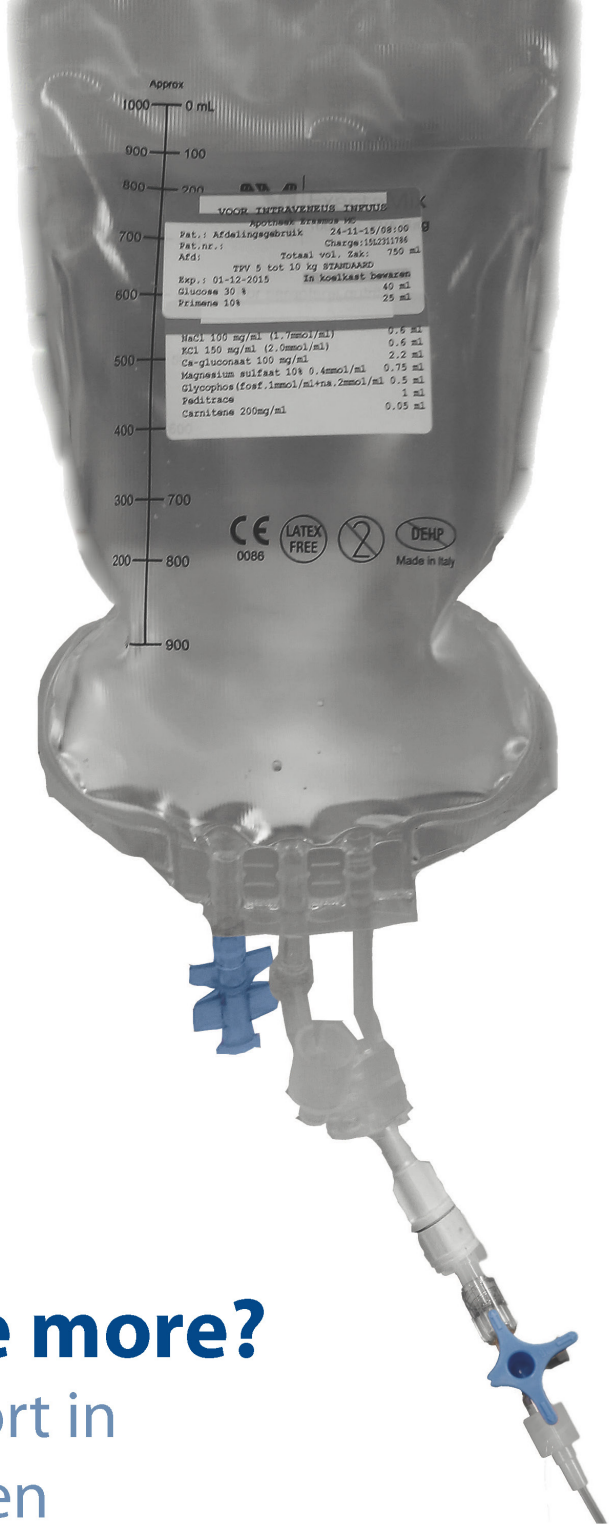

Could less be more?

Nutritional support in critically ill children

Dorian Kerklaan

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Voedingsstrategieën bij kritisch zieke kinderen

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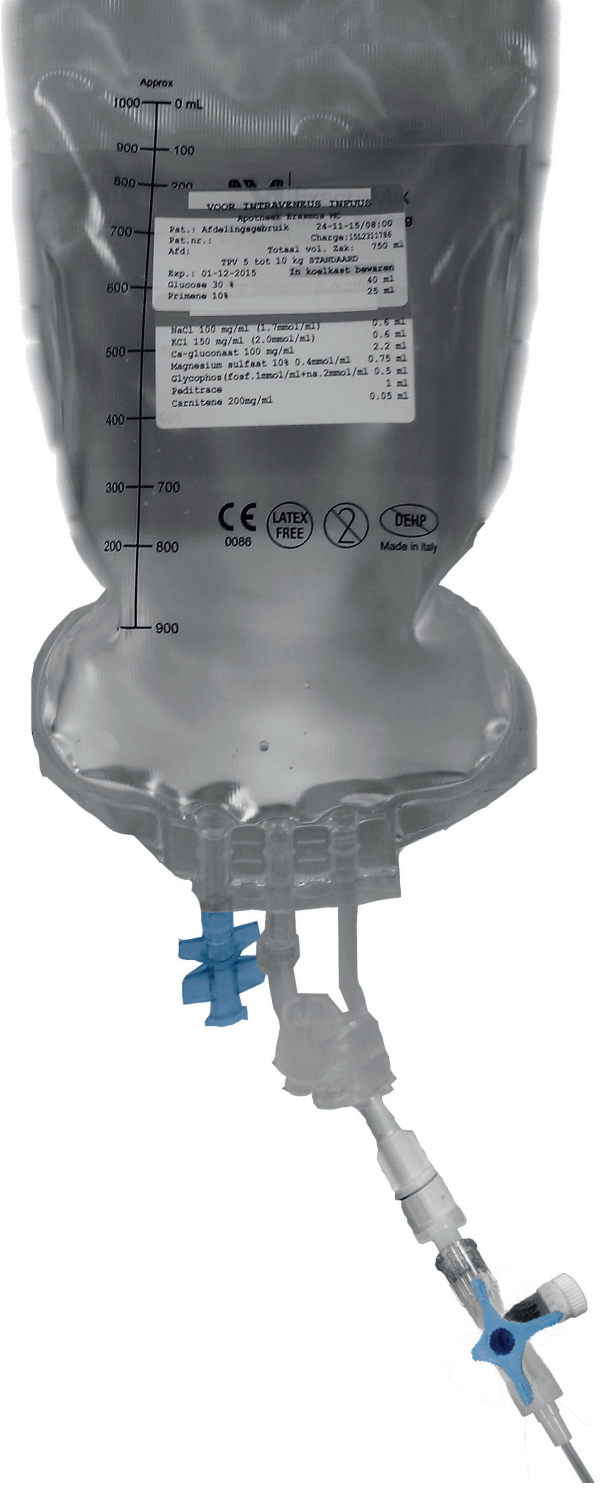
CONTENTS

PART I

INTRODUCTION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CHAPTER 1

General introduction

Adapted from:

Nutritional support and the role of the stress response in critically ill children

Koen F.M. Joosten, Dorian Kerklaan, Sascha C.A.T. Verbruggen

Current Opinion in Clinical Nutrition and Metabolic Care 2016;19:226-233

Nutritional challenges in the paediatric intensive care unit

Critical illness is characterised by anorexia and/or feeding intolerance. Critically ill children have limited macronutrient stores and higher energy requirements compared with adults. Without intervention, this results in substantial caloric and macronutrient deficits following paediatric intensive care unit (PICU) admittance, which have been associated with poor outcomes and impaired growth[1,2]. Therefore, current guidelines recommend to initiate nutritional support as soon as possible after admission[3,4], as it is associated with improved recovery and outcome in critically ill children[2,5]. However, these international consensus-based guidelines mostly rely on expert opinion and studies in adults and noncritically ill children, as there is a scarcity of high-level evidence on all aspects of nutritional support in critically ill children[6].

These low-grade and inconclusive guidelines are likely to represent a barrier to implementation[7,8], allowing wide variations in nutritional practices between PICUs[9,10].

Several recent high-quality trials in critically ill adults have raised questions on the presumed benefits of full-replacement nutrition *early* during critical illness[11,12]. Also in critically ill children, the optimal route, amount, and timing of nutritional support are expected to be dependent on the phase of the stress response in critical illness.

The stress response of critical illness

The concept of stress was already introduced more than 300 years ago, to describe a regular occurring event that enables an organism to cope with daily changes in the environment[13]. However, excessive stress, as seen in critical illness, is a well-recognised precedent of harm[13], and in order to survive it, a stress response is initiated. The teleological goal of this response is to provide effective supply of blood, energy and substrates to the injured site and vital tissues[14]. The neuro-endocrine, immunologic and metabolic responses to trauma or severe illness evolve over time[15,16]. This concept of different phases of stress response probably also applies to critically ill children. The following three phases of illness in critically ill children admitted to the PICU are proposed: the acute phase, the stable phase and the recovery phase, all characterised by specific neuro-endocrine, metabolic, and immunologic alterations (Table 1). We hypothesise that these phase-specific changes necessitate different macronutrient intakes.

Table 1. *Definitions of the three phases of the stress response in critically ill children*

	Definition
Acute phase	First phase after event, characterised by requirement of (escalating) vital organ support
Stable phase	Stabilisation or weaning of vital organ support, whereas the different aspects of the stress response are not (completely) resolved
Recovery phase	Clinical mobilisation with normalisation of neuro-endocrine, immunologic and metabolic alterations

Characteristics of the acute phase of critical illness

The acute phase of critical illness in children is characterised by the requirement of (escalating) vital organ support. The concomitant stress response, initiated by activation of an inflammatory cytokine cascade and the central nervous system, is aimed at surviving critical illness. A conceptual overview of the neuro-endocrine, metabolic and immunologic alterations is depicted in Figure 1.

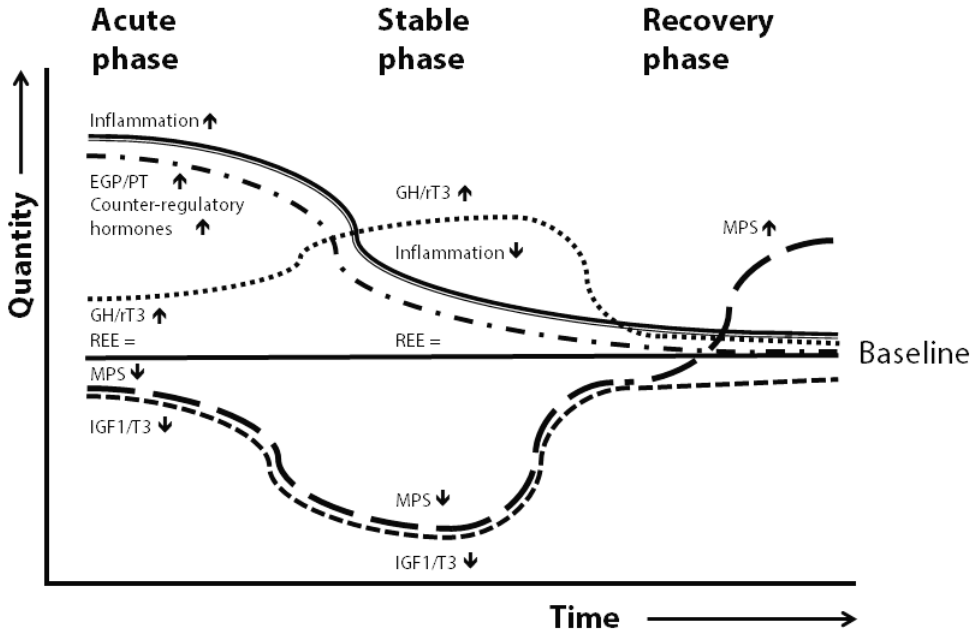

Figure 1. Conceptual overview of the different phases of critical illness with corresponding neuro-endocrine, immunologic and metabolic changes

EGP, endogenous glucose production; PT, protein turnover; GH, growth hormone; rT3, reverse triiodothyronine; REE, resting energy expenditure; MPS, muscle protein synthesis; IGF-1, insulin-like growth factor; T3, triiodothyronine; counter-regulatory hormones are cortisol, catecholamines and glucagon

Neuro-endocrine response

Despite activation of the hypothalamic-pituitary axis to release the anterior pituitary hormones corticotrophin (ACTH), thyroid stimulating hormone (TSH) and growth hormone, concentrations of most peripheral effector hormones, such as triiodothyronine (T3, active thyroid hormone) and insulin-like growth factor (IGF-1) are low due to inactivation or target organ resistance[17-19]. In absence of adrenal insufficiency, levels of cortisol rise substantially, mainly due to reduced metabolism in liver and kidneys[20,21].

Immunologic and metabolic response

The metabolic response is hypercatabolism. To guarantee substrate delivery to vital tissues, free amino acids and fatty acids (FFA) are mobilised by muscle protein breakdown and lipolysis, caused by elevated levels of cortisol and other counter-regulatory hormones (catecholamines and glucagon)[19,22,23]. This results in increased triglycerides levels and reduced high- and low-density-lipoproteins, especially in children with sepsis[24]. Hyperglycaemia develops due to increased endogenous glucose production and peripheral insulin resistance[25]. Hypercatabolism in the acute phase is primarily induced by inflammation and is more pronounced in multiorgan failure[26]. After the initial cytokine release, other markers of immune cell activation become apparent, such as acute phase $CD64^{+}$ expression on neutrophils and monocytes[27]. When comparing measured to predicted resting energy expenditure (REE), different metabolic patterns appear to interchange within the child during the clinical course of severe illness[28-32]. This might be explained by the varying and often opposing effects of the different components of the acute phase response on metabolic rate.

Duration of the stress response

This first phase can take hours to days after an event (such as trauma, sepsis or surgery) and, based on circumstantial evidence, might last shorter in surviving critically ill children than in critically ill adults. In the majority of children with meningococcal disease, blood glucose, cortisol and ACTH levels normalise within 48 hours suggesting an early resolution of the stress response concerning counter-regulatory hormones and glucose metabolism[33,34].

In critically ill and post-surgical neonates, the plasma levels of catecholamines, thyroid hormones and IGF-1 return to baseline even faster than in older children[35,36], with the earliest return of anabolic protein metabolism found after acute injury in preterm neonates[37].

Nutrient administration in the acute phase of critical illness

The acute stress response is affected by nutrition. However, in contrast to previous ideas, hypercatabolism and subsequent muscle atrophy are not reversed with increased provision of nutrients during this phase[26,38]. Recent high-quality trials in adults have extensively investigated the provision of artificial nutrition during this phase[11,12], and showed no beneficial effects of early initiation of parenteral nutrition[39-41]. Nutrient restriction early in critical illness enhanced the central and peripheral neuro-endocrine response by further lowering T3, thyroxine (T4) and TSH levels as well as the T3 (active thyroid hormone)/reverseT3 (inactive thyroid hormone) ratio. The T3/rT3 ratio was also further reduced by the application of a tight glucose control protocol in critically ill children[42]. This decrease in T3/rT3 ratio was associated with a better outcome both in critically ill adults and children[42,43], possibly indicating that changing the peripheral conversion of T4 from metabolically active T3 to inactive rT3 during the first days of critical illness is adaptive and beneficial for recovery[42].

Autophagy

The benefits of withholding artificial nutritional support during the acute phase may also be explained by the stimulating effect on autophagy[44,45]. Autophagy is an essential survival mechanism by which cells break down their own (damaged) components to recycle intracellular nutrients and generate energy during starvation[46-49]. Besides its role as cellular housekeeper, autophagy is involved in protein quality control of tissue and organs. Additionally, it regulates both innate and adaptive immune responses, partly by efficient clearance of intracellular pathogens. Activation of autophagy by withholding parenteral nutrition during acute critical illness might result in a better, more balanced physiological response with greater protein synthesis, energy production and maintenance of cell structure[41,44,45,49]. On the other hand, when autophagy is suppressed by forced overfeeding early in critical illness, the risk of organ failure and cell death may increase, resulting in worse clinical outcome. Preservation of autophagy in skeletal muscle partially explained why parenteral nutrient restriction reduced ICU-acquired weakness and enhanced recovery[38]. Although nutrient restriction is regarded as a risk factor for muscle atrophy, increased energy intake is associated with worsened muscle function in critically ill adults and animal models[38,44]. Prolonged upregulation of autophagy may lead to increased degradation of organelles and a failure to maintain energy provision, resulting in increased apoptosis and cell death[50]. The beneficial effects of nutrient restriction are therefore likely to be limited to the acute phase of critical illness.

Early enteral nutrition in critically ill children

Enteral nutrition is positioned as the preferred route over parenteral nutrition in critically ill children, and guidelines recommend initiation within 48 hours[4]. It prevents gut atrophy, preserves gut integrity and immunity, and hence decreases the risk for bacterial translocation and systemic infection[51,52]. In a retrospective study of 5105 critically ill children, early enteral nutrition, defined as the provision of 25% of target calories enterally over the first 48 hours of admission, was shown to be associated with a lower mortality rate in those with a PICU length of stay of at least 96 hours[53]. However, the observational design calls for caution in assuming that this association is causal, since patients who tolerate enteral nutrition early, are likely to have a better prognosis. In children with burns, early enteral nutrition (started within 3-6 hours) was clinically superior to late enteral nutrition (after 48 hours) with a lower mortality rate, shorter hospital stay and less weight loss[54], but data from this distinct patient group cannot automatically be applied to the general PICU population. Despite the current tendency to provide early enteral nutrition during PICU stay, initiation is often delayed and administration is frequently interrupted due to clinical procedures, gastro-intestinal intolerance and a number of misconceptions (Table 2)[55-59].

This results in a discrepancy between the amount of prescribed and delivered calories, with overall 50-60% of the prescribed calories not being delivered when using the enteral route[2,71,72].

Table 2. *Perceived barriers to (early) enteral nutrition in critically ill children*

	Barriers	Facts
Delayed initiation	(Non)-invasive positive pressure ventilation	Early enteral feedings are feasible, well tolerated, and cost-effective in mechanically ventilated children[60,61]
	Gastro-intestinal surgery	Early enteral nutrition after small and large operations in children, including intestinal resection, is safe and feasible. It promotes rapid elimination of intestinal paresis, early activation of motor function, mucosal regeneration and early activation of absorptive function, thereby reducing infection rate and length of hospital stay[62,63]
	Use of vasoactive drugs	Enteral nutrition in patients on vasoactive drugs improves gut blood flow and is associated with no difference in gastro-intestinal outcomes and a tendency towards lower mortality[61]
Interruption of delivery	High GRV	Available large RCTs in adults consistently showed no beneficial effect of GRV monitoring[64], with a higher chance of achieving nutrient goals if GRV is not monitored[65] The accuracy of GRV measurement to predict enteral nutrition intolerance has not been studied in critically ill children[66]
	Procedures requiring fasting, including surgery and planned extubation	A reduced fasting protocol by use of clear fluids is safe and feasible[67]
	Absence of bowel sounds	Auscultation of bowel sounds has limited clinical utility and should not be used to guide provision of enteral nutrition[68]
Fluid restriction	Diagnosis dependent, often in cardiac or renal patients	Use of energy and protein enriched formulas might increase the chance of achieving caloric goals[69]. Interdisciplinary team interventions improve nutrition delivery[70]

GRV, gastric residual volume; RCT, randomised controlled trial

Early parenteral nutrition in critically ill children

Evidence on the impact of (supplemental) parenteral nutrition on clinical outcomes in critically ill children is currently lacking[6]. Some nonrandomised studies, or studies with surrogate outcome measures, have pointed toward potential disadvantages of parenteral nutrition in this population. In a retrospective study of 204 nonsurgical critically ill children eligible for enteral nutrition provision, supplementation of parenteral nutrition was associated with a higher nosocomial infection rate than administration of enteral nutrition alone (34.0 vs.10.9%, *P* less than 0.001)[73]. The use of parenteral nutrition was one of the most significant predictors for nosocomial infections in a prospective cohort of 1106 cardiac PICU patients (odds ratio 1.2, 95% confidence interval 1.1-1.4)[74]. Use of parenteral nutrition has shown to be the single significant factor determining energy intake in mixed-effect modelling and is also identified as risk factor for overfeeding[1,75], possibly because higher provision of energy is possible, while administration is less interrupted compared to enteral nutrition. In septic adolescents, metabolic side effects, such as enhanced endogenous glucose production and lipolysis, were

encountered with high parenteral protein intake (3 g/kg/day), raising concerns of an increased insulin resistance[76]. High doses of parenteral glucose are associated with side-effects, as lipogenesis and hyperglycaemia, which can safely be prevented by amounts of parenteral glucose below current guidelines[77,78]. Therefore, it remains unclear whether insufficient nutrient administration by the enteral route should be supplemented with parenteral nutrition.

The stable and recovery phase of critical illness

The stable phase

The stable phase of critical illness is represented by stabilisation or weaning of vital organ support, whereas the different aspects of the stress response are not (completely) resolved. In addition to persistent low peripheral hormone levels, this phase is also characterised by a central suppression of the different endocrine axes (Fig. 1)[14]. In contrast to the target organ resistance marking the acute phase, peripheral tissues respond to low T3 concentrations by increase of local hormone availability and effects[79,80]. Despite increased effect of this anabolic hormone, large amounts of protein continue to be wasted, whereas fat stores remain relatively intact[81]. Plasma cytokine concentrations are substantially decreased, but immune cell function remains affected, as shown by persistent alterations in glycoprotein expression. The duration of this phase can range from days to weeks, depending on the age and diagnosis of the child[82]. In mixed populations of critically ill children, levels of anabolic hormones such as T3, growth hormone and (bioavailable) IGF-1 already increase during the first week of admission[36,83]. Recovery of anabolism appears to be in concert with the resolution of inflammation, as shown by the relation between T3 and C-reactive protein (CRP) levels[36] and between early metabolic markers, such as triglycerides levels, and immunologic parameters such as acute phase $CD64^{+}$ expression on neutrophils[24].

However, despite early normalisation of the catabolic counter-regulatory hormone levels, other parameters of the neuro-endocrine, metabolic and immunologic stress response might need more time to resolve.

The recovery phase

Clinical mobilisation of the child, that is no longer in need of vital organ support, together with resolution of the stress response, marks the onset of the recovery phase. This final phase may last weeks to months. Hormone levels gradually return to normal (Fig. 1). The body shifts from catabolism to anabolism with protein synthesis exceeding protein breakdown, resulting in positive nitrogen balance, tissue repair and (catch-up) growth. Restoration of mitochondrial function is achieved with accelerated stimulation of mitochondrial protein (biogenesis)[84]. However, in children with burns a persistent hypermetabolic state is known to delay anabolism and growth[85], and suppressed insulin receptor signalling can be detected up to 250 days postburn[86].

Despite the improvement of neuro-endocrine, immunologic and metabolic status, clinical parameters, such as weight and functional status (measured with the Functional Status Scale in medical and cardiac critically ill children), are known to be worse at discharge[71,87]. Profound muscle weakness, due to muscle wasting and critical illness myopathy as observed with prolonged duration of the stable phase, contributes to morbidity and adverse outcome in the ICU and PICU[88,89] and may even cause long-term functional disability beyond hospital discharge[89].

Nutrient administration in the stable and recovery phase

The focus of nutritional therapy during the stable and recovery phase should be aimed at restoration of lean body mass whereas synthesis of excess fat mass is to be avoided. To prevent muscle weakness, the duration of immobilisation should be reduced as much as possible[90]. A combination of optimal nutritional support and physical exercise/mobilisation appears to be a logical intervention, but no such studies have been performed in critically ill patients[91].

A recent systematic review and a single centre study in mechanically ventilated children, calculated a minimum intake of respectively 57 and 58 kcal/kg/day to achieve a positive nitrogen balance[92,93]. In both studies, a protein intake of 1.5 g/kg/day was required to equilibrate nitrogen balance, reflecting a protein-energy ratio of around 10 energy%protein. Since these two studies made no distinction between the phases of critical illness, it remains unclear if this minimal intake should already be provided in the acute phase or should be reserved for subsequent phases. Because nutritional intake during the stable and recovery phase is not only aimed at equilibrating nitrogen balance, but also at enabling recovery, growth and catch-up growth, caloric intake during these phases needs to be inclined from the above mentioned minimum intake[94,95]. Indeed, higher caloric and protein intake (with a sufficient protein-energy ratio) via the enteral route are associated with higher 60-day survival[2,96], asking for a more aggressive feeding approach than in the acute phase.

Energy expenditure throughout the course of critical illness

Energy requirements for critically ill children vary between individuals and also between the phases of critical illness. REE is one component of total energy expenditure (TEE), the other components are physical activity, the thermic effect of food, and the energy cost of growth. Currently, optimal caloric intake in critically ill children is frequently defined as 90-110% of REE[1,97-99], with an intake below or above this range indicating underfeeding and overfeeding, respectively. In order to prevent the detrimental effects associated with these two types of malnutrition, REE is advised to guide nutritional therapy throughout the course of illness[2,4,100-102]. Ideally, REE should be measured using indirect calorimetry (IC). With IC, a metabolic monitor is attached to the ventilator circuit of the child to derive REE from minute-to-minute measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2)[103]. Alternatively, a canopy mode can be used for spontaneously breathing children. The

child's REE can accurately be reflected by a measurement of at least 5 minutes[104]. However, most measurements will take at least 30 minutes, taking into account the time to connect the metabolic monitor and the time to reach steady state.

Within-day and between-day variations in REE from the acute phase to the stable phase are small in the majority of critically ill children[1,94,105-107], so a single measurement early during admission may serve to guide nutritional therapy. Since REE remains stable, but requirements are likely to change during the different phases of critical illness, the optimal caloric intake in relation to REE is likely to vary as well.

