abstract begrip. Eigenlijk weet ik het nog steeds niet goed uit te leggen. Wanneer ben je nu klaar? Toch zijn jullie elke keer benieuwd naar nieuwe artikelen. Mam, de hoeveelheid liefde die jij aan Amanda en mij geeft is onbeschrijfelijk. Nog steeds kan ik het beste winkelen met jou (sorry Lies)en staan we nog altijd graag in de Duitse kroegen gluhwijn te drinken. Pap, de waarde van hard werken en daarvan de vruchten plukken heb ik van jou geleerd. Van klein meisje in de veilingbak tussen de rozen, naar een promotiefeest had ik niet kunnen bereiken zonder een goede basis. Lieve Amanda, wat ben ik trots op je! Gewoon een studie naast je fulltimebaan oppakken. Gelukkig is het latten met Ram tussen Nederland en Nepal nu eindelijk voorbij!

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