Despite its superiority in predicting REE, only a minority of PICUs uses IC to determine energy requirements[9], because measurements are time consuming and limited to stabilised mechanically ventilated children with mild ventilator settings or spontaneously breathing children without need for oxygen. High purchase and maintenance expenses of metabolic monitors further limit availability of IC. Alternatively, a simplified metabolic equation using ventilator-derived VCO_2 measurements, could allow measurement of energy expenditure in absence of a metabolic monitor[108]. However, this approach needs to be validated for use in critically ill children.

Due to the limited availability and practice of IC, REE is predominantly predicted by age-dependent equations based on weight and/or height. These equations, derived from measurements in healthy children, do not predict energy requirements accurately in critically ill children, resulting in an increased risk of malnutrition during PICU stay[105,109,110]. Several factors, commonly present in the PICU, affect measured REE; fever is found to increase REE, while sedatives and muscle relaxants have shown to decrease it[111]. An increase of REE is also seen in children with burns[112], septic neonates[30,113] and in children after major surgeries, but only temporarily[31]. However, despite these established effects, the application of uniform correction factors to REE for the whole PICU population is simplistic and likely to be inaccurate[4]. Therefore, when IC is not possible, it is preferred to derive REE from Schofield's formula for weight, without the addition of stress or activity factors[4].

Respiratory Quotient

The VCO_2 and VO_2 values obtained by IC are not solely used to calculate REE. Their ratio (VCO_2/VO_2), known as the respiratory quotient (RQ), reflects the utilisation of different substrates. A value >1.0 indicates lipogenesis and can be used to identify carbohydrate overfeeding[114-116]. A high amount of carbohydrates will not always result in an RQ >1.0 because ongoing utilisation of fat for energy, as seen in critical illness, will lower the measured RQ[117]. RQ is also affected by hyperventilation and metabolic acidosis. Therefore, a cautious interpretation of this variable is necessary before adjusting nutritional practices. The measured RQ value can also function as an indicator of caloric overfeeding when it is compared to the predicted RQ based on the macronutrients provided (RQ_{macr})[118,119]. Its adequacy to detect overfeeding is affected by the presence of endogenous energy production, as seen in children with caloric intake below

measured REE[120] and during the acute phase of critical illness[117]. Therefore, application of this parameter may be limited to the stable and recovery phase of critical illness.

In conclusion it can be stated that:

- Low-grade and inconclusive evidence-based guidelines, resulting from a scarcity of high-level evidence on all aspects of nutritional support in critically ill children, are likely to allow wide variations in nutritional practices between PICUs.

- Understanding the stress response to critical illness and the characteristics of its three phases is essential for nutritional recommendations in critically ill children.

- During the course of critical illness, the enteral route is preferred, but several misconceptions concerning the provision of enteral nutrition prevent adequate intake.

- Use of parenteral nutrition in critically ill children is associated with potential disadvantages, but clinical outcome studies are lacking. Parenteral nutrient restriction early during critical illness might be beneficial for short and long-term outcomes by amplifying the acute catabolic stress response and stimulating autophagy and muscle integrity.

- During the stable and recovery phase, inclining caloric and protein requirements allow for a more aggressive feeding approach, together with mobilisation, to enable recovery, rehabilitation and (catch-up) growth.

Outline of this thesis

Part I: Introduction

This thesis aims to provide insight in current nutritional support during stay on the paediatric intensive care unit (PICU), concerning the route, timing and amount of artificial nutrition, with focus on the identification and risk of caloric overfeeding and the use of (supplemental) parenteral nutrition.

Part II: Current nutritional practices

The second part of this thesis describes daily nutritional practice in the PICU. Chapter 2 highlights the variation in current clinical practice regarding several aspects of nutritional support by an international online survey in 156 PICUs across the world. To compare intended with applied nutritional practice, this survey identifies information on local strategies as well as their execution in patients by use of point prevalence data.

Part III: Energy expenditure

The third part focuses on the determination of resting energy expenditure (REE) by indirect calorimetry in critically ill children. Chapter 3 aimed to validate an alternative method for measurement of energy expenditure with indirect calorimetry by use of ventilator-derived VCO_2 measurements in 41 mechanically ventilated children. In Chapter 4 different internationally used definitions of caloric overfeeding are compared in order to find the most adequate method to identify overfeeding. In order to do so, measurements of REE and respiratory quotient from 79 mechanically ventilated children are studied in relation to caloric intake.

Part IV: Supplemental parenteral nutrition

In this part the effect of timing of parenteral nutrition in the PICU is investigated. Chapter 5 reviews the current scarce evidence for the use of parenteral nutrition in the PICU, thereby underlining the need for large nutritional RCTs. In Chapter 6 and 7 a multicentre, international RCT in 1440 critically ill children at nutritional risk is described. The strategy of withholding supplemental parenteral nutrition for one week in the PICU is compared to providing early parenteral nutrition. Primary clinical outcomes are the number of patients with new infections and length of PICU stay.

Part V: General discussion, including future perspectives, and summary

The last part of this thesis is dedicated to the general discussion and suggestions for future research in nutritional support, which can be read in Chapter 8. A summary of the major findings of this thesis can be found in Chapter 9 (English and Dutch).

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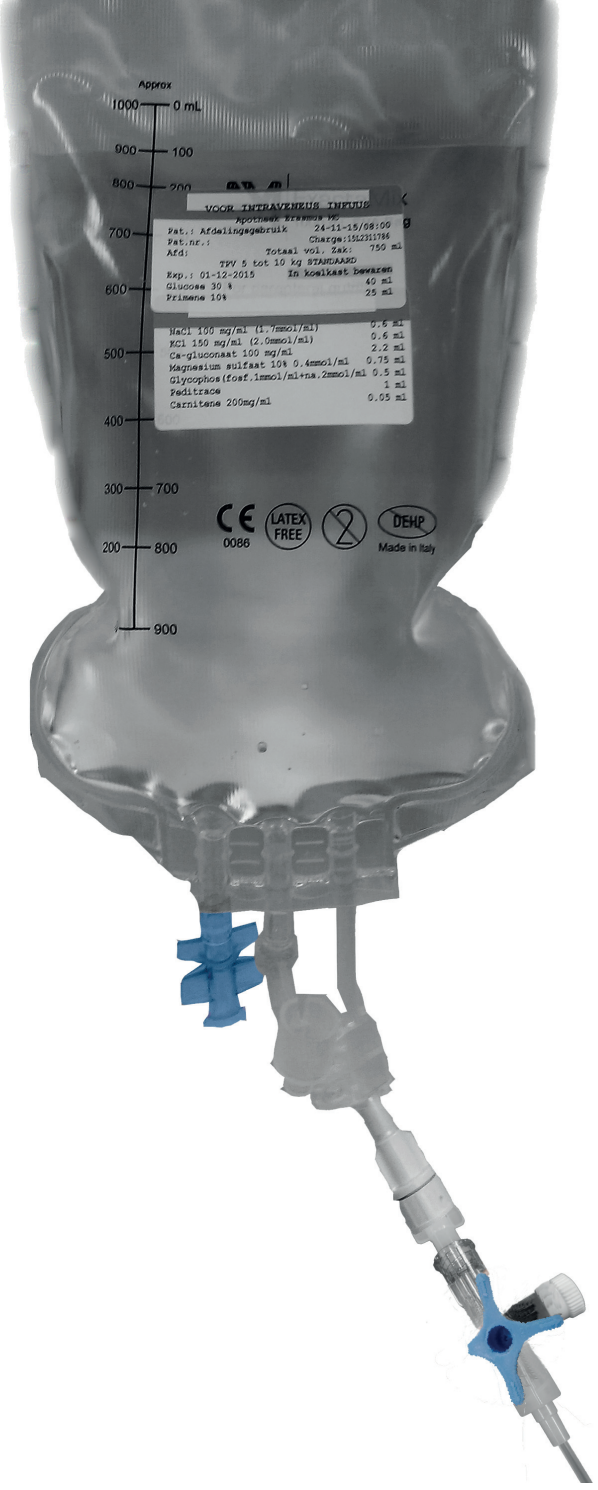
PART II

CURRENT NUTRITIONAL PRACTICES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KCl 150 mg/ml (2.0mmol/ml)
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CHAPTER 2

Worldwide survey of nutritional practices in PICUs

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ABSTRACT

Objective

To assess current nutritional practices in critically ill children worldwide.

Materials and methods

Members of the World Federation of Pediatric Intensive and Critical Care Societies were asked to complete a two-part online, international survey. The first part, the *survey,* was composed of 59 questions regarding nutritional strategies and protocols (July-November 2013). The second part surveyed the *point prevalence* of nutritional data of patients present in a subgroup of the responding PICUs (May-September 2014).

Results

We analyzed 189 responses from 156 PICUs in 52 countries (*survey*). We received nutritional data on 295 patients from 41 of these 156 responding PICUs in 27 countries (*point prevalence*). According to the *survey*, nutritional protocols and support teams were available in 52% and 57% of the PICUs, respectively. Various equations were in use to estimate energy requirements; only in 14% of PICUs, indirect calorimetry was used. Nutritional targets for macronutrients, corrected for age/weight, varied widely. Enteral nutrition would be started early (within 24 hr of admission) in 60% of PICUs, preferably by the gastric route (88%). In patients intolerant to enteral nutrition, parenteral nutrition would be started within 48 hours in 55% of PICUs. Overall, in 72% of PICUs supplemental parenteral nutrition would be used if enteral nutrition failed to meet at least 50% of energy delivery goal. Several differences between the intended (*survey*) and the actual (*point prevalence*) nutritional practices were found in the responding PICUs, predominantly overestimating the ability to adequately feed patients.

Conclusion

Nutritional practices vary widely between PICUs worldwide. There are significant differences in macronutrient goals, estimating energy requirements, timing of nutrient delivery, and threshold for supplemental parenteral nutrition. Uniform consensus-based nutrition practices, preferably guided by evidence, are desirable in the PICU.

INTRODUCTION

Nutritional support affects recovery and outcome in critically ill children[1-3]. Although undernutrition has been the primary focus, overfeeding in PICUs is also associated with increased morbidity[4,5]. Despite its clinical relevance, there is a scarcity of high-level evidence on various aspects of nutritional support in critically ill children[6]. With grade C as the maximum level of evidence, available guidelines for nutrition support in critically ill children are based on insufficient data for evidence-based recommendations.

Consensus-based guidelines provided by expert committees (American Society for Parenteral and Enteral Nutrition [A.S.P.E.N.], European Society for Clinical Nutrition and Metabolism [ESPEN], and the European Society for Paediatric Gastroenterology Hepatology and Nutrition [ESPGHAN]) are based on scant evidence, and are largely driven by expert opinion and extrapolations from studies in adults or noncritically ill children[7,8]. Low-grade or inconclusive evidence-based protocols represent a barrier to implementation with differences most prominent in areas with the weakest evidence[9,10]. This allows wide variations in nutritional practices for patients in European PICUs as shown in previous studies[11,12]. The variability in timing, amount, and composition of nutrition would inevitably result in underfeeding and/or overfeeding, which could potentially impact the clinical outcome of critically ill children and overall health care expenses[13]. While evidence on many aspects of nutrition is lacking, there appears to be consensus on the benefits of early enteral nutrition (EN) and the need to prevent further nutritional deterioration in this population.

The purpose of our study was to assess the current nutritional practice in PICUs across the world. We hypothesized that the limited guidelines available have not been universally implemented, and that current practice is heterogeneous and mostly physician based. Since the guidelines at least agree on the importance of EN[7,14,15], we expected no significant differences in this practice between PICUs. Other factors, such as assessment of energy requirements or use of parenteral nutrition (PN), are more likely to vary between countries and hospitals given the weak recommendations.

To quantify the variations in clinical practice, we distributed a two-part online survey to PICUs across the world. The first part of the *survey* was composed of questions on various aspects of local nutritional practice. The second part was a *point prevalence* survey on nutritional data collected in all patients present in the unit on a single day in a subgroup of the responding PICUs. Answers were analyzed, correlated with PICU characteristics, and differences between the intended (*survey*) and the actual (*point prevalence*) nutritional practices were determined.

MATERIAL AND METHODS

The local Institutional Review Board of the Erasmus MC in Rotterdam waived the need for consent. The participation in this survey was voluntary, and no patient identifiers were collected.
The cross-sectional *survey* was conducted between July and November 2013. The online questionnaire was composed of 59 questions regarding local nutritional protocols and strategies, and provided in English, French, Spanish and Chinese. The second part, the *point prevalence*, conducted between May and September 2014, involved data collection on nutritional practices and intake for the preceding 24 hours. In a subgroup of centers that agreed to participate in this portion of the study, respondents were asked to include data for all patients present in their PICU; no selection criteria were applied. Both questionnaires are available as an *online supplement* (Supplementary Digital Content: http://links.lww.com/PCC/A204).

Testing of clarity, relevance, and clinical sensibility of the English questionnaire was performed by independent clinicians in three centers (Sophia Children's Hospital-Erasmus MC, Rotterdam, the Netherlands; University Hospital of Leuven, Belgium; and the Boston Children's Hospital, Boston, MA). Data from this test were not included in the final analysis and survey results. Afterward, the questions were translated to French, Spanish, and Chinese by native speakers.
An invitation to the *survey* was electronically distributed to members of the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS) by their mailing list and to specific members of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) and Society of Critical Care Medicine involved in nutritional management and through the newsletter of both the ESPNIC and WFPICCS and the WFPICCS homepage and LinkedIn group. A reminder was sent 2 months after the first invitation. Due to incomplete data registration, the exact number of PICUs represented by the WFPICCS database is unknown. Respondents who provided their contact information in the *survey,* were approached to participate in the *point prevalence*.
If more than one questionnaire was returned from a single PICU, the answers were weighted by the inverse of the number of completed questionnaires per center, in order to process conflicting statements within a single institution without disrupting the weight of the answers per PICU. Countries were classified by income according to The World Bank income groups[16]. Individual questions were stratified by continent, income of country, number of PICU beds, admissions per year, and percentage of ventilated patients.

Statistical analysis was performed using IBM SPSS statistics 21 for Windows (IBM, Chicago, IL). Descriptive statistics were used to compare differences in respondent characteristics and survey responses. Nutritional data obtained in the *point prevalence* were compared to

the *survey* results for each participating center. Logistic regression, ordinal or multinomial, depending on the type of outcome, was used to identify the relation between the answers provided and the characteristics of the different PICUs. To correct for cluster effects due to multiple returned questionnaires per PICU, generalized estimating equations were used in conjunction with robust standard error estimates (Huber sandwich estimator). All statistical tests were two-sided, and statistical significance was defined as a *p* value of less than 0.05.
This trial was registered in the Dutch Trial Register at number 4093 (http://www.trialregister.nl).

RESULTS

Response

After distribution of the first part of the *survey,* a total of 251 questionnaires were received. Fifty-two questionnaires were removed because of missing essential data, defined as nutritional data (so only information on PICU characteristics available), and/or data essential for distinguishing PICUs from each other without possibility for clarification. Of the remaining 199 questionnaires, 10 were duplicate replies by the same respondent and therefore deleted. One hundred eighty-nine questionnaires were analyzed, representing 156 PICUs in 52 countries and six continents as shown in Figure 1.
For the *point prevalence,* we collected nutritional data on 295 patients in total, from 41 of the responding PICUs (26%) from 27 countries on six continents with a median input of five patients (interquartile range [IQR], 2-9) per PICU. Characteristics of responding PICUs for the *point prevalence* were similar compared with the overall *survey* respondents (Table 1).

Figure 1. One hundred fifty-six PICUs from 52 participating countries (in gray) participated in the survey, covering six continents

Table 1. *PICU characteristics of the first (n = 156) and point prevalence part (n = 41) of the survey*

Characteristic	No. of PICUs (%)	
	Part 1: Survey (n = 156)	Part 2: Point prevalence (n = 41)
Continent		
Asia	37 (24)	9 (22)
Africa	5 (3.2)	2 (4.9)
Europe	48 (31)	16 (39)
North America	33 (21)	3 (7.3)
Oceania	9 (5.8)	2 (4.9)
South America	24 (15)	9 (22)
Income category (country)		
Low	1 (0.6)	0 (0.0)
Lower middle	20 (13)	2 (4.9)
Upper middle	49 (31)	15 (37)
High	86 (55)	24 (59)
Hospital type		
General hospital	31 (20)	7 (17)
University hospital	51 (33)	15 (35)
Children's hospital	20 (13)	4 (9.8)
University children's hospital	48 (31)	14 (33)
Type of PICU		
Multidisciplinary/mixed	135 (86)	35 (85)
Cardiac	6 (4.0)	2 (4.9)
Medical	8 (5.1)	2 (4.9)
Combination of PICU		
With adult ICU	9 (5.8)	1 (2.4)
With Neonatal ICU	25 (16)	8 (20)
With adult and neonatal ICU	3 (2.0)	0 (0.0)
Not combined	119 (76)	32 (78)
Size of PICU		
1-10 beds	76 (49)	20 (49)
11-20 beds	51 (33)	13 (32)
21-30 beds	23 (15)	7 (17)
>30 beds	6 (3.5)	1 (2.4)
Admissions (patients/yr)		
Median (interquartile range)	500 (296-793)	450 (350-700)
Ventilated patients		
< 25%	22 (14)	5 (12)
25-50%	55 (35)	13 (32)
50-75%	49 (31)	14 (33)
>75%	30 (19)	10 (23)

PICU and patient demographics

The responding PICUs in the first part of the *survey* represented approximately 90,000 admissions per year. Fifty-two percent of PICUs were located in North America and Europe. Fourteen percent of PICUs were situated in low- or lower-middle-income countries, and 86% of PICUs were multidisciplinary. All PICU demographics are shown in Table 1.

Of the 295 patients included in the *point prevalence*, 60% were male patients and 58% younger than 1 year. Median length of stay (LOS) at moment of data collection was 6 days (IQR, 2-15), with a LOS greater than 7 days in 40% of the patients. Median weight was 7 kg (IQR, 4-16), and 46% of the children were mechanically ventilated.

Nutritional support

According to the first part of the *survey*, a nutritional protocol was present in 52% of PICUs; protocol characteristics are shown in Table 2. A Nutrition Support Team (NST) was available in 57% of the PICUs and 51% of the teams visited the ICU daily. The composition of an NST differed; it consisted mostly of dieticians (88%) and pediatric intensivists (51%).

In the *point prevalence* part of the study, median caloric intake did not differ in children fed by EN exclusively (n = 129) between the following four groups (p = 0.18): 1) PICUs with an NST (76 kcal/kg/d), 2) PICUs with a nutritional protocol (76 kcal/kg/d), 3) PICUs with both an NST and nutritional protocol (64 kcal/kg/d), and 4) PICUs without an NST and protocol (58 kcal/kg/d). There was also no difference in the proportion of children receiving EN in PICUs with and without an NST and/or protocol.

Table 2. *Characteristics of nutritional protocols*

Characteristic	**No. of PICUs (%)** Total 156
Protocol available	82 (52)
Information in protocol	
Assessment of energy requirements	72 (89)
Protein requirements	65 (81)
Management of gastric residual volume	57 (71)
Type of EN	72 (89)
Amount of EN	75 (94)
Composition of PN	71 (88)
Amount of PN	72 (89)
Protocol age/weight differentiated	
Not	6 (7.7)
For EN	8 (10)
For PN	7 (8.7)
For both EN and PN	59 (74)

EN = Enteral Nutrition, PN = Parenteral Nutrition

Nutritional requirements

To predict energy expenditure (EE) different equations were used according to the first part of the *survey*, mainly those published by Schofield[17] (25%) and the World Health Organization (WHO)[18] (25%), but also the Harris-Benedict equation[19] (17%). Seventy percent used correction factors, as fever (41% of PICUs), diagnosis (54%) and growth (23%) to calculate energy needs. Twenty-four percent of respondents did not know which equation was used to calculate EE in their unit. Indirect calorimetry (IC) to measure EE was used in 14% of the PICUs. The first

IC measurement was performed if expected stay was longer than 4 days (31% of PICUs), as soon as ventilator settings were appropriate (18%), in case of weight loss (15%) or patient dependent (11%: obese patients, high risk of malnutrition).

Age-based protein targets recommended by the A.S.P.E.N. and ESPEN/ESPGHAN guidelines (ranging from 0.9 to 3 g protein/kg/d) were followed in 31% and 36% of PICUs, respectively[7,8]. Lipid targets ranged from less than 1.5 to more than 3.5 g/kg/d, where the range of 1.5 to 2.5 g/kg/d was predominantly used (41%). Sixteen percent and 7.9% of the respondents did not know what their protein and lipid targets were, respectively.

In the *point prevalence*, median caloric intake was 66 kcal/kg/d (IQR, 49-96) for children on EN exclusively (n = 129); intake per kg of weight decreased significantly with age as expected ($p < 0.001$) (Fig. 2). In 31% of the children, the caloric intake was lower than basal metabolic rate calculated by the weight-based Schofield equation; for the WHO equation, this was 27%. Median protein intake was 1.8 g/kg/d (IQR, 1.2-2.6); only 34% of the children met the intended target protein intake of their PICU as mentioned in the *survey*.

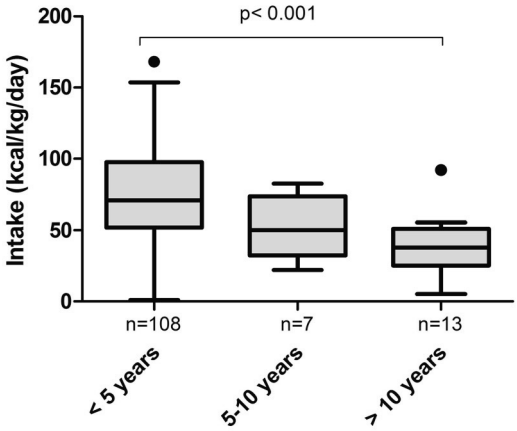

Figure 2. Caloric intake in different age categories in the *point prevalence*; $p < 0.001$ when comparing intake in the three different age categories (Kruskal-Wallis test). Boxes represent 25th to 75th percentile, whiskers by Tukey method

Timing and route of nutrition

In the first part of the *survey*, an early start (within 24 hr after admission) of EN was mentioned for 60% of PICUs (Fig. 3); in 31%, EN would even be started within 12 hours. Fifty-nine percent of the respondents had the perception that they were able to feed patients exclusively by enteral route within 3 days postadmission. The gastric route was preferred for EN in ventilated (67% of PICUs) and nonventilated patients (88%). Prokinetics were prescribed when a patient was not tolerating feeds in 70% of PICUs. EN was stopped or decreased due to the following reasons: high gastric residuals (73% of PICUs), abdominal distension/pain (85%), diarrhea

(32%), vomiting (75%), reduced/altered bowel sounds (23%), hemodynamic instability (62%), or use of muscle relaxants (12%).

Early PN would be started within 48 hours after admission in 55% of PICUs, while in 3.5% of PICUs there would be trials of EN for at least 7 days before starting PN (Fig. 3). When EN was insufficient, respondents from 18% of the PICUs would always supplement PN, whereas in 7.5% supplemental PN would never be utilized. Seventy-two percent supplemented PN if EN failed to meet 50% of target calories; 24% if EN failed to meet 80%. PN was stopped in 64% of PICUs when EN covered more than 80% of the nutritional targets.

At the moment of our *point prevalence* 73% of the children received EN ($n = 216$), predominantly by gastric tube (70%). There was no difference in caloric intake ($p = 0.82$) or in prokinetics use ($p = 0.47$) between children fed by gastric or postpyloric route. Forty-two percent of children with LOS less than 24 hours ($n = 43$) were already receiving EN, and in children with LOS of 2 days or more ($n = 253$), EN was provided in 78%. Twenty-one percent of all children received PN in some form and 10% received a combination of EN and PN; both groups at a median LOS of 6.5 days. The *point prevalence* showed that the ability to administer exclusive EN was overestimated; 40% of children ($n = 74$) present during the *point prevalence* achieved exclusive EN later than perceived by the respondents from the first part of the *survey*.

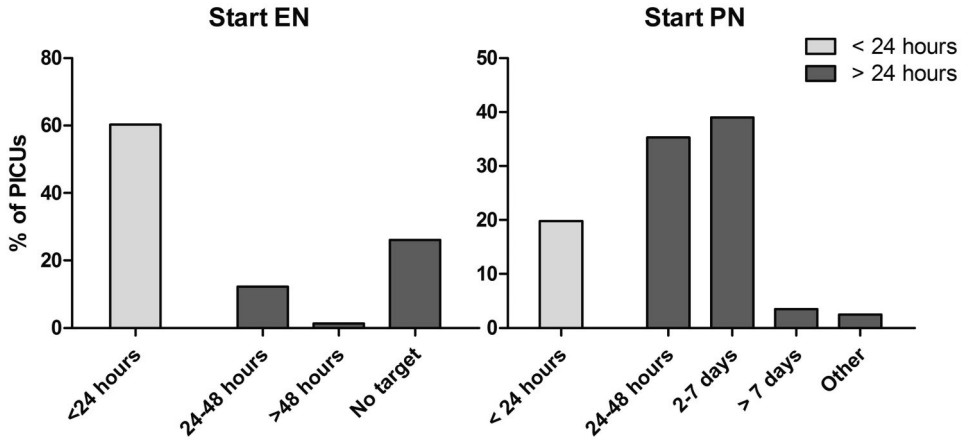

Figure 3. Time to initiation of enteral nutrition (EN) and parenteral nutrition (PN) based on *survey* data. Boxes represent the percentages of PICUs

Glucose and glycemic control

In the first part of the *survey*, target intake of glucose during the first 12-24 hours of admission varied between less than 2 to more than 6 mg/kg/min for different weight ranges (Fig. 4). In 62% of the PICUs, a protocol for some form of glycemic control was available. Target blood glucoses were defined as less than 10 mmol/L (< 180 mg/dL) in 54% and less than 8 mmol/L (< 144 mg/dL) in 23%. Tight glucose control (2.8-4.4 mmol/L or 50-80 mg/dL < 1 year or 3.9-5.5

mmol/L or 70-100 mg/dL 1-16 years) as reported by Vlasselaers et al.[20] was practiced in 10% of PICUs.

At the time of the *point prevalence*, 20 children, median weight 8.1 kg, received exclusive glucose infusion while being admitted less than 24 hours; median glucose intake was 1.7 mg/kg/min (IQR, 0.3-2.3). Seventy-five percent received less glucose than their target glucose intake (Fig. 4).

Insulin was administered in 32 children (11%); 24 children on insulin were admitted to a PICU with a glucose target less than 10 mmol/L (< 180 mg/dL), five to a PICU that practiced tight glucose control as reported by Vlasselaers et al[20].

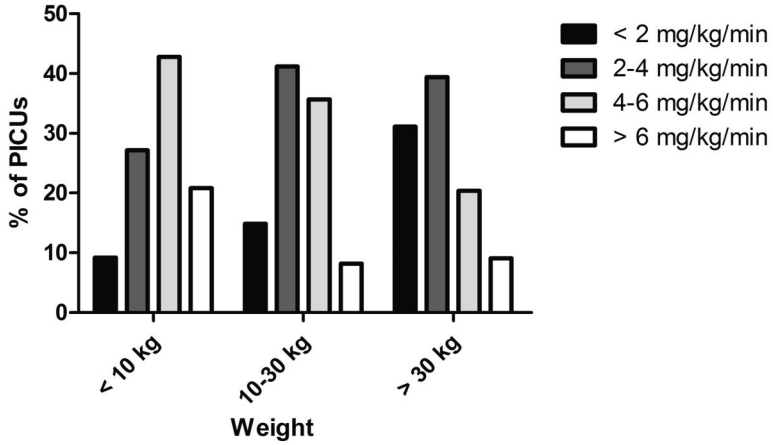

Figure 4. Glucose intake in different weight categories in the first 24 hours after admission based on *survey* data. Intake varied between less than 2 mg/kg/min to more than 6 mg/kg/min in all weight groups. Boxes represent the percentages of PICUs

Administration of parenteral lipids and protein

According to the first part of the *survey*, lipids were supplied in different compositions (Table 3). In 44% of PICUs, a step-up protocol was used that would start at 50% of the maximal dose. Lipid intake was decreased when triglycerides were 3.5-5.5 mmol/L or 310-487 mg/dL (in 69%) and stopped when triglycerides exceeded 5 mmol/L or 442 mg/dL (in 70%). In case of sepsis, lipid administration was decreased or stopped in 50% of PICUs. Reasons provided to decrease or stop the intake of protein were kidney failure (65%) and urea levels more than 15 mmol/L or 42 mg/dL (75%).

Table 3. *Parenteral lipid emulsions used in the PICU (> 1 answer possible per PICU)*

Type	No. of PICUs (%)
100% soy based	105 (67%)
30% soy, 25% olive oil, 15% fish oil, 30% MCT	44 (28%)
100% fish oil	16 (10%)
80% olive oil, 20% soy	27 (18%)
10% fish oil, 40% soy, 50% MCT	5 (2.9%)
50% soy, 50% MCT	3 (1.9%)

MCT = Medium Chain Triglycerides

Geographic and socioeconomic differences

An NST was more often available in PICUs situated in North America ($p = 0.014$), South America ($p = 0.005$), and Oceania ($p = 0.013$) than in Europe and in PICUs with more admissions per year ($p = 0.029$). A higher percentage of nutritional protocols ($p = 0.006$) and support teams ($p < 0.001$) were available in high-income countries than low-middle ones. As expected, protein targets in North American PICUs were more often based on A.S.P.E.N. ($p = 0.011$) and less frequently on ESPEN/ESPGHAN guidelines ($p < 0.001$) than protein targets in Europe. EN was started earlier in PICUs in high-income countries (mean, 6-24 hr; 81% within 24 hr) than in lower-middle-income countries (mean, 13-48 hr; 74% within 24 hr, $p = 0.012$). PN was started later in PICUs in North America (median, 2-4 d, $p = 0.02$) and Asia (median, 2-4 days, $p = 0.06$) than in PICUs in Europe (median, < 48 hr) in a child intolerable to enteral feeds. An overview of the adjusted odds ratios per continent is provided in Supplementary Table 1.

DISCUSSION

Nutritional practices vary greatly between PICUs worldwide. Several aspects of nutritional support differ significantly, such as macronutrient goals, preferred route and timing, estimation of energy requirements, and the threshold for supplemental PN use. These differences were apparent between PICUs in general and between geographic and socioeconomic regions. Many of these areas currently lack evidence. This variability has been described before in PICUs in several European countries[11,12]. In addition, applied nutritional practice (*point prevalence*) deviates from local protocols or strategies (*survey)* on multiple occasions, increasing the variation of clinical nutritional practice even more. Similar results were recently shown by Martinez et al.[21], describing nutritional practices by detailed prospective data collection in 524 mechanically ventilated patients from 31 international PICUs. They found a wide variation in EN recommendations not in agreement with national guidelines.

Variation in practice was not only observed between PICUs in our current study; we also received conflicting statements within single institutions. We corrected for this issue, by weighting by the inverse of the number of completed questionnaires per center. The conflicting statements underline the observed variation of nutritional practices, which occurs not only between but also within individual institutions. A similar discordance in practice within institutions was reported in a U.K. survey of glycemic control in PICUs[22].

Globally, guidelines for nutritional support have been released by nutritional organizations. The American (A.S.P.E.N). and European (ESPEN/ESPGHAN) societies provide specific guidelines for nutrition in critically ill children[7,8]. However, they do not advise on every aspect of nutritional support. Agreements and differences between these guidelines and current practice, as shown by our survey, are summarized in Supplementary Table 2.
Overall, the most striking similarity between guidelines and local implementation is the preference for EN as the preferred route of nutrient delivery and its early initiation in critically ill children.

A specialized NST and feeding protocol are recommended by the A.S.P.E.N guidelines for critically ill children[7]. Availability of an EN protocol is associated with a lower prevalence of hospital-acquired infections[3], implementation of an NST with an increase in EN use, and decreased reliance on PN[23]. Our *survey* showed that a nutritional protocol and/or NST were available in approximately half the PICUs. In our *point prevalence,* we found no significant difference in caloric intake and use of EN between patients from centers with and without a protocol. However, since this was a secondary analysis, it cannot prove or disprove the utility of NST/protocols in general. In single centers, a stepwise EN algorithm has been shown to significantly improve the timing of EN initiation and the ability to reach nutrient delivery goals[24,25]. The role of protocols and NSTs in optimizing clinical outcomes in the PICU population needs to be further examined in well-designed trials.

The ESPEN/ESPGHAN guidelines prefer the measurement of resting energy expenditure (REE) to the use of equations. The A.S.P.E.N. guidelines recommend targeted use of IC in a select group of patients with suspected metabolic alterations or malnutrition. Both state that in the absence of IC, reasonable values can also be derived from formulas, for example, Schofield[17], but only when applied without the use of universal correction factors[7,8]. Several other sources state that nutritional therapy should be targeted at REE throughout the course of illness[26,27]. However, due to the limited availability and practice of IC[11], and also to inaccurate predictive equations[26-28], it is difficult to assess REE in critically ill children. Use of the WHO and Schofield equations, most commonly used to determine requirements, may lead to underfeeding and overfeeding and potentially impacts morbidity and mortality[3,4]. We confirmed the finding of previous studies[11] that IC to measure REE is used in a small minority of European (20%) and

worldwide (14%) PICUs. In contrast with both guidelines, energy needs were calculated with use of correction factors in the majority of PICUs in absence of IC. In the *point prevalence,* two thirds of the children on exclusive EN received more calories than Basic Metabolic Rate (BMR) calculated by the Schofield or WHO formula.

Timing of nutrition is not widely covered by the pediatric ESPEN/ESPGHAN and A.S.P.E.N. guidelines. The adult guidelines from the same societies agree on the importance of early EN but contain contradictory recommendations regarding PN[14,15,29]. The importance and benefits of early EN are generally accepted in previous studies in adults and children[1,30-33], and in critically ill children, a higher intake by enteral route is associated with a lower 60-day mortality[3]. In our *survey* as well as in the *point prevalence,* EN was initiated early; within 24 hours after admission to the PICU. Overall, characteristics of EN support were quite similar between PICUs, with a preference for the gastric route. Also PN was started early, within 48 hours. The mentioned difference in PN initiation time between Europe and North America could reflect the contradictory recommendations in adult guidelines in these regions, which agree on the importance of early EN but not on the time at which supplemental PN should be started[15,29]. The optimal timing and dose of PN is still under debate[34]. We are currently conducting a trial comparing early versus late supplemental PN in critically ill children who are intolerant of EN (ClinicalTrials.gov: NCT 01536275), which is expected to complete enrolment by the end of 2015.

Prospective data from PICUs on patients receiving EN show that only 38-86% of energy goals were administered via this route[5,35]. A variety of barriers impede EN delivery in the PICU setting[36,37]. Only 60% of the patients of the *point prevalence* were actually on exclusive EN within the time frame mentioned in the *survey*. Although postpyloric feeding might improve caloric intake[38], most patients evaluated in our *survey* and *point prevalence* were fed by the gastric route with no difference in nutrient intake compared to children fed via the postpyloric route (*point prevalence)*. The time to feed patients exclusively by the enteral route was short; 59% of respondents thought their PICU was able to feed their patients within 3 days, but this time was overestimated.

Glucose targets in the ESPEN/ESPGHAN pediatric guidelines are supported by limited evidence; A.S.P.E.N. does not provide recommendations on macronutrient intake due to insufficient data. In our *survey* glucose intake targets during the first 12-24 hours tended to range between 2 and 6 mg/kg/min and decreased with increasing weight. The upper limit of glucose intake for critically ill children according to ESPEN/ESPGHAN (5 mg/kg/min, based on the maximal oxidation rate) was exceeded by more than 7% of PICUs. Our *point prevalence* showed that in 75% of the patients, glucose intake differed from the glucose targets mentioned in the first part of the *survey*. However, we should be very careful to draw conclusions from that number,

because only 20 children received glucose infusion exclusively during the first 24 hours of admission. Target blood glucose levels varied between tight control[20] and a target glucose less than 10 mmol/L or 180 mg/dL. This discrepancy in definitions and implementation in glucose management has been highlighted before[39,40]. The discrepancy in definitions and implementation stems from the fact that uncertainties about risks and benefits remain[20,41]. A recent U.K. trial showed no benefit[42] and another trial in North America is underway.

The strength of our study is the fact that we surveyed the local nutritional strategies as well as their implementation in clinical practice. Furthermore, to our knowledge, it is the first study to describe the practices in relation to income characteristics of countries in six continents.
However, our survey may not provide accurate representations of these geographic regions. No response rate can be calculated, since the exact number of PICUs represented by WFPICCS is unknown. The total number of PICUs in all countries joined in the WFPICCS, as identified in the literature, is at least 969, so our 156 PICUs represent a small proportion of all PICUs worldwide. Our *point prevalence* data represent a small fraction of children in the PICUs per center as well as in the cohort invited to participate.
The smaller number of PICUs in the *point prevalence* study may have caused an aggravation of the selection bias, since it is possible that we mainly received *point prevalence* data from PICUs with a strict protocol adherence. Hence, observations may not depict actual practices in these centers. However, characteristics of responding PICUs for the *point prevalence* were similar compared with the overall *survey* respondents (Table 1).
Furthermore, many physicians have limited knowledge of nutritional practices in their centers. Our study may also be limited by the possibility that nonrespondents of this survey were less interested in nutritional practices leading to a selection bias and possible distorted reflection. On the other hand, this selection bias may strengthen our conclusion, if even in the nutrition-minded respondents, adherence to available guidelines is limited.
Finally, the heterogeneity of the PICU population may have caused some difficulties; many of the questions required an unambiguous answer, so only most applicable answers were provided. And, as feeding practices differ between populations, answers from combined PICUs (with neonates or adults; respectively, 20 and 6% of the responding PICUs in this study) may falsely increase the perception of variability.

Nevertheless, our survey clearly demonstrates the international variation in nutritional practice in critically ill children and the differences due to the limited available guidelines, especially on macronutrient administration and calculation of energy targets. Evidence-based guidelines are needed, but are challenging to develop due to a heterogeneous PICU population. Guidelines can be either very specific in respect to disease and settings, leading to wide variation of practice, or be generally applicable with risk of being unfocused and therefore irrelevant in specific situations.

CONCLUSION

In terms of requirements, timing and route, nutritional practices among critically ill children vary greatly between PICUs worldwide. Even the limited available guidelines are not consistently followed, and high-level evidence is urgently needed.

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SUPPLEMENTARY TABLES

Supplementary Table 1. *Adjusted Odds Ratios (OR) per continent*

PICU variable	OR (95% CI)	P-value
Nutritional protocol		
Asia	3.96 (1.53-10.25)	0.005
Africa	+∞	*
North America	3.96 (1.35-11.66)	0.013
South America	0.95 (0.33-2.76)	0.92
Oceania	0.87 (0.25-3.06)	0.83
Europe (reference)		
Nutritional support team		
Asia	1.2 (0.51-2.83)	0.68
Africa	+∞	*
North America	0.32 (0.13-0.79)	0.14
South America	0.17 (0.05-0.59)	0.005
Oceania	0.11 (0.02-0.62)	0.013
Europe (reference)		
Protein target by A.S.P.E.N.		
Asia	0.7 (0.27-1.81)	0.46
Africa	+∞	*
North America	0.31 (0.12-0.76)	0.011
South America	0.72 (0.24-2.17)	0.56
Oceania	1.05 (0.32-3.47)	0.94
Europe (reference)		
Protein target by ESPEN/ESPGHAN		
Asia	3.00 (1.29-6.99)	0.011
Africa	+∞	*
North America	15.6 (4.18-58.28)	<0.001
South America	1.3 (0.53-3.22)	0.57
Oceania	6.4 (1.06-38.84)	0.044
Europe (reference)		
Start of enteral nutrition		
Asia	1.31 (0.50-3.46)	0.58
Africa	+∞	*
North America	2.08 (0.79-5.49)	0.14
South America	1.19 (0.42-3.38)	0.74
Oceania	0.17 (0.04-0.67)	0.012
Europe (reference)		
Start of parenteral nutrition		
Asia	3.43 (1.43-8.22)	0.06
Africa	+∞	*
North America	3.10 (1.53-6.29)	0.002
South America	0.92 (0.36-2.35)	0.85
Oceania	1.50 (0.56-4.01)	0.42
Europe (reference)		
Glucose intake children < 10 kg		
Asia	0.64 (0.19-1.1)	0.08
Africa	+∞	*
North America	0.44 (0.21-0.92)	0.029
South America	0.73 (0.29-1.87)	0.50
Oceania	0.40 (0.14-1.14)	0.085
Europe (reference)		

OR= Odds Ratio, CI= Confidence Interval

*Because the estimated odds ratio converged to 0 or infinity, Wald confidence intervals and p-values could not be calculated

***Supplementary Table 2**. Overview of nutritional recommendations by A.S.P.E.N. and ESPEN/ESPGHAN and clinical practice*

Element	A.S.P.E.N. (2009)[7]	ESPEN/ESPGHAN (2005)[8]	Our survey
Target group	Nutrition in critically ill children	Parenteral nutrition in children Special sections for critically ill children	Nutrition in critically ill children
Nutritional assessment	Screening to identify (risk of) malnutrition	Regular measurements of height, weight and head circumference (<3 years). Skin fold thickness and mid arm circumference reflect body fat and protein. Biochemical measurements are not ideal	Nutritional status assessed on admission and during stay, mostly by weight (94%), height (50%) and biochemical measurements (60%)
Nutritional protocols/ support	Support team and protocols may enhance delivery of nutrition, no effect on outcome	An NST should monitor the process of PN	An NST (57%) and protocol (52%) available to most PICUs, no effect on caloric intake or % EN.
Energy requirements	EE assessment throughout course of illness. Standard equations often unreliable for estimate of EE. IC desirable in subgroup of patients, if not available, energy provision based on formulas without correction factors	Reasonable values for EE from prediction equations without stress factors. Measurement of REE may be useful in the individual patient	Standard equations commonly used; in 70% of PICUs in combination with correction factors, as fever (41%), diagnosis (54%) and growth (59%). IC available in 14% of PICUs
Timing of nutrition	No recommendations. Current practice is initiation of EN in 48-72 hours	Time of initiation of PN will depend on individual circumstances and age and size of the child. Inadequate nutrition up to 7 days may be tolerated in older children	Early initiation of EN and PN. Supplementation of inadequate EN with PN in majority of PICUs. Reaching nutritional targets by EN remains challenging
Macronutrient intake (general)	Insufficient data at moment of publication to make evidence-based recommendations	Only parenteral recommendations	
1. Glucose		Glucose intake in critically ill children limited to 5 mg/kg/min	Varying glucose targets, mostly 2-6 mg/kg/min Median glucose intake first 24 hours 1.7 mg/kg/min
2. Protein	0-2 years: 2-3 g/kg/day 2-13 years: 1.5-2 g/kg/day 13-18 years: 1.5 g/kg/day	Neonates: 1.5-3 g/kg/day 2 months-3 years: 1.5-2 g/kg/day 3-18 years: 1-2 g/kg/day Critically ill children (3-12 years old): 3 g/kg/day amino acids	Varying protein targets, 66% not meeting target

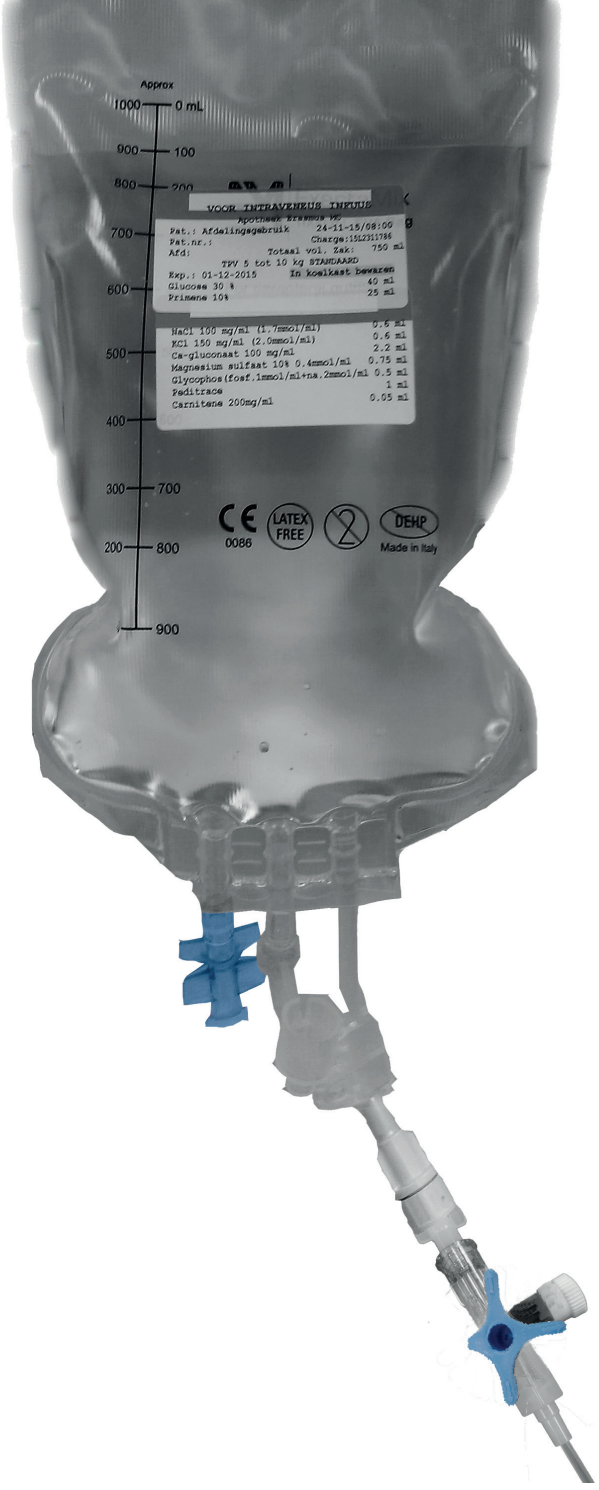
***Supplementary Table 2**. Continued*

Element	A.S.P.E.N. (2009)[7]	ESPEN/ESPGHAN (2005)[8]	Our survey
3. Lipids (parenteral)	Most centers start at 1 g/kg/day and advance over a period of days to 2-4 g/kg/day with monitoring of TG levels	All children: infants max. 3-4 g/kg/day lipids, older children 2-3 g/kg/day. In PICU: more frequent monitoring and adjustment to TG levels	Lipid target predominantly 1.5-2.5 g/kg/day, adjusted to TG levels
Route of nutrition	EN preferred, if tolerated. PN if EN is insufficient. Insufficient data to recommend appropriate site. Gastric route is preferred, postpyloric may be indicated to improve caloric intake or in children at high risk of aspiration or intolerant to gastric feeds	No recommendations on EN	EN preferred. PN if EN is insufficient. Gastric route is preferred in ventilated (67%) and nonventilated (88%) patients. Prokinetics are used if a patient is not tolerating feeds
Immunonutrition	Not recommended based on available literature at moment of publication	Not recommended based on available literature at moment of publication	No data

PICU= Pediatric Intensive Care Unit, NST= Nutritional Support Team, EN= Enteral Nutrition, PN= Parenteral Nutrition, REE= Resting Energy Expenditure, TG= triglycerides, IC= Indirect Calorimetry

PART III

ENERGY EXPENDITURE


Approx
1000
900
800
700
600
500
400
300
200
100
0 mL
100
700
800
900
VOOR INTRAVENEUS INFUUS
Pat.: Afdelingsgebruik
24-11-15/08:09
Pat.nr.:
Charge:15Z2311786
Afd:
Totaal vol. Zak: 750 ml
TPV 5 tot 10 kg STANDAARD
Exp.: 01-12-2015
In koelkast bewaren
Glucose 30 %
40 ml
Primene 10%
25 ml
NaCl 100 mg/ml (1.7mmol/ml)
0.6 ml
KCl 150 mg/ml (2.0mmol/ml)
0.6 ml
Ca-gluconaat 100 mg/ml
2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml
0.75 ml
Glycophos(fosf.1mmol/ml+na.2mmol/ml
0.5 ml
Peditrace
1 ml
Carnitene 200mg/ml
0.05 ml
CE
0086
LATEX FREE
DEHP
Made in Italy

CHAPTER 3

Validation of ventilator-derived VCO_2 measurements to determine energy expenditure in ventilated critically ill children

Dorian Kerklaan, Marjolein E. Augustus, Jessie M. Hulst, Joost van Rosmalen, Sascha C.A.T. Verbruggen, Koen F.M. Joosten

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ABSTRACT

Background and aims

Indirect calorimetry (IC) is considered the gold standard to determine resting energy expenditure (REE), but its availability in PICUs worldwide is limited. Ventilator-derived VCO_2 values could potentially improve the possibility of performing REE measurements. We investigated whether ventilator-derived VCO_2 values are comparable to IC-derived VCO_2 values and can be used in clinical practice to determine REE.

Methods

VCO_2 values were simultaneously collected in mechanically ventilated children from IC (Deltatrac®) and Servo-I® ventilator on a minute base over at least a 10 minute period of steady state. REE was calculated using the modified Weir formula (for IC) or REE=5.5*VCO_2 (L/min)*1440 (for the Servo-I® values) and compared with frequently used predictive equations by Schofield and the WHO to calculate REE.

Results

Measurements were performed in 41 children; median age 2 years. The mean relative difference between VCO_2 measured by IC and Servo-I® was 15.6% (p=0.002), and limits of agreement in the Bland-Altman analysis were wide. Comparable measurements, defined as a difference ≤10% between IC and Servo-I® VCO_2 values, were seen in 18 children (44%), but this proportion was 70% in children ≥15 kg. In this group, REE could be accurately predicted using Servo-I®-derived VCO_2 values and this method was superior to the use of predictive equations. The Servo-I®-derived VCO_2 values were not sufficiently accurate for the large proportion of children weighing <15kg.

Conclusions

In children ≥15 kg, VCO_2 measurements of the Servo-I® seem sufficiently accurate for use in clinical practice and may be used to determine energy expenditure in the future.

INTRODUCTION

Adequate nutritional support is essential in the care of children admitted to the paediatric intensive care unit (PICU) to prevent the negative consequences of underfeeding and overfeeding[1,2]. Measurement of resting energy expenditure (REE) through indirect calorimetry (IC) is the preferred method to determine energy requirements in critically ill children. Predictive equations by Schofield[3] and the World Health Organization (WHO)[4], which are based on weight and/or weight/height, do not accurately predict REE in critical illness[5,6]. Mechanically ventilated children are at greater risk of not meeting nutritional needs[7]. In this group, IC can be performed by measurement of O_2 consumption (VO_2) and CO_2 elimination (VCO_2) using metabolic monitors; from this REE is calculated using the modified Weir formula (REE (kcal/day) = [3.941*VO_2 + 1.106*VCO_2]*1440[8]). Worldwide, measurement of REE is limited, because IC is only available in 14% of the PICUs[9]. Recently, we have shown that REE can be calculated from only the VCO_2 values derived from IC instruments in critically ill children by the following formula: REE=5.5*VCO_2 (L/min)*1440[10].
Modern ventilators are also able to measure CO_2 via an infrared sensor and to calculate its production per minute (VCO_2) based on instantaneous flow. Ventilator-derived VCO_2 values provide a continuous measurement and thus a potentially more accurate reflection of the 24 h metabolic status. Since VCO_2 values can be automatically subtracted from the ventilator, this may be a promising alternative for IC.

The aim of our study was to investigate whether ventilator-derived VCO_2 values are comparable to IC-derived VCO_2 values and to determine if ventilator based assessment of REE is more accurate than predominantly used equations.

MATERIALS AND METHODS

Subjects
Children up to the age of 18 years on mechanical ventilation through the Servo-I® with VCO_2 module (Maquet, Rastatt, Germany) were included in the study when admitted to our PICU. Ventilator settings had to meet the criteria of Deltatrac® Metabolic Monitor usage: inspired oxygen fraction (FiO_2) less than 0.6, tube leakage <10% (determined by comparing inspired and expired tidal volumes) and Positive End Expiratory Pressure (PEEP) < 10 cmH_20. Patients on High Frequency Oscillation (HFO), Extra Corporeal Membrane Oxygenation (ECMO) and Nitric Oxide (NO) support were excluded. The institutional review board of the Erasmus MC approved the study protocol (MEC-2014-169), and (parental) informed consent was obtained before the study was started. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Measurements

VCO_2 values were simultaneously collected over 1 min intervals from IC (Deltatrac II® Datex-Ohmeda, Finland) and ventilator (Servo-I® with the Capnostat-III sensor, Maquet, Rastatt, Germany) over at least a 10-min period during steady state (less than 10% fluctuation in VCO_2 and VO_2 by IC). Before each study, the calorimeter was calibrated with a reference gas mixture (95% O_2, 5% CO_2, Datex Division Instrumentarium Corp.) The properties of the Deltatrac® metabolic monitor have been described before[11]. Per-minute measurements from IC with an RQ < 0.67 or >1.3 or ventilator-derived VCO_2 values of 0 were discarded, since these values are physiologically impossible.

REE by IC was calculated using the modified Weir formula (REE (kcal/day)=[3.941*VO_2 + 1.106*VCO_2]*1440[8]). For the Servo-I®-derived VCO_2 values REE was calculated using the following formula: REE=5.5* VCO_2 (L/min)*1440[10].

REE was calculated using the following predictive equations: Schofield-weight, Schofield-weight/height^3 and the WHO (based on weight)[4]. The following clinical data were recorded from the Patient Data Management System (PDMS) for all patients: sex, age, weight and height, diagnosis category, ventilation mode and settings, ICU stay and survival, FiO_2, temperature, PRISM score on admission, use of catecholamines/sedatives/muscle relaxants and beta blockers and length of stay at moment of measurement.

Statistical analysis

Descriptive statistics were expressed as means ± standard deviations (SD) in case of normally distributed data; otherwise data are expressed as medians with interquartile ranges (IQR). Relative differences between IC and other methods were calculated as follows: ((value IC - value other method)/ value IC)*100%. Paired samples t-tests were performed to check if there was a difference in mean values between methods. Spearman's correlation coefficient (ρ) was used to describe the association between methods of measurement in case of non-normality. This correlation coefficient was also used to describe the association between patient weight and the absolute value of the relative difference between methods. Linear regression analysis was performed to detect proportional and fixed bias between Servo-I®-derived VCO_2 values and IC-derived VCO_2 values. This method was chosen because the predictor (IC-derived VCO_2 values) is expected to be free of error (due to steady state measurements).

Bland-Altman analysis was used to assess the agreement 1) between Servo-I® and IC-derived VCO_2 values and 2) between IC-derived REE values and calculated REE values (Servo-I® and predictive equations)[12]. Accuracy was also quantified by the proportion of comparable measurements, defined as a relative difference ≤10% between values derived from the Servo-I® or predictive equations, and those of IC, to be clinically useful. Inaccuracy was quantified by the proportion of measurements with a relative difference >30%, to determine the prevalence of large errors[13]. Differences between the children with and without comparable measurements were analysed using independent samples t-tests, Mann-Whitney tests or chi-square tests, depending on the outcome used.

The statistical analyses were performed using IBM SPSS statistics 21 for Windows (IBM, Chicago IL, USA). All statistical tests were two-sided and statistical significance was defined as a p-value <0.05.

RESULTS

Measurements were performed in 41 children, the median age was 2.3 years (IQR 0.3 to 8.4) and 56% were male. Seventy-two percent of the children were admitted with a medical diagnosis, mostly due to respiratory insufficiency (39%). Patient characteristics are shown in Table 1a. A controlled ventilation mode was used in 66% of the children; median fractional inspired O_2 was 0.26 (IQR 0.21 to 0.31). Metabolic measurements, performed on the 2nd day of ICU stay (median), lasted 30 minutes on average. Ventilator settings and metabolic measurement data are shown in Table 1b.

Table 1a. *Patient characteristics for all children and for subgroups based on compatibility of the indirect calorimetry (IC) and ventilator method (defined as a difference ≤10% or >10% between IC and ventilator-derived VCO_2 values*

		All children N=41	**Difference ≤10%** N=18	**Difference >10%** N=23	**P-value**
Age (yr)	Median (IQR)	2.3 (0.3-8.4)	7.4 (3.3-11.9)	0.6 (0.2-4.6)	<0.001[b]
Age < 3 year	%	51.2	22.2	73.9	0.002[c]
Male sex	%	56.1	55.6	56.5	0.95[c]
Weight (kg)	Median (IQR)	12.7 (6.1-28.5)	22.5 (14-41.8)	6.3 (4.6-16)	0.001[b]
Weight < 10 kg	%	46.3	16.7	69.6	0.002[c]
Height (cm)	Median (IQR)	88 (63-135)	121 (103-150)	65 (54-98)	<0.001[b]
Diagnosis	%				0.85[c]
Surgery		29.3	27.8	30.4	
Medical		71.7	72.2	69.6	
- Respiratory		38.7			
PRISM score	Median (IQR)	10 (5-16)	12 (7-16)	9 (5-17)	0.44[b]
LOS ICU (days)	Median (IQR)	7 (4-17)	9 (4-24)	7 (4-11)	0.76[b]
Survival	%	92.7	94.4	91.3	0.70[c]
Temperature (°C)	Mean ± SD	37.3 ± 1.0	37.6 ± 1.2	37.1 ± 0.7	0.18[a]
Use of medication	%				
Sedatives		87.8	88.9	87.0	0.85[c]
Catecholamines		24.4	27.8	21.7	0.66[c]
Muscle relaxants		7.3	11.1	4.3	0.41[c]
Beta blockers		0	0	0	1.00[c]

P-values are calculated for differences between the two subgroups using the following tests: [a]Independent samples t-test, [b]Mann-Whitney test, [c]Chi-square test.
IQR= Interquartile Range, PRISM= Paediatric Risk of Mortality, LOS= Length of Stay, ICU= Intensive Care Unit, SD= Standard Deviation

Table 1b. *Ventilator settings and metabolic measurement data for all children and for subgroups based on compatibility of the indirect calorimetry (IC) and ventilator method (defined as a difference ≤10% or >10% between IC and ventilator-derived VCO_2 values)*

		All children N=41	**Difference ≤ 10%** N=18	**Difference >10%** N=23	**P-value**
Ventilation mode	%				0.94[c]
Support		34.1	33.3	34.8	
Control		65.9	66.7	65.2	
FiO_2	Median (IQR)	0.26 (0.21-0.31)	0.28 (0.21-0.36)	0.25 (0.21-0.30)	0.57[b]
Tidal volume (ml)	Median (IQR)				
Inspiratory		89 (34-157)	142 (96-185)	36 (20-90)	0.002[b]
Expiratory		91 (34-180)	143 (95-198)	35 (19-97)	0.001[b]
Tube leak (%) (inspiratory-expiratory tidal volume)	Mean ± SD	-1.9 ± 8.6	-4.8 ± 10.2	0.3 ± 6.4	0.07[a]
Respiratory rate (/min)	Median (IQR)	38 (25-47)	26 (23-35)	43 (38-50)	0.02[b]
Heart rate (/min)	Median (IQR)	116 (103-139)	113 (99-124)	128 (101-142)	0.27[b]
LOS at moment of measurement (days)	Median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	0.75[b]
Length of measurement (min)	Mean ± SD	30 ± 9.5	34 ± 8	33 ± 11	0.71[a]
VCO_2 Deltatrac (ml/min)	Median (IQR)	75.2 (41.6-116.1)	108.6 (94-132.9)	45.9 (28.3-78.6)	<0.001[b]
VCO_2 Servo-I (ml/min)	Median (IQR)	74.0 (27.5-118.0)	111.6 (94.8-135.9)	33.4 (12.6-75.3)	<0.001[b]

P-values are calculated for differences between the two subgroups using the following tests: [a]Independent samples t-test, [b]Mann-Whitney test, [c]Chi-square test.
IQR= Interquartile Range, FiO_2= Fraction inspired Oxygen, LOS= Length of Stay, SD= Standard Deviation

Correlation between Servo-I®-derived VCO_2 values and IC-derived values was excellent [ρ=0.965 (95% CI: 0.935 to 0.981)]. However, despite being a necessary condition for agreement, high correlation does not automatically imply good agreement. Figure 1a shows the Bland-Altman plot for agreement between the two methods for measuring VCO_2 values. Measurements were not comparable with a mean relative difference of 15.6% (p=0.002, one-sample t-test), due to underestimation of VCO_2 values by the Servo-I®. The 95% limits of agreement were wide (-42.4 % and 73.6%). Linear regression of Servo-I®-derived VCO_2 values on IC-derived values showed a regression line with a slope of 1.15 (95% CI: 1.07 to 1.23) and an intercept at -15.66 (95% CI: -23.32 to -8.01). The slope of this regression line was significantly different from 1 (p<0.001), and the intercept was significantly different from 0 (p<0.001), reflecting both proportional and fixed bias.

Comparable measurements, defined as a difference ≤10% between Servo-I®-derived VCO_2 values and those of IC to be clinically useful, were seen in 18 children (44%). When comparing these 18 children to the 23 children with a difference >10%, it was shown that children with comparable measurements were significantly older (median 7.4 vs. 0.6 years, p<0.001), and taller (median 121 vs. 65 cm, p < 0.001) with higher weight (median 23 vs. 6.3 kg, p=0.001), suggesting that the size of the differences between the methods decreases with age and weight (Table 1a). There was no significant difference in diagnosis, PRISM score, heart rate, temperature, use of medication, ventilation mode or supplied oxygen fraction between these 2 groups of children. Median VCO_2 values of the Servo-I® (112 vs 33 ml/min, p<0.001) and of IC (109 vs 46 ml/min, p<0.001) were significantly higher, as were the median inspiratory (142 vs 36 ml, p=0.002) and expiratory (143 vs 35 ml, p=0.001) tidal volumes and the respiratory rate (Table 1b). Measurements with a difference >30% between Servo-I®-derived VCO_2 values and those of IC were seen in 11 children (27%).

Since ventilator settings are weight-based, we plotted the relative difference between VCO_2 values derived from IC and Servo-I® by weight in kg (Fig. 1c). As shown in this figure, in children weighing less than 15 kg (n=21), there was a substantial bias with only 19% of measurements being comparable (difference ≤10%). In children weighing 15 kg or more (n=20), 14 children (70%) had comparable measurements (difference ≤10%). Among this group there was no significant correlation (Spearman's ρ=-0.222, p=0.347) between weight and the absolute value of the relative difference between the two methods, suggesting that the accuracy does not depend on weight for children weighing more than 15 kg (see also Fig. 1c). Five percent of measurements in children weighing 15 kg showed a difference >30%. Therefore a weight of 15 kg could be a clinically acceptable threshold for reliability of the Servo-I®-derived VCO_2 values. We used this threshold in the remaining analyses.

REE values derived from IC were compared to REE values calculated from Servo-I®-derived VCO_2 values. Correlation was high [ρ=0.954 (95%CI: 0.915 to 0.975)]. There was a mean relative difference of 19% with wide 95% limits of agreement; -36.3% and 74.4% as shown in Figure 1b. The linear regression analysis showed both fixed (p=0.001) and proportional bias (slope 1.09, p=0.038).

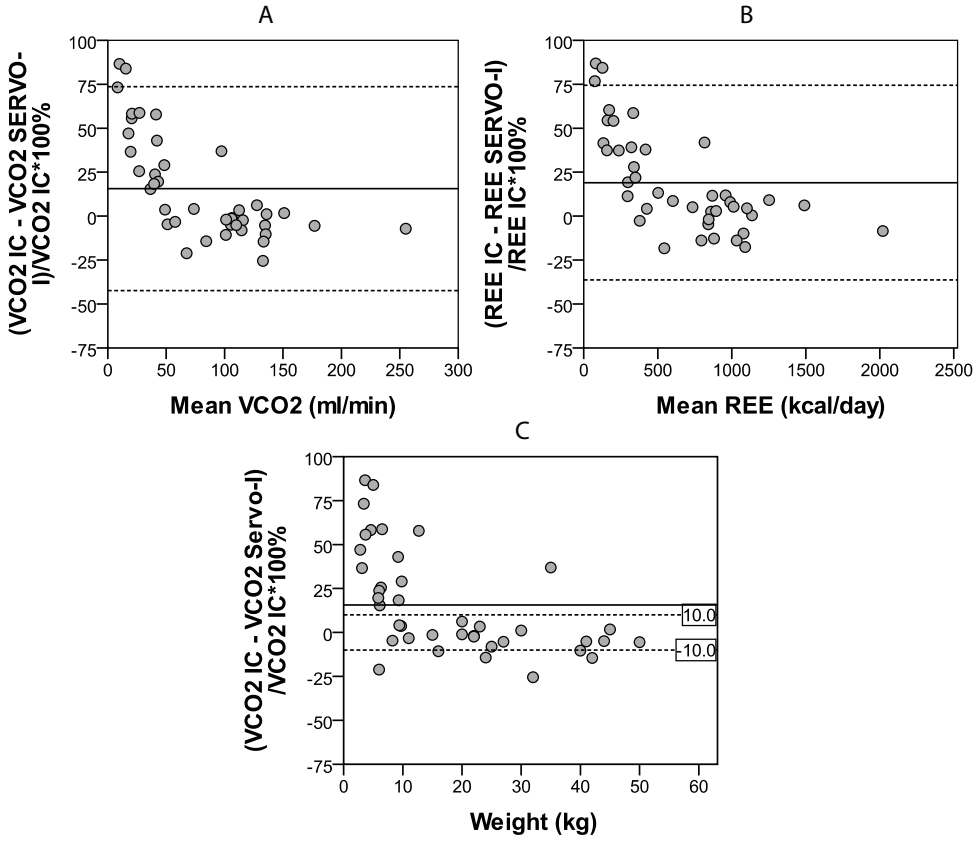

Figure 1. Bland-Altman plots for agreement a) between VCO_2 values derived from indirect calorimetry (IC) and Servo-I® measurements with a mean relative difference of 15.6% (panel A), b) between REE values derived from IC and Servo-I® measurements with a mean relative difference of 19% (Panel B), and relative differences between VCO_2 values derived from IC (Deltatrac®) and Servo-I® measurements by weight (kg) (panel C). The mean relative difference is represented by the solid horizontal line; dotted lines indicate 95% limits of agreement (panels A and B) or 10% difference between methods (panel C)

In the 20 children weighing 15 kg or more, the agreement of the REE values on the Bland-Altman plot was considerably better. The mean relative difference between methods was 1.3% (p=0.668), with 95% limits of agreement of -24.6% and 27.2% (Fig. 2a).

This mean relative difference in children ≥15 kg was significantly smaller than that of the Schofield-weight (-13.4%, p=0.03), Schofield-weight/height (-13.2%, p=0.03) and WHO (-15.0%, p=0.07) equations. As shown by the Bland-Altman plots (Fig. 2), limits of agreement were narrowest for Servo-I® based REE when compared with the REE based on predictive equations. In children ≥15 kg, the proportion of comparable measurements (difference ≤10% with IC-derived REE) was highest, whereas the proportion of measurements with a difference >30% was lowest for the Servo-I® based REE, when compared with proportions of the equations-based REE (Fig. 3).

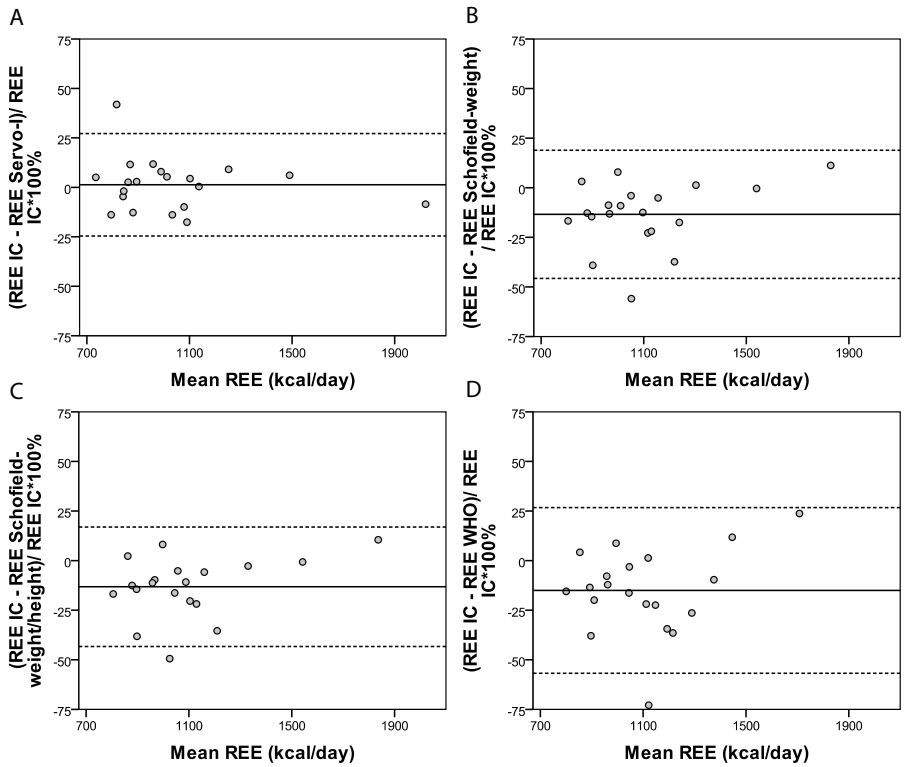

Figure 2. Bland-Altman plots for agreement between REE values derived from indirect calorimetry (IC: Deltatrac®) and REE values derived a) from Servo-I® measurements, b) from the Schofield-weight equation, c) from the Schofield-weight/height equation and d) from the WHO equation. The mean relative difference is represented by the solid horizontal line; dotted lines indicate 95% limits of agreement

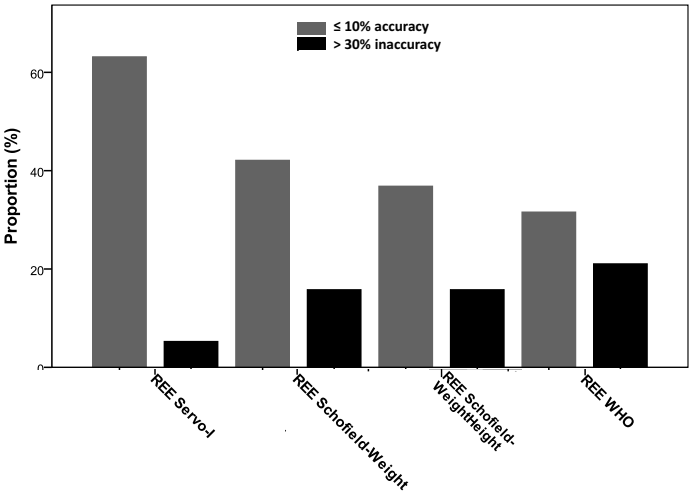

Figure 3. Accuracy and inaccuracy quantified by the proportions of measurements with a relative difference ≤10% and >30% when comparing REE derived from Servo-I® and predictive equations with indirect calorimetry derived REE in children ≥15 kg

DISCUSSION

In this study we compared the VCO_2 values by IC (Deltatrac®) and ventilator (Servo-I®) in 41 mechanically ventilated critically ill children; VCO_2 values were highly correlated, but not comparable due to underestimation of VCO_2 values by the Servo-I®. 95% limits of agreement in the Bland-Altman analysis were wide, showing poor agreement. Clinically useful measurements (difference ≤10% between VCO_2 values of the Servo-I® and those of IC) were seen in children with higher weight. In the 20 children weighing ≥15 kg, VCO_2 measurements were comparable between IC and Servo-I® and the derived REE values were more precise than predominantly used predictive equations with a smaller difference and narrower limits of agreement. In 81% of the children weighing <15 kg, measurements by the Servo-I® deviated >10% from those of IC, which made the use of measurements in these children very limited.

The wide limits of agreement may be due to the technical specifications of the sampling methods; especially the underestimation by the Servo-I® in children <15 kg may be affected by the characteristics of the sensor. VCO_2 is the volume of eliminated CO_2 calculated over one minute. CO_2 is mainly measured in the exhaled breath of alveoli (phase 2 and 3 of the capnogram, Fig 4), while breath from the upper airways is void of CO_2 (dead space, phase 1 of capnogram).

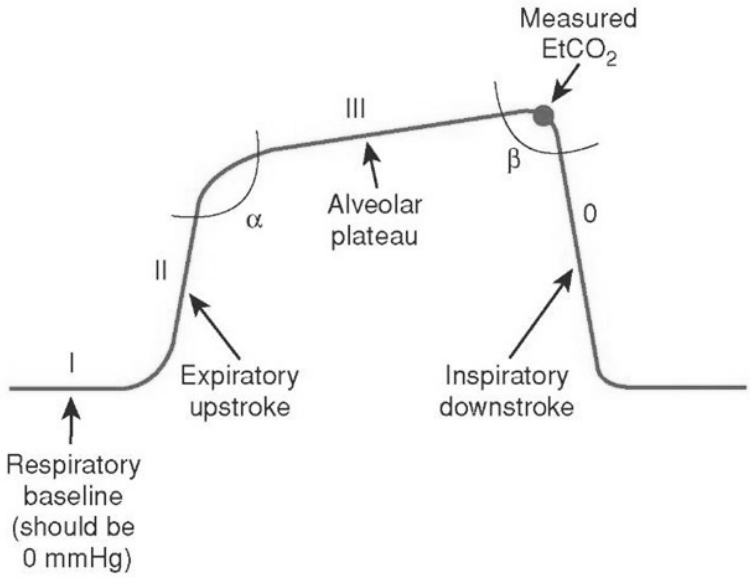

Figure 4. Capnogram divided in 4 phases. Phase I represents airway dead space. It is the CO_2 -free portion of the exhaled breath from the conducting airways. Phase II (expiratory upstroke) represents the mixing of airway dead space gas with alveolar gas, and is characterised by a significant rise in CO_2. The steep slope is due to fast-emptying alveoli. Phase III is the alveolar plateau; it reflects the level of effective ventilation of the alveoli. The gradual rise in the slope is due to late-emptying alveoli. Phase IV is the inspiratory down stroke, the beginning of the next inspiration

The value of CO_2 depends on the technical performance and location of the CO_2 sensor. In the Servo-I® the CO_2 fraction is measured mainstream simultaneously with the airway flow by an infrared sensor attached to the endotracheal tube. Tidal volume CO_2 ($TVCO_2$) is then calculated based on the fraction and the instantaneous flow over a single breath. When the transition from phase 2 to phase 3 of the capnogram cannot be clearly identified by the sensor, or if there is no alveolar plateau in phase 3, this detection method fails and CO_2 values may be underestimated or even absent.

This is predominantly a problem in small lungs[14], and is also affected by the exhalation time of the child. If the exhalation time is too short as compared to the rise time of the CO_2 analyser, the alveolar plateau is not reached and CO_2 is underestimated. This might have been a problem in our study; we found significantly higher respiratory rates in children with non-comparable measurements leading to decreased exhalation time and therefore worse detection of the alveolar plateau. Next to that, adding the Capnostat® airway adapter to the ventilation circuit leads to an increase in dead space and even to extra turbulence due to the difference in diameter. In smaller children with smaller airways, this increase is relatively large, resulting in blending of inspired and expired gasses leading to inaccurate measurements. A last explanation for the underestimation of VCO_2 values in smaller children, is the difficulty of distinguishing the inspiratory and expiratory phase in children with higher respiratory rates. Since the CO_2 in inspired gas is approximately 0, false interpretation of this gas for expired gas, will underestimate the true CO_2 values. The method of measurement is different for IC by the Deltatrac® device, which uses an air-dilution method, which is independent of the tidal volume and exhalation time of the patient measured[15]. This might explain the wide limits of agreement between the two methods.

In theory, the ventilation mode might also influence the technical performance of the two methods, mainly since respiratory rates vary between the different modes. We did not find a significant difference in ventilator mode between children with and without clinically comparable measurements; this is in accordance with findings of previous studies where no significant influence of ventilator mode on VCO_2 measurements were found in critically ill children and adults[16,17].

REE could be accurately predicted based on ventilator-derived VCO_2 values (mean relative difference of 11.3% with narrow limits of agreement), but only in children with a weight ≥15 kg (n=20). This prediction was more precise than those by the frequently used predictive equations to determine REE in critically ill children. The use of weight ≥15 kg could therefore be a clinically acceptable threshold.

Our study is limited by its specific study population, due to the restriction of Deltatrac® usage to mechanically ventilated children with an FiO_2 <0.6 and tube leak <10% and without additional nitric oxide therapy. Secondly, in the smallest children many VCO_2 values needed to

be discarded because the values were 0 due to the inaccuracy of the device. Larger prospective studies on the validation of Servo-I®-derived VCO_2 values in children weighing ≥15 kg are needed.

However, our results show that in clinical practice, the measurement of VCO_2 values by the Servo-I® is a promising option for the determination of energy requirements in children ≥15 kg on mechanical ventilation.

CONCLUSION

Measuring VCO_2 by use of a ventilator (Servo-I®) is feasible. In children weighing ≥15 kg, VCO_2 measurements and derived REE predictions of the Servo-I® seem sufficiently accurate for use in clinical practice, since their performance is superior to the performance of frequently used predictive equations. This method is not suitable for the large proportion of children weighing <15kg. In clinical practice VCO_2 measurements derived from the ventilator can be used to calculate REE to guide nutritional therapy in children weighing ≥15kg.

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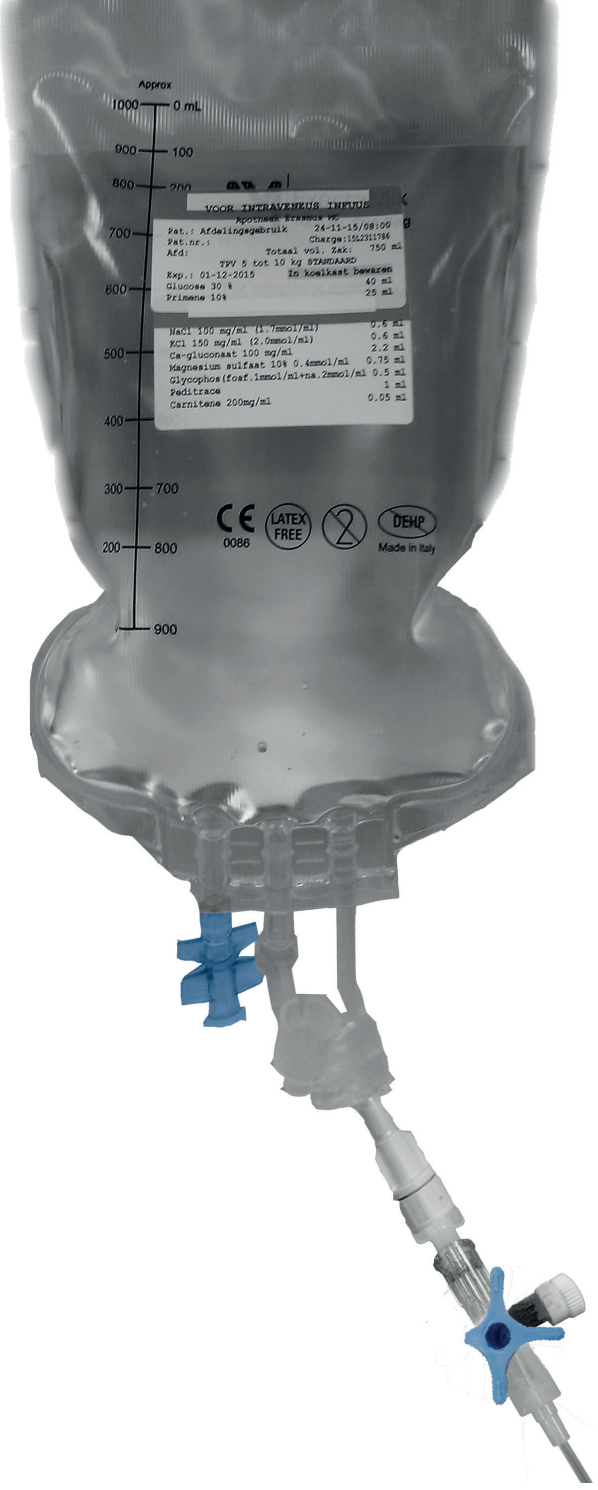
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Glucose 30 %
40 ml
Primene 10%
25 ml
Nacl 100 mg/ml (1.7mmol/ml)
0.5 ml
KCl 150 mg/ml (2.0mmol/ml)
0.6 ml
Ca-gluconaat 100 mg/ml
2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml
0.75 ml
Glycophos(fosf.1mmol/ml+na.2mmol/ml
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1 ml
Carnitene 200mg/ml
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CHAPTER 4

Use of indirect calorimetry to detect overfeeding in critically ill children; finding the appropriate definition

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ABSTRACT

Objectives

Overfeeding during critical illness is associated with adverse effects such as metabolic disturbances and increased risk of infection. Because of the lack of sound studies with clinical endpoints, overfeeding is arbitrarily defined as the ratio caloric intake/measured resting energy expenditure (mREE) or alternatively as a comparison of measured respiratory quotient (RQ) to the predicted RQ based on the macronutrient intake (RQ_{macr}). We aimed to compare definitions of overfeeding in critically ill mechanically ventilated children based on mREE, RQ and caloric intake to find an appropriate definition.

Methods

Indirect calorimetry measurements were performed in 78 mechanically ventilated children, median age 6.3 months. Enteral and/or parenteral nutrition was provided according to the local guidelines. Definitions used to indicate overfeeding were the ratio caloric intake/mREE of >110% and >120% and by the measured $RQ>RQ_{macr} + 0.05$.

Results

The proportion of patients identified as overfed varied widely depending on the definition used, ranging from 22% ($RQ>RQ_{macr}+ 0.05$), to 40% and 50% (caloric intake/mREE of >120% and >110% respectively). Linear regression analysis showed that all patients would be identified as overfed with the definition $RQ>RQ_{macr}+ 0.05$ when the ratio caloric intake/mREE exceeded 165%. Caloric intake was higher in children with a standard deviation score weight for age <-2.

Conclusions

The proportion of mechanically ventilated patients identified as overfed ranged widely depending on the definition applied. These currently used definitions fail to take into account several relevant factors affecting metabolism during critical illness and are therefore not generally applicable to the pediatric intensive care unit population.

INTRODUCTION

Nutritional support affects outcome in critically ill children[1-3]. Undernutrition has long been the primary focus for nutritional research, but overfeeding is also prevalent in pediatric intensive care units (PICUs)[1,4-6]. Caloric overfeeding is associated with increased mortality in critical ill adults[7]. It may lead to liver dysfunction by increasing the risk for hepatobiliary complications, such as steatosis and cholestasis, and might increase the risk of infection secondary to hyperglycemia[8]. Overfeeding of glucose leads to lipogenesis with an increase in carbon dioxide[9], resulting in a difficulty to wean from the ventilator[10,11]. Furthermore, overfeeding during critical illness might evoke a phenotype of autophagy deficiency as a potentially important contributor to mitochondrial, organ and skeletal muscle damage, particularly when amino acid enriched parenteral nutrition (PN) is provided[12,13]. Also in critically ill children, unintended consequences of overfeeding are likely to occur[14].

To prevent these detrimental effects, nutritional therapies are ideally guided by resting energy expenditure (REE) throughout the course of illness[15]. REE can be measured (mREE) by indirect calorimetry or predicted by use of equations, and might be affected by the type, severity and stage of disease[16-18]. Because there is a lack of studies using clinical endpoints to determine the optimal caloric intake in critically ill children, recommendations on minimum caloric intake are often based on equilibrating energy or protein balances[19,20]. So far, however, no clinical endpoint or (surrogate) marker has been studied to determine the optimal maximum caloric intake in this population. Overfeeding is arbitrarily defined as a ratio caloric intake/REE >110%[7,21-23] or >120%[14,24-28] (see related studies in Table 1). As an alternative method the comparison of measured respiratory quotient (RQ) to the predicted RQ based on the macronutrient intake (RQ_{macr}) is suggested[29,30]. The measured RQ is derived from the ratio of CO_2 production over O_2 consumption and reflects the use of different substrates. An RQ value >1.0 indicates lipogenesis, and is frequently used to identify carbohydrate overfeeding[29]. RQ_{macr} is the weighted average of the RQs of the different macronutrients administered, which can be obtained from the modified Lusk table. A difference >0.05 between RQ and RQ_{macr} has been proposed to define overfeeding[29,30].

The aim of the present study was to compare different definitions of overfeeding in critically ill mechanically ventilated children based on measurements of mREE, RQ and caloric intake and to find an appropriate definition to study the effect of overfeeding on clinical endpoints in future trials.

Table 1. *Overview of clinical studies concerning overfeeding in critically ill children*

Study	Design, Patients	Applied definition overfeeding	% overfeeding	Risk factors for overfeeding Outcome
Taylor et al., Clin Nutr. 2003 Nutritional support in critically ill children	Retrospective study in 95 children in PICU ≥3 days Median age 7.7 (range 1-18.6) years	Ratio caloric intake/ pREE (Schofield-weight) >110%	18% (n=135) patient days	Parenteral nutrition
Hulst et al., Nutrition. 2005 Adequate feeding and the usefulness of the respiratory quotient in critically ill children	Prospective study in 98 mechanically ventilated children, median age 14.6 days (range 0-15.2 y)	Ratio caloric intake/ mREE >120%	69% patient days	None identified
Oosterveld et al., Pediatr Crit Care Med. 2006 Energy expenditure and balance following pediatric intensive care unit admission: a longitudinal study of critically ill children	Observational study in 46 children, median age 4 (IQR 0-18) years	Ratio caloric intake/ mREE >110%	28% patient days	Parenteral nutrition
De Neef et al., Clin Nutr. 2008 Nutritional goals, prescription and delivery in a pediatric intensive care unit	Prospective study in 84 mechanically ventilated children in PICU ≥3 days, median age 4.7 (IQR 0.9-18.9) months	Ratio caloric intake/ pREE (WHO)>110%	26.5% patient days	None identified
Mehta et al., Pediatr Crit Care Med. 2011 Energy imbalance and the risk of overfeeding in critically ill children	Prospective study in 33 mechanically ventilated children, median age 2 (range 0.1-25.8) years	Ratio caloric intake/ mREE >120%	83% (n=24) children	Age < 1 year
Kyle et al., J Acad Nutr Diet. 2012 Nutrition support in critically ill children: underdelivery of energy and protein compared with current recommendations	Retrospective study in 240 children in PICU >2 days	Ratio caloric intake/ pREE (Schofield-weight) >110%	30% (n=344) patient days	None identified
Dokken et al., JPEN J Parenter Enteral Nutr. 2015 Indirect calorimetry reveals that better monitoring of nutrition therapy in pediatric intensive care is needed	Prospective study in 30 mechanically ventilated children, median age 15.5 (range 3-168) months	Ratio caloric intake/ mREE >120%	60.5% (n=63) patient days	None identified
de Betue et al. Clin Nutr. 2015 Achieving energy goals at day 4 after admission in critically ill children; predictive for outcome?	Prospective study in 325 children at day 4 after admission, median age 0.14 (range 0-18) years	Ratio caloric intake/ pREE (Schofield-weight) >120%	74% of children on PN and EN combined (n=240) 43% of children only on EN (n=140)	Younger children, Malnourishment Multivariate analysis: being overfed not associated with change in no. of days until discharged alive, no. of days on the ventilator, no. of days on antibiotics, no. of new infections or site of infection

IQR = Interquartile Range, PICU = Pediatric Intensive Care Unit, mREE = measured Resting Energy Expenditure, pREE = predicted Resting Energy Expenditure, WHO = World Health Organization, EN = Enteral Nutrition, PN = Parenteral Nutrition

METHODS

Neonates and children up to the age of 18 years admitted to our level III multidisciplinary PICU were consecutively included in the study when they met the criteria for indirect calorimetric measurements: mechanical ventilation with a Servo ventilator (Siemens-Elema, Solna, Sweden); FiO_2 <0.6, tube leakage <10% and hemodynamic stable condition (blood pressure and heart rate within 2 standard deviation (SD) of age-related values).
The institutional review board of the Erasmus MC approved the study protocol, and written parental informed consent was obtained before children entered the study. Data, including age, sex, weight, primary diagnosis, surgical status, days on mechanical ventilation, length of ICU stay, route of nutritional support, and energy and macronutrient intake were recorded. The severity of illness on admission was assessed by the Pediatric Risk of Mortality score (PRISM)[31]. Nutritional status on admission was defined by weight for age (WFA) SD-scores using Dutch Growth Standards[32]; children were categorized as underweight if their WFA SD-score was <-2.

Indirect calorimetry measurements were performed as soon as possible after admission. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2), standardized for temperature, barometric pressure, and humidity were measured for at least 2 hours using the Deltatrac® (Datex Division Instrumentarium, Helsinki, Finland) metabolic monitor. Measured REE (mREE) was calculated with the modified Weir formula[33]. The properties of the Deltatrac® metabolic monitor have been described previously[34]. The RQ was calculated from the measured VO_2 and VCO_2 levels[24].

Children were fed enterally and/or parenterally according to the local feeding protocol[25] and the judgement of the attending physician. A glucose infusion was provided during the first 12 to 24 hours after admission aimed at a carbohydrate intake of 4 to 6 mg/kg/min (children<30kg) or 2 to 4 mg/kg/min (>30kg)[35,36]. Enteral nutrition (EN), consisting of human milk or standard formula, was started as soon as possible in all patients, either continuously or intermittently through a postpyloric or nasogastric tube. PN was started within 48 hours after admission in case of insufficient EN, either by peripheral infusion or by central venous access. Fluid and electrolyte intakes were adjusted to individual requirements.
Energy goals for EN were based on the body weight-based Schofield equation[37] on the first day of admission and on the Recommended Dietary Allowances for the subsequent length of stay (Dietary Reference Intake: energy, protein and digestible carbohydrates, 2001, Health Council of the Netherlands: The Hague). Parenteral energy goals were based on the weight-based guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) throughout PICU stay[38]. Actual total daily intake of energy, carbohydrate, protein and fat were derived from patient records on the day of calorimetry.

An RQ of administered macronutrients (RQ_{macr}) was calculated based on the modified Lusk table after determination of the ratio of carbohydrate to fat for the total nonprotein calories of the intake provided on the day of the measurement[29]. The measured RQ was compared to the RQ_{macr}. The RQ was assumed to approximate the RQ_{macr}, if $RQ = RQ_{macr} \pm 0.05$[29,30]. No corrections were made for losses of macronutrients in stools when EN was given[39]. The following definitions of energy overfeeding were used and compared:

1) Caloric intake/mREE >110%

2) Caloric intake/mREE >120%

3) $RQ > RQ_{macr} + 0.05$

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (Released 2012. SPSS Armonk, NY: IBM Corp.). Results are expressed as proportion, mean and standard deviation, or median and interquartile range (IQR). Differences between groups were analyzed by use of the Mann-Whitney and Kruskal-Wallis test. Pearson's correlation coefficient (r) was used to evaluate the strength of the relation between RQ and carbohydrate intake, and between the continuous variables on which the definitions are based: $RQ\text{-}RQ_{macr}$ and the ratio caloric intake/mREE. Linear regression analysis was used to further define the relation between $RQ\text{-}RQ_{macr}$ and the ratio caloric intake/mREE. Two-tailed P-values <0.05 were considered significant.

RESULTS

Patients

Measurements were performed in 78 children (51 boys). Clinical and nutritional characteristics are shown in Table 2. Median age was 6.3 (Interquartile Range [IQR]1.5 to 29.3) months. An SD-score for WFA<-2 was found in 23 children (30%). The reason for admission was medical in 77% of the children, with 32% respiratory insufficiency. The median length of stay at the time of measurement was 1 day (IQR 1 to 3) after PICU admission. All children were mechanically ventilated and sedated with midazolam and/or morphine. Seventy-four percent of the children received EN; 57% were fed by EN exclusively; and 18% received a mixture of EN and PN. Total PN was provided in 15% of the children; 10% of the children received only glucose infusion at time of measurement.

Table 2. *Clinical and nutritional characteristics of the patients*

		N = 78
Male sex	N (%)	51 (54%)
Age		
Months	Median (IQR)	6.3 (1.5-29.3)
Age < 1 year	N (%)	46 (59)
Weight (kg)	Median (IQR)	6.4 (3.9-12.6)
SD-score WFA	Mean (±SD)	-1.3 (±1.8)
< -2	N (%)	23 (30)
Diagnosis	N (%)	
Medical		60 (77)
Surgery		18 (23)
PICU length of stay (days)	Median (IQR)	8 (5-13.5)
Mortality	N (%)	3 (7)
PRISM score	Median (IQR)	10 (5-16)
mREE		
Total	Median (IQR)	312 (217-640)
Per kg	Mean (±SD)	48 (±9.6)
RQ		
Measured	Mean (±SD)	0.88 (± 0.08)
RQ > 1	N (%)	5 (6.4)
Macronutrients	Median (IQR)	0.90 (0.86-0.96)
Body temperature	Mean (±SD)	37.5 (± 0.6)
Temp ≥ 38.5°C	N (%)	7 (9)
Day of measurement	Median (IQR)	1 (1-3)
Day > 7	N (%)	8 (10)
Route of nutrition	N (%)	
Exclusive EN		44 (57)
Exclusive PN		12 (15)
EN and PN combined		14 (18)
Glucose only		8 (10)
Intake		
Kcal/kg/day	Mean (±SD)	52 (±29)
Caloric intake>mREE	N (%)	45 (58)
Protein (g) per kg	Median (IQR)	1.1 (0.5-2.1)
Fat (g) per kg	Median (IQR)	1.3 (0.4-2.7)
Carbohydrates mg/kg/min	Mean (±SD)	5.4 (±2.8)

IQR = Interquartile Range, SD = Standard Deviation, WFA = Weight for Age, PICU = Pediatric Intensive Care Unit, PRISM = Pediatric Risk of Mortality score (maximum total score 74), mREE = measured Resting Energy Expenditure, RQ = Respiratory Quotient, EN = Enteral Nutrition, PN = Parenteral Nutrition

Energy overfeeding

Table 3 shows patient demographics and nutritional characteristics in relation to the different definitions of energy overfeeding studied.

For the total population, mean mREE was 48 (±9.6) kcal/kg compared to a mean caloric intake of 52 (±29) kcal/kg/day. The mean RQ was 0.88 (±0.08). Fifty percent of the children (n=39) were provided with >110% of mREE and 40% (n=31) with >120%. These children had a significant lower SD-score WFA (-1.8 vs -0.5, p=0.004) and, as expected, had a significant higher intake of calories (p<0.001), protein (p<0.001), fat (p<0.001), and carbohydrates (p<0.001) per kilogram compared to the children without overfeeding. Children with an SD-score WFA<-2 had a significant higher intake of calories per kilogram than children with an SD-score WFA≥-2 (61 vs 48 kcal/kg/d, p=0.031). The ratio caloric intake/mREE was 119% in children with an SD-score WFA<-2 and 100% in the children with an SD-score ≥-2 (p=0.091).

In 22% of the children (n=17) RQ was higher than RQ_{macr} + 0.05. Fourteen of these children (82%) were also identified as overfed according to the ratio caloric intake/mREE >120% definition. Children identified as overfed by RQ had a significant higher intake of calories (71 vs 44 kcal/kg/d, p=0.001), protein (2.2 vs 0.9 g/kg/d, p<0.001), and fat (2.9 vs 0.9 g/kg/d, p<0.001) per kilogram and a higher ratio caloric intake/mREE (71 vs 44 kcal/kg/d, p<0.001) compared with the children with an RQ<RQ_{macr} ± 0.05. There was a significant positive correlation between RQ-RQ_{macr} and the ratio caloric intake/mREE (r=0.627, p<0.001) (Fig. 1). Caloric overfeeding as defined by RQ (RQ exceeding RQ_{macr} + 0.05) occurred if the ratio caloric intake/mREE exceeded 165%, reflecting a mean caloric intake of 79 kcal/kg/day in our population.

Table 3. *Characteristics of children identified as overfed according to predefined definitions*

		Caloric intake/ mREE >110% N = 39	**Caloric intake/ mREE >120%** N = 31	**RQ>RQ_{macr}+0.05** N = 17
Male sex	N (%)	22 (56)	18 (58)	7 (41)
Age (months)	Median (IQR)	3.6 (1.0-17)	3.7 (1.0-18)	4.6 (1.7-15)
Weight (kg)	Median (IQR)	4.2 (3.4-8.8)	4.2 (3.4-8.8)	4.5 (3.5-8.4)
SD-score WFA	Mean (±SD)	-1.9 (±1.8)	-1.8 (±1.7)	-1.8 (-3.8- -1.3)
<-2	N (%)	14 (36)	11 (36)	8 (47)
mREE/kg	Mean (±SD)	50 (±8.3)	52 (±8.8)	50 (40-54)
RQ measured	Mean (±SD)	0.90 (± 0.08)	0.90 (± 0.08)	0.95 (0.93-0.98)
Intake				
Kcal/kg/d	Mean (±SD)	70 (±25)	71 (±24)	71 (53-92)
Protein g/kg/d	Median (IQR)	1.7 (1.0-2.5)	2.1 (±0.9)	2.2 (1.3-2.5)
Fat g/kg/d		2.5 (1.3-3.5)	2.9 (±1.5)	2.9 (2.0-4.1)
Carbohydrates mg/kg/min		6.8 (5.4-8.6)	6.9 (5.7-8.6)	6.5 (3.7-8.4)
Route of nutrition	N (%)			
Exclusive EN		26 (67)	21 (68)	11 (65)
Exclusive PN		6 (15)	4 (13)	2 (12)
EN and PN		6 (15)	6 (19)	4 (24)
Glucose only		1 (3)	-	-

IQR = Interquartile Range, SD = Standard Deviation, WFA = Weight for Age, PICU = Pediatric Intensive Care Unit, mREE = measured Resting Energy Expenditure, RQ = Respiratory Quotient, EN = Enteral Nutrition, PN = Parenteral Nutrition

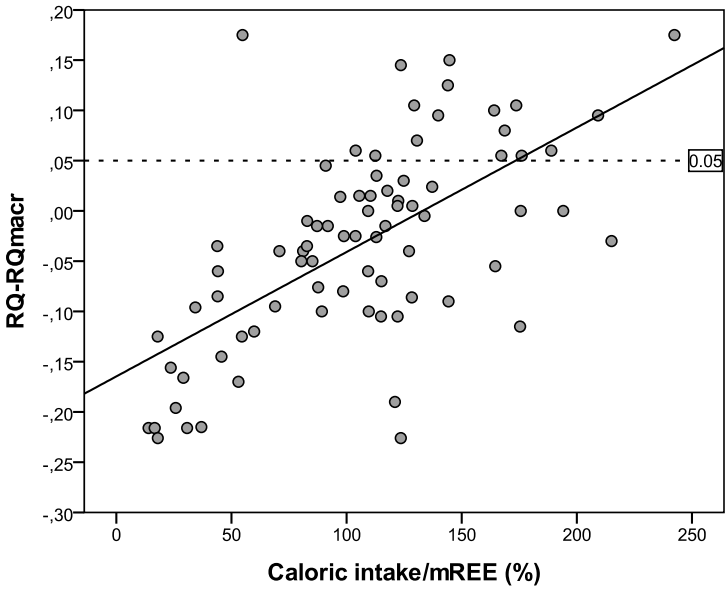

Figure 1. Correlation between RQ-RQ_{macr} and caloric intake/mREE (r=0.627, p<0.001). Dotted line represents the generally applied cut-off value for overfeeding

RQ = Respiratory Quotient, mREE = measured Resting Energy Expenditure

DISCUSSION

This study showed that when different definitions indicating overfeeding were applied to a group of critically ill mechanically ventilated children, a wide variation in the proportion of children identified as overfed was found, ranging from 23% to 50%. RQ exceeded RQ_{macr} +0.05 from a ratio caloric intake/mREE of 165%.

Overfeeding in critically ill children has been predominantly reported with the definition based on the ratio caloric intake/REE (Table 1)[14,21-25,27,28]. The proposed and frequently used upper limits of 110% or 120% are, however, consensus based and not derived from sound studies with clinical endpoints. A recent systematic review in which 9 studies were summarized and a recent single-center study by Jotterand Chaparro et al., investigated the influence of energy and protein intake on protein balance in critically ill children. It was found that a *minimum* intake of respectively 57 and 58 kcal/kg/day and of 1.5 g protein/kg/day were required to achieve a positive protein balance[19,20]. Taking into account a ratio caloric intake/mREE >110% and >120%, a subgroup analysis of our study showed that 36% and 23% of the children, respectively, did not achieve this minimal energy intake of 57 kcal/kg/day but would be identified as being overfed. This identification of a patient as being overfed while they can be presumed to have a negative protein balance would be a contradiction, regardless of the

fact that a positive protein balance should be interpreted as an intermediate and not a clinical outcome measure[40]. Based on our data the upper limit of caloric intake was found to be 165% of the ratio caloric intake/mREE based on RQ-$RQ_{macr,}$ reflecting a caloric intake of 79 kcal/kg/day. This upper limit is more in line with the identified minimum intakes than the most frequently used limits of 110% and 120%.

An age-dependent definition of overfeeding, however, might be necessary. In the single-center study by Jotterand Chaparro et al., it was shown that nitrogen balance was equilibrated with a caloric intake close to mREE in children younger than 3 years, and 122% of mREE in children older than 3 years[19].

Another reason to question the use of the ratio caloric intake/mREE to identify overfeeding throughout the course of PICU stay is the effect of the phase of critical illness. Several studies have shown that REE remains stable during the first week after admission[16,21,41]. This implies that, when using this ratio to guide nutritional therapy, the upper limit of caloric intake remains stable in this period as well, even if the patient is recovering, and extra energy is presumed necessary for tissue repair and growth. Furthermore, REE is measured in rest, whereas the patient in the recovery phase will be mobilizing. These patients have a higher energy need than patients who are not able to mobilize, but this increase in caloric requirements cannot be identified with current methods.

So far, only one study, with a limited number of surgical infants, investigated the relation between caloric intake and the phases of the metabolic stress response using an RQ>1.0, reflecting lipogenesis, to define overfeeding[11]; it was found that the rate of overfeeding was lower in the resolving stress group, defined by a C-reactive protein (CRP) level of 2 mg/dL or less, compared to the acute stress group (CRP >2 mg/dL) (33.4 vs 69.2%, $p<0.001$). Although inflammatory parameters such as a CRP level might be used to guide caloric intake, it is not clear how soon energy intake can be increased without the risk of overfeeding, because no single metabolic or hormonal markers or parameters have consistently shown to indicate the start of the anabolic phase. When the child is in the recovery phase and is able to mobilize, optimal caloric intake might be as high as the recommended intake for healthy children[24] or even higher to compensate for catch-up growth.

The risk of overfeeding might also be affected by the nutritional status of the child. More attention is paid to nutritional support of malnourished children or children at nutritional risk[42] and absolute weight-based intake goals are lower for malnourished patients than nonmalnourished peers[25]. Also in our study, caloric intake was higher in children with an SD-score WFA<-2. Therefore nutritional goals are more easily reached in this population, but with a concomitant increased risk of overfeeding. Besides the increased caloric intake, malnourishment is likely to affect energy expenditure by an altered body composition. In a recent study, mREE in malnourished critically ill children was found to be 80% of predicted[43], highlighting the need for measurement of energy requirements to identify overfeeding in

this specific group of children. This hypometabolic state was reflected in an increased ratio caloric intake/mREE of 145%[43]. We also found that children identified as being overfed by the ratio caloric intake/mREE, had a significantly lower SD-score, compared to children without overfeeding. This contrasting combination of lowered mREE and caloric overfeeding described in malnourished children, might be linked to an amplification of mitochondrial dysfunction associated with the stress response[43,44]. Therefore the effect of nutritional status on the risk of overfeeding may be intertwined with the phases of critical illness.

Because the difference of RQ-RQ_{macr} reflects the use of different macronutrients within a patient, it acts as a more functional parameter to describe overfeeding throughout the course of illness and for different age groups. The use of this parameter might be, however, limited when caloric intake is less than mREE[45] and during the acute phase of critical illness when endogenous energy production is present, even with adequate energy provision[46]. RQ is also affected by factors unrelated to feeding[29].
Our study is further limited by the small number of patients, the lack of clinical endpoints, and the fact that we only performed single measurements. Therefore, it should be followed by larger prospective studies on the effect of intake on clinical outcomes, preferably with a longitudinal design.

To conclude, the proportion of mechanically ventilated patients identified as overfed ranged widely from 23% to 50% depending on the criteria applied. The currently used definitions to describe overfeeding fail to take into account several relevant factors associated with critical ill children and are therefore not generally applicable to the PICU population. We advocate the development of a definition for overfeeding dependent on age, nutritional status and phase of illness, preferably based on clinical outcome measures.

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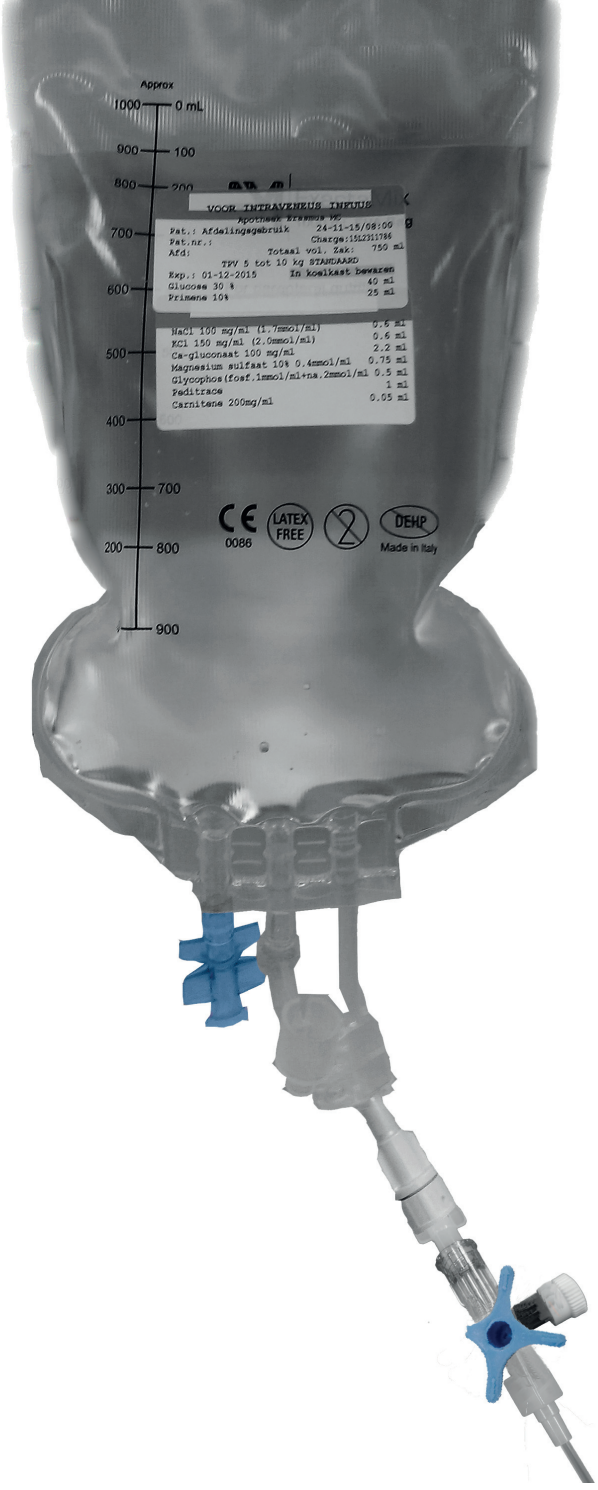
PART IV

SUPPLEMENTAL PARENTERAL NUTRITION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VOOR INTRAVENEUS INFUUS
Apotheek Bremen BV
Pat.: Afdelingsgebruik 24-11-15/08:00
Pat.nr.: Charge:15L2315786
Afd: Totaal vol. Zak: 750 ml
TPV 5 tot 10 kg STANDAARD
Exp.: 01-12-2015 In koelkast bewaren
Glucose 30 % 40 ml
Primene 10% 25 ml
NaCl 100 mg/ml (1.7mmol/ml) 0.6 ml
KCl 150 mg/ml (2.0mmol/ml) 0.6 ml
Ca-gluconat 100 mg/ml 2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml 0.75 ml
Glycophos(fosf.1mmol/ml+na.2mmol/ml 0.5 ml
Peditrace 1 ml
Carnitene 200mg/ml 0.05 ml
CE 0086
LATEX FREE
DEHP
Made in Italy

CHAPTER 5

Evidence for the use of parenteral nutrition in the pediatric intensive care unit

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* contributed equally

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ABSTRACT

Background and aims

During hospitalization in a pediatric intensive care unit (PICU), critically ill children are fed artificially. Administered via the preferred enteral route, caloric targets are often not reached. Hence, parenteral nutrition is given to this patient population. In this review we analyzed the available evidence from randomized controlled trials (RCTs) that supports the use of parenteral nutrition in children during critical illness.

Methods

A search strategy in Ovid MEDLINE and Ovid EMBASE was created and trial registries were screened to identify the relevant RCTs. Studies were included if they were randomized controlled trials, involved pediatric patients admitted to PICU, and compared different dosing/compositions of parenteral nutrition. Descriptive studies and reviews were excluded.

Results

Of the 584 articles identified by the search strategy, only 114 articles were retained after title screening. Further abstract and full text screening identified 6 small RCTs that compared two dosing/composition strategies of parenteral nutrition. These trials reported differences in surrogate endpoints without an effect on hard clinical endpoints. The RCTs observed improvements in these surrogate endpoints with the use of more calories or when parenteral glutamine or fish oil was added.

Conclusions

The few RCTs suggest that surrogate endpoints can be affected by providing parenteral nutrition to critically ill children, but the studies were not statistically powered to draw meaningful clinical conclusions. Large RCTs with clinically relevant outcome measures are urgently needed to support the current nutritional guidelines that advise the use of parenteral nutrition in the PICU.

INTRODUCTION

For critically ill children who require an admission to the Pediatric Intensive Care Unit (PICU), nutritional support is advised as soon as possible to prevent or reduce catabolism, with the intention to enhance recovery while allowing normal growth[1]. The enteral route is preferred as it has been suggested that feeding via the gut maintains gut integrity and may reduce the risk of infection, in comparison with feeding via the parenteral route[1]. However, when only enteral nutrition (EN) is provided during PICU stay, caloric targets are often not reached. This is explained by intestinal dysfunction as part of the critical illness, the administered medication that affects the gastrointestinal tract, frequent interruptions of enteral feeding and the need for fluid restriction[2]. Hence, a caloric deficit quickly builds up in critically ill children, the severity of which has been associated with poor outcomes and impaired growth[3,4]. Children are particularly vulnerable for accumulating a pronounced caloric deficit as their relative energy requirements are 2-3 times higher than those of adults. Reaching the preset caloric targets is easier when parenteral nutrition (PN) is administered. However, feeding children via the parenteral route has shown to increase the risk of metabolic disturbances such as hyperglycemia and dyslipidemia and to be associated with more nosocomial infections[5]. Therefore, the question remains if, and when, PN should be initiated for critically ill children in the PICU.

The currently available guidelines are not very specific on how energy requirements should be determined for critically ill children nor on how the caloric deficit should best be prevented. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines state that the initiation of PN depends on the clinical condition and the age and size of the infant or child[6]. These guidelines advocate to start PN in infants shortly after admission to PICU whenever EN fails, but in older children and adolescents longer periods of inadequate nutrition may be tolerated. The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines make no specific recommendations for the use and dosing of PN for children treated in the PICU[1]. However, the A.S.P.E.N. guidelines state that for older children, a caloric deficit can be tolerated for up to one week. These different and rather non-specific recommendations have resulted in nutritional practices that vary widely among PICUs worldwide[7].

Therefore, we performed an up to date review to assess all available evidence from randomized controlled trials (RCTs), with hard clinical as well as surrogate endpoints, that supports the use of parenteral nutrition in children during critical illness.

METHODS

An extensive search strategy in both Ovid MEDLINE and Ovid EMBASE was created and trial registries were screened to identify the relevant RCTs. Studies were included if they were randomized controlled trials, involved pediatric patients admitted to PICU, and compared different dosing/compositions of parenteral nutrition. Parenteral nutrition was defined as intravenously administered macronutrients (carbohydrates, lipids, proteins) of which dosing differed between treatment groups in the included RCTs.

The time frame of the search strategy was from the inception of these databases up to September 7, 2015. Also non-English language studies were taken into account. In addition, trial registries were screened and reference lists of all potentially relevant studies were analyzed manually. The detailed search strategies are described in Supplementary Table 1. We included only randomized controlled trials, and any eventual post-hoc analyses thereof, of pediatric patients admitted to the PICU that compared different dosing/compositions of parenteral nutrition. Descriptive studies and reviews were excluded. Also studies involving the adult or premature newborn population were excluded. We focused on timing and dosing as well as composition of parenteral macronutrients and did not address other nutritional aspects in the PICU. The initial focus was on studies with hard clinical outcome measures (such as infections, length of PICU stay, or mortality). However, a systematic review from 2009 revealed that one study used a clinical outcome measure. Therefore, we also included studies with surrogate endpoints (such as nitrogen balance or markers of inflammation). The quality assessment of the individual studies was based on the Jadad score[8] and the Black and Downs score[9].

Two authors (TF, DK) independently screened the search results. Two selection criteria were premised for title and abstract screening. First, the study population had to consist of term neonates, infants, children or adolescents treated in the PICU. Secondly, the studies needed to investigate parenteral nutritional support during hospitalization in PICU. For the full text screening, these criteria were further narrowed to (a) an age range of 37 weeks gestational age to 18 years of age and (b) to randomized controlled trials in which dosing and/or timing of mixed-bag PN or one of its components (amino acids, lipids, glucose) differed between the randomly allocated groups. Hence, studies comparing EN strategies were excluded. TF and DK independently determined eligibility. In case of discrepancy, SV and KJ decided on inclusion by consensus.

RESULTS

After title screening, 114 articles were retained (Fig. 1). The main reasons for these initial exclusions were (a) non-PN related aspects of nutrition, such as dosing of EN and (b) non-randomized controlled trials. After further screening of the abstracts and an additional manual

search, 8 articles were retained[10-17]. Of these, full text reading resulted in exclusion of another 2 articles, one that was related to EN instead of PN and one was not a RCT[15,16]. Table 1 gives an overview of the 6 trials, of which 1 was a post-hoc analysis of one of 5 RCTs[11], that were identified as relevant for this review. As the retained studies used different interventions and outcome measures they could not be analyzed in a formal meta-analysis.

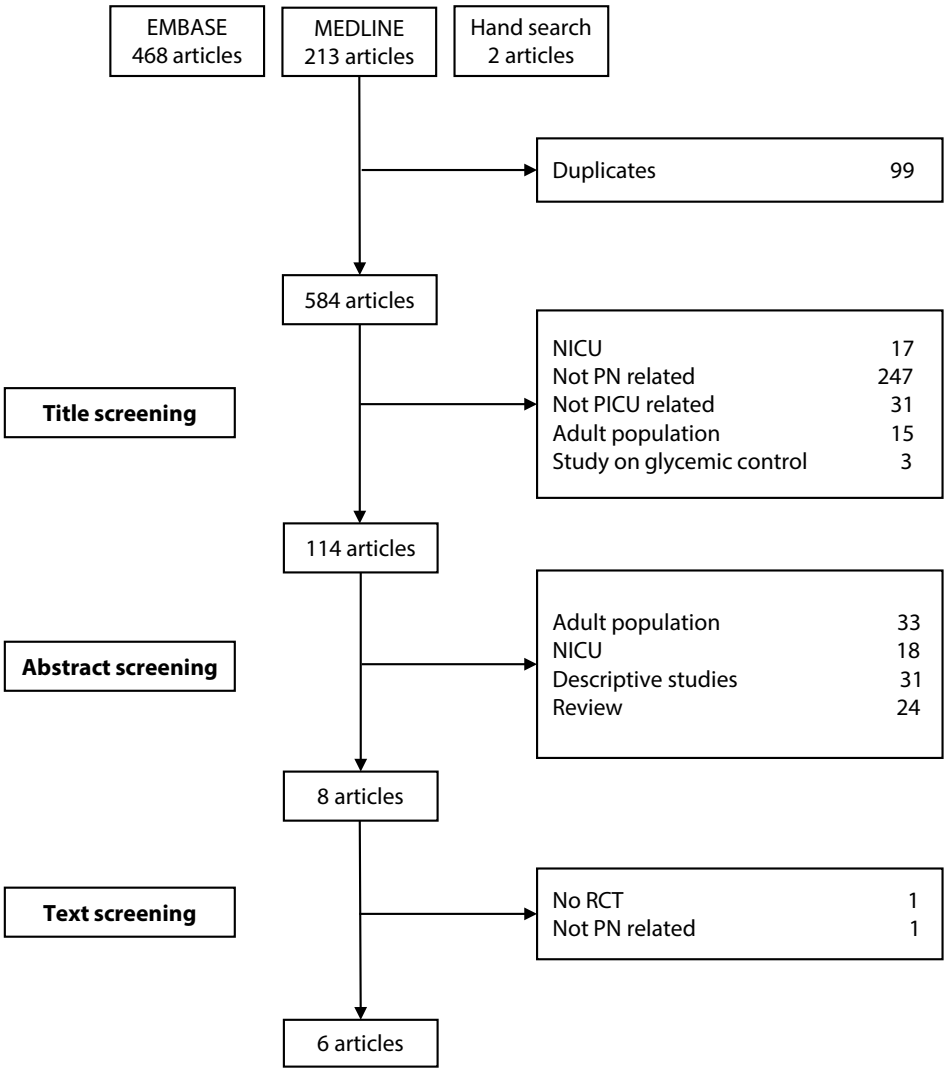

Figure 1. Flowchart of screening process
NICU=Neonatal Intensive Care Unit, PN=Parenteral Nutrition, RCT=Randomized Controlled Trial

Table 1. *Overview of 5 RCTs and 1 post-hoc analysis identified as support of use of parenteral nutrition (PN) in critical ill children*

Study	*Patients*	*Comparator*	*Intervention*	*Outcome parameters*	*Limitations*
Jordan I. et al. Clin Nutr. 2015 Glutamine effects on heat shock protein 70 and interleukines 6 and 10: Randomized trial of glutamine supplementation versus standard parenteral nutrition in critically ill children[13]	101 patients (1 month -14 years) with severe sepsis or post major surgery	Standard PN (SPN)	Standard PN plus Glutamine 0.33g/kg/d (SPN + Gln)	High Heat Shock Protein-70 longer maintained in SPN + Gln. No difference in interleukin 6, interleukin 10	1) Surrogate endpoints
Larsen B. et al. JPEN J Parenteral Enteral Nutr. 2015;39:171-179 Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants[11]	32 patients (neonates 40 weeks ± 2.2 weeks) post cardiac surgery	Standard group Intralipid®	Intervention group Lipoplus® (50% MCT, 40% LCT, 10% Fish oil)	Intervention group: Procalcitonin lower in at day 1, Leukotriene B4 higher at day 1 and 7, but lower at day 10. Lymphocyte concentration lower	1) Post-hoc analysis 2) Underpowered to draw clinical conclusions 3) Intervention already started before surgery
Lekmanov A. et al.Anesteziol Reanimatol 2013; Jan-Feb;(1):49-51 Study of glutamine solution use efficiency in pediatric patients with heavy thermic burns and concomitant injuries in the intensive care unit[14]	40 patients (2-15 years old) with thermic burns	Standard PN	Standard PN plus glutamine (2 ml/kg)	Intervention group: shorter duration of mechanical ventilation. No differences in levels of protein, albumin or glutamine	1) No statistical analysis description 2) Methods inaccurately described 3) Glutamine levels not different between groups
Larsen B. et al. Clin Nutr. 2012 Jun;31(3):322-9 Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial[17]	32 patients (neonates 40 weeks ± 2.2 weeks) post cardiac surgery	Standard group Intralipid®	Intervention group Lipoplus® (50% MCT, 40% LCT, 10% Fish oil)	Intervention group: TNF alpha plasma levels lower prior to and after surgery. Pro-inflammatory markers lower	1) Surrogate endpoints 2) No clinical outcome difference 3) Intervention already started before surgery

Chaloupecky, V. et al. J Thorac Cardio-vasc Surg 1997;114:1053-60 Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support[10]	37 patients (2 months -1 year) post cardiac surgery	Standard group Glucose 10% 25 kcal/kg *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group Glucose 10-20% and amino acid 0.8 g/kg/d 33 kcal/kg *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group: Nitrogen balance less negative on day 1. Standard group: decrease in plasma levels of branched amino acids (valine, leucine, isoleucine), alanine, glycine and proline on day 2	1) Surrogate endpoints 2) Short intervention time
Chaloupecky, V. et al. Cor et Vasa 1994;36:26-34 The effect of early parenteral nutrition on amino acid and protein metabolism in infants following congenital heart disease surgery in extracorporeal circulation[12]	29 patients (6.5 months ± 3 months) post cardiac surgery	Standard group Glucose 10% *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group Glucose 20% and amino acid 0.8 g/kg/d *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group: Nitrogen balance less negative on day 1. Standard group: decrease in plasma levels of branched amino acids (valine, leucine, isoleucine), glutamine, arginine and proline on day 2	1) Surrogate endpoints 2) Short intervention time

The RCT by Larsen et al., as well as the post-hoc analysis of this RCT, investigated 32 infants undergoing elective open-heart surgery with cardiopulmonary bypass and compared the effect of the pre- and post-operative administration of two types of parenteral lipid formulas, namely Intralipid® (LCT soybean oil) in the control group and Lipoplus® (50% MCT, 40% LCT, 10% Fish oil) in the intervention group[11,17]. In the primary trial[17], the authors report significantly lower plasma concentrations of TNF-alpha and IL-6 (primary outcome measures) on the first postoperative day in the treatment group receiving Lipoplus®. On day 7, the plasma TNF-alpha and IL-6 concentrations were no longer different. Also duration of stay in PICU/hospital, incidence of sepsis, inotrope scores or ventilator days (secondary outcome measures) were similar in both groups. The post-hoc analysis[11] also reported lower levels of other inflammation biomarkers (procalcitonin, leukotriene B4, lymphocytes) in the Lipoplus® group.

Two RCTs by Chaloupecky et al. were studies of 29 and 37 infants, respectively, undergoing cardiac surgery, in which the impact on proteolysis and plasma amino acid profiles of early parenteral administration of a higher dose of amino acids and of glucose as compared with a low dose maintenance glucose infusion on the first postoperative day was investigated[10,12]. Thereafter, all patients received enteral nutrition in equal amounts. The authors reported less negative nitrogen balances, less proteolysis as suggested by urinary 3-methylhistidine excretion, and higher levels of plasma amino acids during the first postoperative day in the intervention group who received more parenteral amino acids and glucose. Although clinical outcome measures were not explicitly described, the authors report no severe complications such as low cardiac output syndrome, renal failure, sepsis or mortality in any of the groups. Duration of intubation and inotropic support did not differ between treatment groups.

The RCT by Jordan et al. investigated 98 children suffering from severe sepsis or admitted after major surgery who were identified as requiring parenteral nutrition. The study compared the impact of glutamine-supplemented parenteral nutrition in the intervention group with standard parenteral nutrition in the control arm[13]. The authors report that glutamine-supplemented parenteral nutrition evoked a higher plasma concentration of heat shock protein 70 on day 5, whereas plasma concentrations of IL-6 and IL-10 were not affected. Clinical outcome measures were not significantly different in the 2 study groups.

The RCT by Lekmanov et al. studied 40 children with severe thermic burns and concomitant injuries and compared the effect of glutamine-supplemented total parenteral nutrition during at least one week in the intervention group to standard total parenteral nutrition in the control group[14]. The authors reported no significant differences between the two groups for the serum levels of protein, albumin and glutamine on day 5 and 7 of PICU stay, but found a significantly shorter duration of mechanical ventilation in the intervention group (7 days versus 12 days in the control group). This result should be interpreted with caution, since the methods section was incomplete without information on the statistical analyses. Also plasma concentrations of glutamine were not significantly different between the two groups.

Quality assessment revealed low scores for the 2 RCTs by Chaloupecky et al.; namely a Jadad score of 1 and a Black Downs score of 9/31 for both trials, and the RCT by Lekmanov et al.; Jadad score of 2 and Black Downs score of 4/31. The study by Larsen et al. had a higher Jadad score of 3 but the Black and Downs score was only 17/31. The trial of Jordan et al. scored the highest with a Jadad score of 5 and a Black and Downs score of 27/31. As only 6 studies were retained, a funnel plot to assess publication bias could not be created.

DISCUSSION

This systematic review could identify only 6 small RCTs that investigated the impact of a different dose or composition of PN in critically ill infants or children treated in the PICU. Of these 6 studies, 4 investigated infants after cardiac surgery and two included children with sepsis or after other major surgery, or burns respectively. The focus of these few studies was on intermediate or surrogate endpoints, such as nitrogen balances and inflammation markers, which appeared to be beneficially affected by providing more or altered parenteral nutrition early during critical illness. As the studies were small, all were statistically underpowered to detect a clinically relevant effect on patient-centered endpoints. Only the RCT by Lekmanov et al. reported a significant reduction of the duration of mechanical ventilation in children receiving glutamine-supplemented parenteral nutrition. However, with limited information on the used methodology which lacked a statistical analysis plan, the accuracy of these results cannot be determined. Hence, strong clinical conclusions cannot be drawn from these studies. As a result, no recommendations can be made regarding the optimal timing for initiation and composition of parenteral nutrition for use in critically ill infants and children.

The lack of large RCTs on the use of parenteral nutrition in critically ill infants and children is striking. However, this is an observation that is not limited to the nutritional field. Indeed, there are only 7 randomized controlled trials of PICU patients that have addressed a clinical question with a large enough sample size to be able to detect a difference in patient-centered, hard clinical outcomes[18-25], of which 3 are related to metabolic aspects[19,20,23]. This overall lack of large RCTs in PICU patients suggests difficulties in recruiting large numbers of patients, due to the fact that the number of PICU patients and the size of the PICUs worldwide are smaller than for adult intensive care.

All the trials retained by the search strategy of this systematic review focused on surrogate endpoints, such as nitrogen balances and inflammation markers. This may hold some risks. Surrogate nutritional outcome measures are often used to describe mechanistic effects of an intervention. However, there is often a weak relationship, if any, between these surrogate endpoints and the important patient-centered clinically relevant outcomes. Sometimes surrogate endpoints can be misleading as they may inadvertently suggest a benefit whereas the clinical outcomes indicate harm. For example, a large well-designed RCT of critically ill adults

found that the administration of growth hormone, with the intention to improve anabolism and outcome, improved nitrogen balances but increased mortality[26]. Also another large trial showed that early PN in adult ICU patients reduced markers of inflammation while it increased infections, weakness and organ failure and slowed down recovery[27]. Surrogate outcome measures are also the main focus of limited pediatric studies on glutamine-supplemented parenteral nutrition, that failed to show any advantage in critically ill children, just as enteral supplementation of glutamine[28]. Glutamine supplementation is no longer supported in adult critical care, based on the results of recent large high-quality RCTs that showed either no effect on morbidity or revealed and increased late mortality with glutamine supplementation[29-31].

In contrast to the PICU, there appears to be a greater consensus in the neonatal ICU, in favor of early parenteral supplementation. However, again the evidence generated by large RCTs with hard clinical endpoints is quite limited. In a Cochrane review, Trivedi et al[32] included 7 RCTs comparing the effect of intravenous early amino acid administration (within 24 hours after admission) with late initiation (>24 hours) in 394 low-birth-weight neonates on short-term in-hospital outcomes including mortality, early and late growth or neurodevelopment. There were no differences in length and occipitofrontal circumference, however nitrogen balance improved with early administration of amino acids. The impact on other outcomes was not reported. Only with early initiation of parenteral lipids, an improved neonatal growth has been suggested by two RCTs of very-low-birth-weight infants[33,34].

In contrast with the pediatric critically ill patient population, recent large and high quality trials have provided more evidence to support nutritional recommendations for adult critically ill patients[27,35-37]. The EPaNIC (the impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients trial) compared early parenteral supplementation of insufficient enteral feeding with tolerating the caloric deficit that accumulates when only EN is given in 4640 adult ICU patients[27]. This study found that not using PN during the first week in ICU resulted in fewer new infections, less ICU acquired weakness with earlier weaning from mechanical ventilation[38], less liver dysfunction[39] and reduced need for renal replacement therapy, together resulting in an earlier live discharge from the ICU and from the hospital[27]. The SPN (the impact of supplemental parenteral nutrition on infection rate, duration of mechanical ventilation and rehabilitation in ICU patients) trial compared the initiation of PN on day 4, when adult patients were not yet receiving 60% of their caloric needs, with tolerating a nutritional deficit with EN until day 8[37]. The SPN trial showed no differences in the clinically relevant outcomes. The early Parenteral Nutrition trial investigated whether PN should be started very early in critically ill patients when there was a short-term relative contra-indication to EN and apart from a shorter duration of mechanical ventilation (which was a tertiary outcome measure) there were no other clinical benefits[36]. The evidence generated from these trials has resulted in a change in clinical practice of adult intensive care, with a tendency to delay initiation of PN and to accept the macronutrient deficits for up to one week in ICU[40].

While the evidence from high quality RCTs no longer supports the early use of PN for critically ill adult patients, and while the literature may suggest the opposite for preterm newborns, there is currently no evidence to support any of the current PN practices for critically ill patients from term neonates to adolescents. Although several observational studies of large cohorts of critically children have shown a relation between the adequacy of feeding and of protein intake during the first 10 days of admission and lower risk of death[4,41], the adult literature calls for caution in assuming that this association is causal. Hence, whether and for how long the substantial macronutrient deficit that accumulates in critically ill infants and children on enteral feeding only can be tolerated remains an open question.

Further research is therefore necessary to address this question and to determine the role of PN in the PICU population. In order to answer this important question, the study should be large enough to have enough statistical power to detect relevant differences in hard clinical endpoints. The results of the currently ongoing multicenter randomized controlled PEPaNIC trial (Clinical Trials.gov NCT 01536275), will hopefully elucidate some of the controversial topics. The PEPaNIC trial is a study of 1440 critically ill infants and children, and compares the effects of early PN with no PN for up to one week in PICU on several patient-centered clinical endpoints such as new infections and the duration of PICU dependency, besides safety endpoints including mortality[42].

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Supplementary Table 1. *Search strategy*

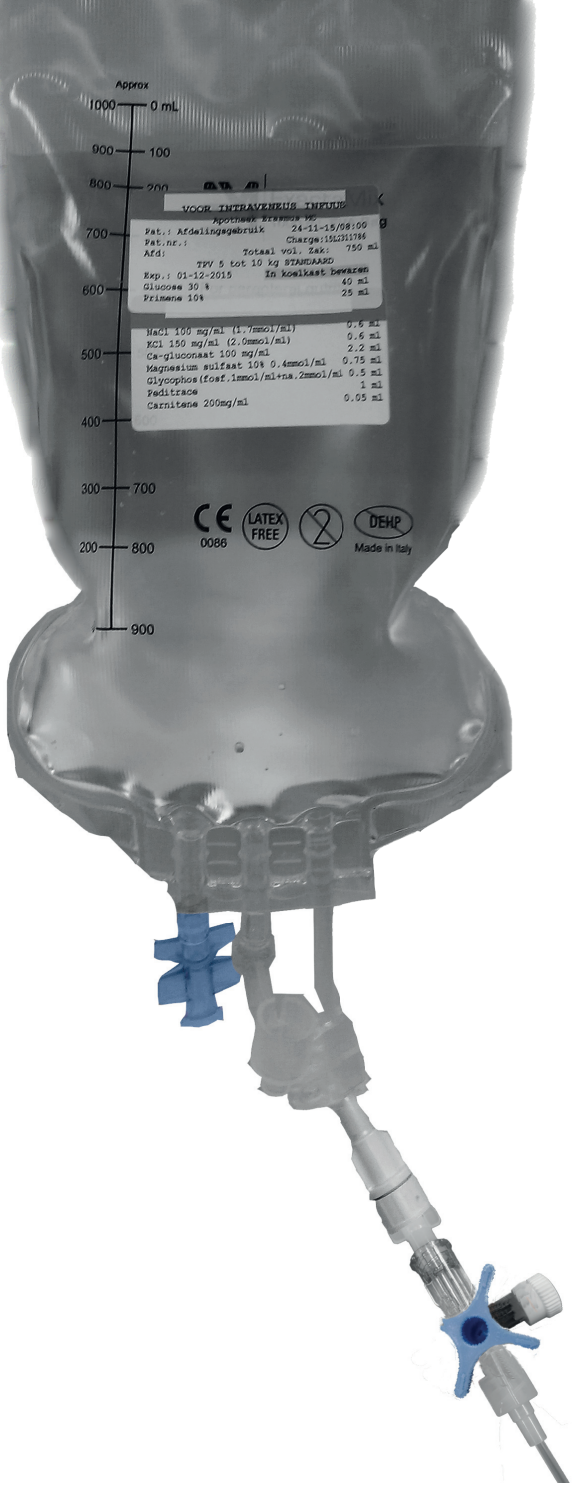
Ovid MEDLINE search strategy	
((Critically ill OR critical illnesses OR "Critical Care"[Mesh:NoExp] OR critical care[tiab] OR "Intensive Care"[Mesh:NoExp] OR intensive care[tiab] OR icu[tiab] OR "Intensive Care Units"[Mesh:NoExp] OR burn unit OR burn center* OR sepsis) AND (children OR toddler*[tiab] OR "Infant"[Mesh:NoExp] OR infant[tiab] OR infants[tiab] OR "Infant, Newborn"[Mesh:NoExp] OR newborn[tiab] OR newborns[tiab] OR neonate[tiab] OR neonates[tiab] OR newborn[tiab] OR newborns[tiab] OR babies[tiab] OR baby[tiab] OR adolescents OR teen[tiab] OR teenager[tiab] OR teenagers[tiab] OR youth[tiab] OR pediatric[tiab] OR paediatric[tiab])) OR "Intensive Care Units, Pediatric"[Mesh:NoExp] OR PICU[tiab]	86939
AND	
("Parenteral Nutrition"[Mesh:NoExp] OR "Parenteral Nutrition, Total"[Mesh:NoExp] OR parenteral feeding*[tiab] OR intravenous feeding*[tiab] OR "Parenteral Nutrition Solutions"[Mesh])	1339
AND	
("randomized controlled trials as topic"[MeSH Terms] OR ("randomized"[All Fields] AND "controlled"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "randomized controlled trials as topic"[All Fields] OR ("randomized"[All Fields] AND "controlled"[All Fields] AND "trial"[All Fields]) OR "randomized controlled trial"[All Fields])	131
Alternative:	
(Randomized Controlled Trials as Topic OR Random Allocation OR Double Blind Method OR Single Blind Method OR clinical trial OR clinical trial, phase i[Publication Type] OR clinical trial, phase ii[Publication Type] OR clinical trial, phase iii[Publication Type] OR clinical trial, phase iv[Publication Type] OR controlled clinical trial[Publication Type] OR randomized controlled trial[Publication Type] OR multicenter study[Publication Type] OR clinical trial [Publication Type] OR Clinical Trials as topic OR (clinical AND trial*) OR ((singl* OR doubl* OR treb* OR tripl*) AND (blind* OR mask*)) OR placebos OR placebo* OR randomly allocated OR (allocated AND random*))	213
Ovid EMBASE search strategy	
#56 #54 AND #55	468
#55 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR'randomization' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR 'placebo' OR (randomi?ed AND controlledAND trial* AND [embase]/lim) OR (rct AND [embase]/lim) OR ('random allocation'/exp OR 'random allocation' AND [embase]/lim) OR ('randomly allocated' AND [embase]/lim) OR ('allocated randomly' AND [medline]/lim) OR (allocated NEAR/2 random AND [embase]/lim) OR ('single blind$' AND [embase]/lim) OR ('double blind$' AND [embase]/lim) OR ((treble OR triple) NEAR/2 blind$ AND [embase]/lim) OR (placebo$ AND [embase]/lim) OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR ('case report'/exp OR 'case report' AND [embase]/lim) OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR 'letter')	1,607,926
#54 #52 AND #53	2,848
#53 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	42,795
#52 #38 OR #39 OR #51	99,572

Supplementary Table 1. *Continued*

#51 #49 AND #50	98,815
#50 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34OR #35 OR #36 OR #37	3,186,376
#49 #1 OR #4 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	421,442
#48 'amino acid mixture plus electrolyte solution'/exp	11
#47 'parenteral solution':ab,ti	204
#46 'peripheral parenteral nutrition'/exp	51
#45 'parenteral solution'/exp	838
#44 'intravenous feeding':ab,ti	519
#43 'intravenous feeding'/exp	965
#42 (parenteral NEXT/1 feeding*):ab,ti	1,670
#41 'parenteral nutrition':ab,ti	21,366
#40 'parenteral nutrition'/exp	38,418
#39 'pediatric intensive care nursing'/exp	123
#38 picu:ab,ti	4,994
#37 paediatric:ab,ti	56,331
#36 pediatric:ab,ti	234,760
#35 youth:ab,ti	43,555
#34 teenagers:ab,ti	11,785
#33 teenager:ab,ti	2,643
#32 teen:ab,ti	4,479
#31 'adolescents':ab,ti	148,727
#30 'adolescent':ab,ti	98,521
#29 'adolescent'/de	1,246,280
#28 babies:ab,ti	37,712

Supplementary Table 1. *Continued*

#27 baby:ab,ti	38,356
#26 'neonates':ab,ti	64,110
#25 'neonate':ab,ti	26,829
#24 'newborn':ab,ti	121,130
#23 'newborn'/exp	479,511
#22 'infants':ab,ti	237,450
#21 'infant':ab,ti	150,122
#20 'infant'/exp	886,678
#19 toddler*:ab,ti	8,002
#18 children:ab,ti	972,537
#17 'child'/exp	2,153,189
#16 'sepsis':ab,ti	92,883
#15 'sepsis'/exp	177,007
#14 (burn NEXT/1 center*):ab,ti	1,806
#13 'burn unit':ab,ti	1,238
#12 'burn unit'/exp	638
#11 'intensive care unit'/exp	91,129
#10 'icu':ab,ti	58,026
#9 'intensive care':ab,ti	126,347
#8 'intensive care'/de	93,067
#7 'critical care':ab,ti	28,770
#6 'critical illness':ab,ti	6,656
#4 'critically ill':ab,ti	39,234
#1 'critically ill patient'/exp	21,467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Primene 10%
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0.5 ml
KCl 150 mg/ml (2.0mmol/ml)
0.6 ml
Ca-gluconaat 100 mg/ml
2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml
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CHAPTER 6

Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial

Dorian Kerklaan*, Tom Fivez*, Sascha Verbruggen, Ilse Vanhorebeek, Sören Verstraete, Dick Tibboel, Gonzalo Garcia Guerra, Pieter J. Wouters, Ari Joffe, Koen Joosten, Dieter Mesotten*, Greet Van den Berghe*
*contributed equally

Trials 2015;16:202

ABSTRACT

Background

The state-of-the-art nutrition used for critically ill children is based essentially on expert opinion and extrapolations from adult studies or on studies in non-critically ill children. In critically ill adults, withholding parenteral nutrition (PN) during the first week in ICU improved outcome, as compared with early supplementation of insufficient enteral nutrition (EN) with PN. We hypothesized that withholding PN in children early during critical illness reduces the incidence of new infections and accelerates recovery.

Methods/design

The Pediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) study is an investigator-initiated, international, multicenter, randomized controlled trial (RCT) in three tertiary referral pediatric intensive care units (PICUs) in three countries on two continents. This study compares early versus late initiation of PN when EN fails to reach preset caloric targets in critically ill children. In the early-PN (control, standard of care) group, PN comprising glucose, lipids and amino acids is administered within the first days to reach the caloric target. In the late-PN (intervention) group, PN completing EN is only initiated beyond PICU day 7, when EN fails. For both study groups, an early EN protocol is applied and micronutrients are administered intravenously. The primary assessor-blinded outcome measures are the incidence of new infections during PICU stay and the duration of intensive care dependency. The sample size (n = 1,440, 720 per arm) was determined in order to detect a 5% absolute reduction in PICU infections, with at least 80% 1-tailed power (70% 2 tailed) and an alpha error rate of 5%. Based on the actual incidence of new PICU infections in the control group, the required sample size was confirmed at the time of an *a priori* planned interim-analysis focusing on the incidence of new infections in the control group only.

Discussion

Clinical evidence in favor of early administration of PN in critically ill children is currently lacking, despite potential benefit but also known side effects. This large international RCT will help physicians to gain more insight in the clinical effects of omitting PN during the first week of critical illness in children.

BACKGROUND

Nutritional support for children in intensive care

The state-of-the-art nutrition used for critically ill children is essentially based on expert opinion, small studies with surrogate endpoints and extrapolations from adult studies or from studies in healthy children outside the Intensive Care Unit (ICU). It is widely accepted that in healthy children, nutrition not only serves to maintain body tissues but also allows growth, which is considered of particular importance during infancy and adolescence[1,2]. In hospitalized children, especially in the young, the current European and American guidelines for nutrition recommend early parenteral nutrition (PN) to prevent/correct malnutrition and to sustain appropriate growth when enteral nutrient (EN) supply is insufficient[3,4]. Observational studies suggest that about a quarter of children, most notably infants, admitted to pediatric intensive care units (PICUs) develop a pronounced caloric deficit[1]. The stores of energy, fat and protein in children are limited, leaving children to rely on muscle mass to provide necessary substrates for metabolism. The energy deficit observed with acute critical illness in children has been associated with adverse outcome[5]. Based hereon, it is current practice in PICUs to start PN in the acute phase of critical illness to supplement insufficient EN with the intention to avoid underfeeding[3,4]. However, overfeeding may also be harmful[6-9]. It is difficult to administer the correct amount of nutrition, avoiding overfeeding as well as underfeeding.

Varying nutritional guidelines and clinical practices

It is currently advised to assess energy expenditure considered to reflect energy requirements, through the use of indirect calorimetry during the course of critical illness and to use this technique for determining individualized targets to guide nutritional therapy[10]. However, a European survey conducted in 2004 showed that only 17% of the PICUs use this technique[11] and the technique itself has not been well standardized[12,13]. In the most critically ill, major caveats are present, such as respiratory support with more than 60% oxygen and the use of uncuffed tubes resulting in unpredictable measurements. The use of standard equations to predict energy expenditure and/or requirements also carries the risk of overfeeding and underfeeding[14-16].

Experts worldwide agree that there are insufficient data to make evidence-based recommendations for the optimal target of caloric intake in critically ill children and for the optimal time after onset of critical illness by which this target should be reached. The lack of widely accepted caloric targets for critically ill children results in nutritional strategies that vary substantially across centers. The current European and American guidelines for nutrition in hospitalized children recommend PN to prevent or correct malnutrition and to sustain appropriate growth when EN supply is insufficient[10,17]. Most guidelines advise to do this early so that the recommended daily allowances for children are reached on day 2 or 3 after PICU admission. These recommendations are based on evidence from cohort studies without a

control group, case series or expert opinion (Grade D level).
The ongoing controversy on optimal amount, composition and timing of administration of PN in critically ill children may in fact conceal the fact that there is no hard evidence for any use of PN in critically ill children. Supported by the results of a Cochrane systematic review, Joffe et al. concluded that randomized trials investigating the role of intravenous nutritional support during the first week of critical illness in children should be performed and should include a control arm in which no nutritional support is administered or hypocaloric goals (below basal metabolic rate) for nutritional support are used[18].

Rationale of the study and study hypothesis

A recent randomized controlled trial (RCT) in critically ill adults[19] showed that the early provision of PN worsened rather than improved outcomes as compared with withholding PN and thus tolerating a substantial caloric deficit up to 1 week in ICU. Also, other studies did not show clinical benefit of early PN in adult ICU patients[20,21]. Hitherto, no well-designed RCT has been performed in critically ill children. The aim of the PEPaNIC trial (the acronym stands for Pediatric version of the effect of Early Parenteral Nutrition to complete insufficient enteral nutrition in ICU patients) is to investigate whether a strategy of withholding PN during the first 7 days in the PICU (late PN) provides clinical benefit over the current practice of early PN in critically ill children. We hypothesize that withholding PN for 1 week in the PICU reduces new infections and shortens the duration of PICU stay.
This hypothesis is currently being tested in a multicenter superiority RCT performed in three large, tertiary referral PICUs (University Hospitals Leuven, Leuven, Belgium; Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands; Stollery Children's Hospital, Edmonton, AB, Canada). The centers were invited to participate based on a self-declared routine use of early PN in the PICU. It was anticipated that this routine use of early PN differs among centers. This was considered to be an asset as it contributes to the external validity of the PEPaNIC trial.

METHODS/DESIGN

Ethical approval

The study protocol and (deferred) informed consent forms were approved by the institutional ethical review boards in Leuven, Belgium (ML8052 Amend-ID0005), Rotterdam, The Netherlands (NL38772.000.12) and Edmonton, AB, Canada (Pro00038098). Informed consent is given in writing by the parents or the legal guardians, confirmed by the child when older than 7 years, after providing all information orally in plain language and in writing. For planned admissions, informed consent is obtained prior to surgery/procedure. For unplanned admissions, informed consent is obtained within 24 hours after admission on the PICU (deferred informed consent as

the nutritional therapy should be initiated from PICU admission onward).

Patients' eligibility – Inclusion criteria

Upon admission to the participating PICUs, all critically ill children are screened for nutritional risk and eligibility for inclusion in the PEPaNIC clinical study[22]. All non-eligible patients, identified by the local investigators, are logged.

Critically ill children, newborn to 17 years (inclusive or exclusive depending on the local definition of a pediatric patient) old, with a STRONGkids (Nutritional risk score) score of 2 points or more and who are likely to stay in the PICU for more than 24 hours, are eligible for inclusion[22].

Exclusion criteria

Patients fulfilling one or more of the following criteria are excluded:

- STRONGkids score lower than 2 on PICU admission[22]
- Not critically ill (for example, anticipated oral intake within 24 hours)
- Non-pediatric patients (aged 17 or older, compare with above)
- Premature newborns (<37 weeks gestational age upon admission in the PICU)
- 'Do not resuscitate' code at the time of PICU admission
- Expected death within 12 hours
- Readmission to PICU after already having been randomized
- Enrollment in another intervention trial
- Transfer from another PICU or neonatal ICU after a stay of more than 7 days
- Ketoacidotic or hyperosmolar coma
- Inborn metabolic diseases requiring specific diet
- Short bowel syndrome or other conditions requiring PN for more than 7 days prior to PICU admission

Data collection at study entry

At baseline, data on demographic (age, gender, race/ethnicity, (pre-)admission bodyweight and height) and clinical characteristics of the patients are obtained. For all patients, severity of illness scores are calculated such as the PEdiatric Logistic Organ Dysfunction (PELOD) score and, for cardiac surgery patients, the Risk-Adjustment in Congenital Heart Surgery or RACHS score. The Pediatric Risk of Mortality (PRISM) score cannot be used for this study as the nutritional management is expected to affect the highest blood glucose concentration during the first 24 hours. In addition, co-morbidities prior to admission are noted. These comprise, among others, the presence of a genetic syndrome, gestational age at birth, presence/history of cancer, diabetes mellitus, kidney failure and infection upon admission.

Randomized treatment allocation

Randomization procedure

Randomization to early PN or late PN in a 1:1 ratio, is performed centrally (KU Leuven, Belgium) by use of a dedicated computerized system, accessible in all centers around the clock, 7 days a week. The computer algorithm allocates every consecutive, eligible patient per center to one of the two treatment arms in a blinded fashion by use of permuted blocks per diagnostic stratum to create parallel groups. The block size is unknown to bedside physicians, nurses and members of the research team. Patients are stratified per study site according to age groups (<1 year and ≥1 year) and the following primary diagnostic categories on admission:

I. Medical PICU admissions (infectious or non-infectious): (a) neurological (b) other.
II. Surgical PICU admissions (elective or emergency) according to referral discipline (a) cardiac surgery (b) other.

Treatment allocation and blinding

Concealed allocation to the randomized treatment was realized by use of the computerized randomization system described above. It was considered not feasible to blind treating physicians and patients for the allocated treatment during the time window of the randomized intervention. After discharge to the normal ward, all treating physicians are unaware of the randomized treatment allocation. All outcome assessors and investigators not directly involved in the patients care, such as statisticians, infectious disease specialists and laboratory personnel, are fully blinded to treatment allocation.

Common strategy for early EN in both study arms

The initiation and increase of EN, and the use of gastroprokinetics are prescribed in the standing orders for EN in each center. Both groups receive micronutrients (trace elements, minerals and vitamins) intravenously from day 2 onwards until the amount of EN given reaches 80% of the caloric target.

Randomized interventions

Patients randomized to the early-PN strategy (standard of care or control group) receive this type of nutrition according to current management in each of the participating centers, which were recruited based on a routine use of early PN. For patients randomized to the late-PN group (intervention group), all PN is withheld during the first week in the PICU. The international setting of the trial brings some variation in the control group (see study rationale and hypothesis), while the intervention group is strictly standardized ('no PN during the first week in PICU').

Standard of care or control group: early-PN

In the Leuven (BE) PICU, patients randomized to the early-PN group receive a mixture of glucose 30% and Vaminolact® (Fresenius, Uppsala, Sweden) in equal amounts upon admission to PICU, comprising 150 mg/ml glucose and 4.7 mg/ml nitrogen. For patients who require fluid restriction, total fluid intake is 50 ml/m^2/h on days 1 and 2 (the day after admission and further referred to as day 2), and 60 ml/m^2/h on day 3. Patients not requiring fluid restriction receive 100 ml/kg/day for the first 10 kg bodyweight, 50 ml/kg for the next 10 kg, and 20 ml/kg for the bodyweight over 20 kg, to be reached within 3 days. For all patients on intravenous (IV) nutrition, and within the fluid limitation described above, lipids (SMOFlipid® (20g/100ml) Fresenius, Uppsala, Sweden) are added from the second morning after admission, initially at a dose of 1.5 g/kg/day, increasing to a maximum of 3 g/kg/day, depending on the age. On the third morning after admission, pharmacy-prepared PN preparations are prescribed, unless adequate enteral nutritional intake is expected. PN preparations contain a mixture of glucose 50% and SMOFlipid® covering respectively 60 to 70% and 40 to 30% of calculated energy target and a 1.5 to 2.5 g/kg protein intake, according to age, by Vaminolact®. If the body weight is above 5 kg, Vaminolact® is replaced by Vamin 18® (Fresenius, Uppsala, Sweden). Any enterally-delivered energy is taken into account twice daily to reduce the energy delivered by PN. When EN covers 80% of optimal calculated caloric needs, PN is stopped. When the patient starts to take oral nutrition, the PN and/or EN is reduced and eventually stopped. Whenever enteral or oral intake falls below 50% of calculated caloric needs, the PN is restarted.

In the Rotterdam (NL) PICU, patients randomized to the early-PN group receive a continuous glucose infusion upon admission to PICU (<30 kg; 4 to 6 mg/kg/min, >30 kg; 2 to 4 mg/kg/min). From day 2 onwards the glucose intake is increased for all children on IV nutrition to 8.3 mg/kg/min (5 to 10 kg), 6.9 mg/kg/min (10 to 30 kg) or 4 mg/kg/min (>30 kg). Primene® (Baxter, Kobaltweg 49, 3542 CE Utrecht) (5.5 to 5.7 mg/ml nitrogen) is added from day 2 onward at 25 ml/kg/day (<10 kg) or 20 ml/kg/day (10 to 30 kg). From day 2 onwards, Intralipid® (Fresenius, Uppsala, Sweden) is added initially at a dose of 10 ml/kg/day (<10 kg) or 7.5 ml/kg/day (10 to 30 kg), increasing to 20 or 15 ml/kg/day respectively. For patients who require fluid restriction, intake is adjusted accordingly. Children >30 kg on IV nutrition receive from day 2 onwards Olimel N5 (Baxter, 5.2 mg/ml nitrogen, 115 mg/ml glucose) when central lines are in place or Olimel N4 (Baxter, 4.0 mg/ml nitrogen, 75 mg/ml glucose) when only peripheral lines are in place; the dose is 48 ml/kg/day. Any enterally-delivered energy is assessed twice daily and the energy delivered by PN is reduced accordingly. Energy goals for enteral nutrition are based on the body weight-based Schofield equation[23] (first day of admission) and on the Recommended Dietary Allowances (RDA, Dutch Health Council) for the subsequent length of stay (Dietary Reference Intake: energy, protein and digestible carbohydrates, 2001, Health Council of the Netherlands: The Hague). Energy goals and composition of parenteral nutrition are based on the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

guidelines[4]. When EN covers 80% of calculated caloric needs, PN is stopped. When the patient starts with oral nutrition, PN and/or EN is reduced and eventually stopped. Whenever enteral or oral intake falls below 50% of calculated caloric needs, PN is restarted.

In the Edmonton (CA) PICU, the patient's energy expenditure is assessed upon admission by a registered dietitian when possible. Nutritional support is initiated as soon as possible, with the goal to match energy expenditure (measured or estimated resting energy expenditure of the child). The urgency of initiation of nutrition support is dependent on nutritional risk prior to admission, disease state and age. If indirect calorimetry cannot be done, 65% of basal metabolic rate by the Food and Agriculture Organization-World Health Organization (FAO-WHO) is used to determine caloric requirement. This number is adjusted daily by the dietitian based on the acute phase response and clinical picture of the child. If nutritional requirements cannot be met enterally, PN is added to achieve caloric target. On admission to PICU, patients receive a glucose infusion of approximately 3 to 4 mg/kg/minute taking into account the total fluid prescribed by medical staff. At that time EN is initiated when possible. On the morning of day 2, if the patient is not already on full enteral feeding, 20% IV lipids are initiated at 0.5 g/kg/day. On the morning of day 3, if the patient is not already on full enteral feeding, lipid infusion is increased to 1 g/kg/day and a solution of amino acids and concentrated glucose is added. The caloric goal is Basal Metabolic Rate when the patient is intubated and Total Energy Expenditure when the patient has been extubated.

Intervention group: late-PN

In the 3 centers, patients randomized to the late-PN group receive a mixture of glucose 5% and NaCl 0.9% at, respectively, 60% and 40% of the total flow rate that is required to obtain optimal hydration, as prescribed by the attending physician, taking into account the volume of EN that is being delivered. No other forms of PN (lipid or protein infusions) are administered. When the amount of EN that is administered still covers less than 80% of the calculated targets after 1 week in the PICU, supplemental PN is initiated on day 8 according to the current PN protocols in each center.

The medical and nursing staff of the PICU were all informed and trained extensively during regular meetings before the start of the trial and were familiarized with the protocol. In order to optimize protocol compliance, the protocol was programmed in the patient data management system (PDMS). The use of this program was explained to every nurse, trainee and resident on the PICU and was always supervised by the senior staff.

Adherence to the protocol in Leuven and Rotterdam was guaranteed by using a PDMS guided system and by careful follow-up by study nurses. In Edmonton, a paper protocol was used and adherence checked by an independent study nurse and physician.

Criteria for stopping the study intervention

When in the intervention arm (late-PN group), blood glucose concentration falls spontaneously (without exogenous insulin) below 50 mg/dl, the standard infusion of glucose 5% is switched to 10% glucose until blood glucose concentration is higher than 80 mg/dl and stable. Thereafter, the infusion of glucose 10% is stopped again and switched back to glucose 5%.

Blood glucose management

In Leuven, patients in both study groups receive continuous insulin infusion to target blood glucose levels of 50 to 80 mg/dl when aged <1 year and 70 to 100 mg/dl when aged ≥ 1 year. Blood glucose and potassium are monitored systematically every 1 to 4 hours on the blood gas analyzer (ABL Radiometer, Copenhagen, Denmark) using undiluted arterial blood samples drawn via a VAMP® system (Edwards Lifescience Pontbeekstraat 4 1702 Groot-Bijgaarden)[24] and insulin infusion is adjusted when needed.

In Rotterdam, patients in all age groups receive continuous insulin infusion using a step-wise nurse-driven glucose control protocol to target blood glucose levels of 72 to 145 mg/dl, except for patients with traumatic brain injury for whom the target is set at 108 to 145 mg/dl[25]. Blood glucose and potassium are monitored systematically every 1 to 3 hours on the blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark) using arterial or capillary blood samples.

In Edmonton, patients in all age groups receive continuous insulin infusion at the discretion of the attending physician when blood glucose levels exceed 180 mg/dl. The attending physician sets the lower target range limit.

Other procedures and guidelines

Other medical treatments are not described by the study protocol. Patients are weaned from the ventilator and from hemodynamic support according to standardized guidelines used in each participating PICU. End-of-life decisions, when further intensive care is considered to be futile, are taken in consensus by senior PICU physicians and the referring specialist.

Handling of re-admissions to the PICU

Patients who are readmitted to the PICU after a participation in PEPaNIC are not eligible for reinclusion. Patients who are readmitted to the PICU within 48 hours of discharge and who are still within the 7 days' time window of the initial randomization receive the nutrition strategy they were randomly assigned to during the initial PICU admission. Patients readmitted more than 48 hours after PICU discharge will be fed at the discretion of the attending physician (standard care).

Outcome measures

Primary endpoints

The two primary endpoints of this RCT are: (i) the incidence of new infections during PICU stay and (ii) the duration of PICU dependency. The latter will be reported as the crude number of PICU stay days and as the time to live discharge from PICU, to account for mortality as a competing risk.

Also, the proportion of patients from the intention-to-treat population who stayed 8 days or more in PICU will be reported. This is not only reflecting the proportion of prolonged critically ill patients but also examines effects of the randomized intervention beyond the time window of the randomized intervention in PICU.

The incidence of new infections for all patients in the three centers will be scored in consensus by the same two assessors (infectious disease specialists), who are blinded for treatment allocation. This assessment is based on an *a priori* drafted protocol[19], which makes use of prescribed antibiotics and clinical infection and inflammation data.

As the timing of PICU discharge to a regular ward may be affected by the availability of beds on regular wards, which could induce bias, we *a priori* decided to analyze 'time to discharge from PICU' as 'time to *ready for* discharge from PICU'. A patient is considered 'ready for discharge' as soon as all clinical conditions for PICU discharge have been fulfilled (no longer in need for, or at risk of, vital organ support).

Secondary safety endpoints

Secondary safety endpoints comprise: (i) death during PICU stay and during the time window of the randomized intervention (up to day 8), (ii) the proportion of patients with at least 1 episode of severe hypoglycemia (<40 mg/dl), (iii) in-hospital mortality and (iv) 90-day mortality. As a specific Serious Adverse Event (SAE), hypoglycemia resistant to bolus administration of glucose during the time window of the randomized intervention will be reported for both groups.

Secondary efficacy endpoints

1. *Time to (live) discharge from hospital and duration of hospital stay*, for both the index hospitalization and total hospitalization including stay in the referred hospital.
2. *Time to final (live) weaning* from mechanical respiratory support and duration of mechanical ventilation.
3. *Kidney failure*. Proportion of patients in need for renal replacement therapy (RRT) during PICU stay and the duration of RRT (for those patients requiring RRT). Also, the further analysis of the maximum and daily serum level of creatinine and urea during the intervention window and during PICU stay will be reported. Other plasma and urine markers of kidney function will be investigated.

4. *Need for pharmacological or mechanical hemodynamic support* during PICU stay and duration of such need. In addition, time to final (live) weaning from all pharmacological or mechanical hemodynamic support in PICU will be analyzed.
5. *Number of readmissions to the PICU*. The proportion of patients readmitted within 48 hours after discharge will be recorded. Also the proportion of patients readmitted to the PICU beyond 48 hours during their index hospital stay will be reported, as these patients will have been excluded from treatment allocation and will receive standard care.
6. *Liver dysfunction*. Markers of liver function will be measured and proportion of patients with abnormal tests will be compared.
7. *Inflammation*. Effect of the intervention on inflammation will be analyzed by comparing markers of inflammation. Both peak values and time courses will be analyzed.
8. *Duration of antibiotic treatment*. The duration of antibiotic treatment (whenever given) within the intervention window and during the PICU stay will be compared between the groups.
9. *Nutrition delivered during PICU stay*. The macronutrients and calories administered during the intervention window and thereafter during PICU stay will be compared between the treatment groups. Total amount of macronutrients, as well as the amounts administered parenterally and enterally, will be reported.
10. *Structural and functional differences in muscle tissue during PICU stay*. By ultrasonography, skeletal muscle thickness of the quadriceps, as a marker of muscle wasting, will be reported in a subset of patients. In addition, handgrip strength will be measured in a subset of patients older than 6 years.
11. *Intolerance to enteral feeding during PICU stay*. Markers of tolerance to enteral feeding will be determined in a subset of patients. Markers in blood, stool and buccal swab samples will be investigated.

Further pre-planned studies (execution depending on further funding), of which the detailed protocols and the methods for statistical analysis will be reported separately, are here listed below:

1. *Direct healthcare-related costs*. Total, direct healthcare costs during index PICU stay will be compared between the treatment groups[26].
2. *Mechanistic studies*. Explanations of any observed effects of delayed administration of PN as compared with standard of care will be assessed. These will comprise, among others, metabolic, endocrine, inflammation and (epi)genetic analyses, the investigation of the role of severity of illness, the use of indirect calorimetry, the type of blood glucose management, and post-randomization factors such as type and dose of administered macronutrients, and disease evolution[27].

3. *Long-term follow-up*. This will include developmental and neurocognitive assessments, metabolic, endocrine, inflammation and (epi)genetic studies, with a healthy matched control group investigated over time in parallel.

Data collection following recruitment

All systemically applied medications received by the patients during the stay in PICU are registered. Every day the quantities of kilocalories, carbohydrates, lipids and proteins delivered by either PN or EN are calculated and entered into the electronic Case Record Form (eCRF). The need for and the number of days of mechanical ventilatory support, of mechanical and pharmacological hemodynamic support, of renal replacement therapies, days on antibiotics and days requiring a central line are recorded. Blood, urine, buccal mucosa swabs and hair samples are taken upon PICU admission and during PICU stay. Such samples are appropriately handled (collected on ice when required) and immediately stored (at room temperature or at -20°C/-80°C as appropriate) for future measurements. Analyses on blood and urine for the primary clinical analyses include routine chemistry, hematology, and markers of inflammation. Further metabolic, endocrine, inflammatory and (epi)genetic measurements on stored samples in the context of mechanistic analyses are planned. For mechanistic and exploratory studies, ultrasound evaluation of the skeletal muscle, in combination with muscle strength measurements will be performed in a subset of patients[28-30]. Quality of life on admission and after 4 to 6 months is recorded through a validated, semi-structured questionnaire, filled out by the parents, which is repeated at 2 and 4 years after enrollment in the PEPaNIC trial.

Data handling and record keeping

Data are collected electronically in an anonymized eCRF, unambiguously linked to the source file. Data are manually transferred and checked for accuracy into the eCRF by the clinical research assistants' team on a daily basis. Extensive range and consistency checks are performed by the study monitor. All original records, such as consent forms, eCRFs and relevant correspondence, will be archived at the participating centers, according to the local regulations. Vital status at 90 days (and at later follow-up times) will be recorded for all patients, by the National Death Registries. When this information is not available, vital status will be checked through the hospital information system or the regional network of pediatricians and general practitioners. All data are stored anonymously. Investigators involved in the trial do not have direct access to the database. In addition, the study monitor has logged the use of the database. After the trial, the study monitor will store all data in a secured file that is only accessible by the study monitor himself.

Trial organization

The sponsor (KU Leuven) provides direct access to the eCRF, the source data and the study master file for monitoring, for review by the independent ethics committee and regulatory inspection. The sponsor established an independent data safety monitoring board (DSMB). The sponsor appointed one monitor. The monitor verifies that the trial is performed in accordance to the protocol as described in the European Medicine Agency's 'Note for guidance on good clinical practice CPMP/ICH/135/95.' as well as the *Declaration of Helsinki*. Monitoring is performed and reported according to the sponsor's standard operating procedures. The clinical research team guarantees a daily follow-up of patient screening and inclusion, availability of requested clinical data in the clinical patient files and protocol compliance. Non-compliance to the protocol and other questions or problems are reported to the study monitor and discussed with the principal investigators and trial steering committee. SAEs are reported to the study sponsor and, if needed, to the local ethics committee. The study monitor regularly provides the sponsor and the DSMB with reports on inclusions and SAEs. Regular meetings are organized with principal investigators and clinical research teams to discuss the daily progression of the PEPaNIC trial.

The protocol has been instructed in each hospital to all clinical medical and nursing staff through frequent teaching sessions and clinical feedback rounds. The protocol decision support is integrated into the PICU PDMS in Leuven and Rotterdam, facilitating the prescription of the exact amounts of PN and EN according to protocol and clinical evolution.

In order to achieve adequate participant enrollment to reach target sample size, regular meetings and site visits take place every 3 months together with the Rotterdam team and via teleconferences with the Edmonton team.

Regular data auditing is done by the administrative trial team, the DSMB and by the central independent audit procedure in place at the University Hospital of Leuven in compliance with the European Trials Directives.

Statistical analysis plan

One Consolidated Standards of Reporting Trials (CONSORT) diagram will be reported.

Protocol compliance will be documented by comparing the actual amounts of PN and EN during the intervention window and this will be reported as absolute numbers of calories and weight units.

For the primary and secondary endpoints taking place during PICU stay all data will be available. In case of request for discontinuation of the study intervention by patients, parents or legal guardians, this will be respected, but all data will be analyzed. In case of consent withdrawal, the parents will be asked whether the data can be used for analysis. In case this would not be

allowed, all data of that patient will be removed from the database, and this will be reported in the CONSORT diagram. At all time, the intention-to-treat principle will be respected and reported. No data imputation will be undertaken for any of the primary or secondary outcomes.

Variables will be summarized as frequencies and percentages, means and standard errors of the means, or medians and interquartile ranges, as appropriate.
Results will be analyzed with the use of chi-square testing, Student's *t*-test or non-parametric testing (Wilcoxon rank-sum test, Van der Waerden test or Median test), as appropriate. Kaplan-Meier plots will be used to document time-to-event effects, and the time-to-event effect size will be estimated with the use of Cox proportional-hazard analysis. All time-to-event analyses will also be performed on data censored at 90 days. As death is a competing risk for duration of care outcomes, non-survivors will be censored beyond the longest duration of such care required for survivors[19]. All outcomes will be analyzed both with and without adjustment for baseline risk factors, including the diagnostic and age groups, severity of illness, severity of nutritional risk and center. The latter is considered necessary to account for the differences among centers in nutrition given to the control group and the variation in blood glucose control targets. For these analyses, *P*-values will be considered significant when at or below 0.05 without correction for multiple comparisons. To assess whether any eventual impact of the intervention on the primary endpoints is affected by the baseline risk factor subgroups, interaction *P*-values will be calculated (logistic regression or Cox proportional hazard analysis) with a threshold for significance of interaction set at a *P*-value of <0.1. All analyses will be conducted on an intention-to-treat basis.

Sample size calculation and interim analyses
In the design phase of the PEPaNIC trial, and based on the previous adult EPaNIC trial results, the sample size (N = 1,440, 720 patients per arm) was determined in order to detect a reduction in the incidence of new infections during PICU stay from 20 to 15% (Absolute Risk Reduction 5%), with at least 80% 1-tailed power and at least 70% 2-tailed power and at an alpha error of 5%. With this sample size, the trial can also detect a major safety issue, such as a doubling of the PICU mortality rate from 4% (the baseline mortality in the Leuven center) to 8% with a statistical power of 89% in a 2-sided test with an alpha error of 5%. This sample size will also allow to detect a reduction in mean duration of stay in PICU of 1 day with at least 90% power (2-tailed) and 95% certainty.
Two *interim analyses* of the safety endpoints (except 90-day mortality) only were planned (after inclusion of 480 upon specific request of the DSMB, and after inclusion of 50% of the study population). It was *a priori* decided to determine the actual incidence of new infections during PICU stay in the 3 centers, as this was not known exactly for each of the participating centers prior to trial initiation. In order to allow statistical repowering and to judge the necessity of inclusion of more trial sites, the assessment of incidence of new infections during PICU stay

in the control group took place after inclusion of 750 patients. Based on this actual incidence of new PICU infections in the control group, the hypothesized absolute risk reduction of 5% and an alpha error rate of 5%, the sample size of 1,440 patients (720 patients in each arm) was found sufficiently large to yield a statistical power of 77% 2-sided and of 85% 1-sided. As these interim analyses did not assess any of the efficacy endpoints, no adjustments of the *P*-values are needed.

DISCUSSION

The clinical evidence for the administration of PN in critically ill children is missing[18]. Thousands of children are annually exposed to this non-evidence-based treatment, which is assumed to result in faster recovery (benefit). This large international RCT will help PICU physicians to obtain more insight on the possibility of the omission of PN during the first week of critical illness. A significant difference in the safety and/or efficacy endpoints will provide important evidence for optimizing clinical patient care. Also a neutral result will provide important insight, as this would mean that clinicians can safely withhold PN in all comparable patients during the first week of ICU stay, which would have an impact on healthcare spending in the PICU.

TRIAL STATUS

The study was initiated as planned on 18 June 2012. At the time of the safety interim analyses (after 480 and 750 study patients discharged from PICU), the DSMB advised the continuation of the trial and ratified the initial sample size of 1,440 patients as adequate to test the hypothesis. On 1 December 2014, 1,130 patients have been included into the PEPaNIC trial. Recruitment of the last patient is expected for October 2015.

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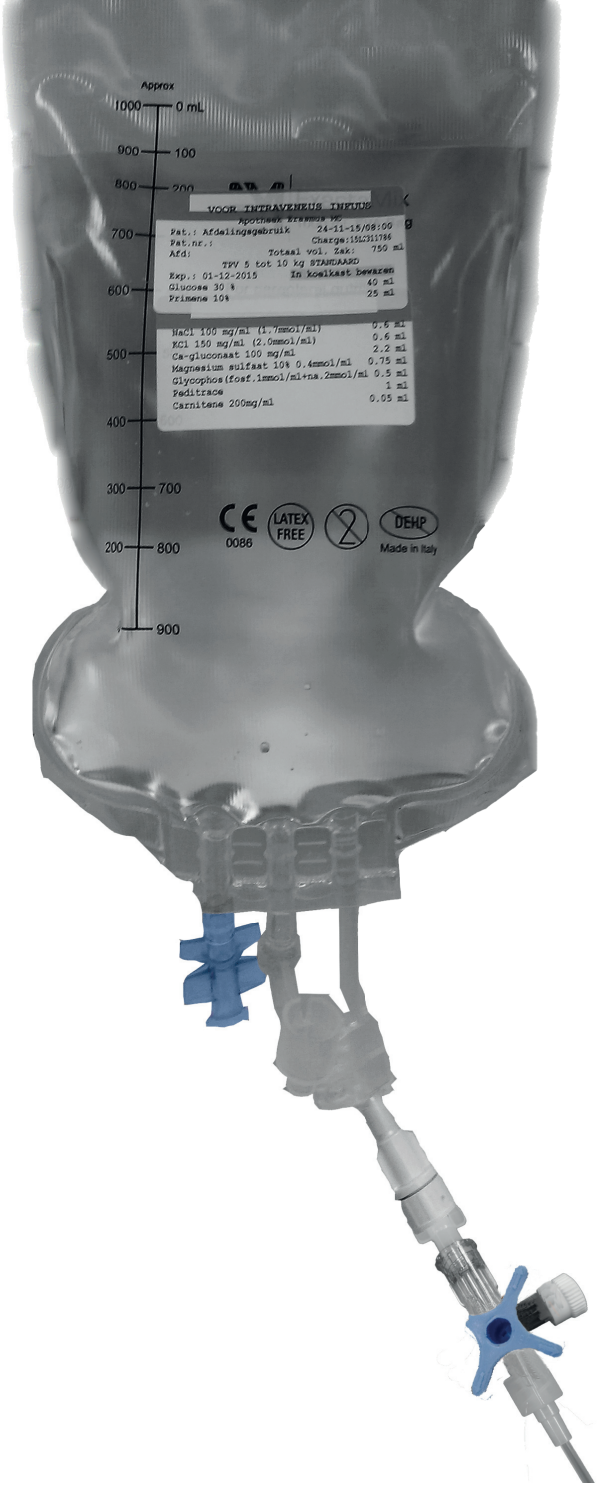
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Exp.: 01-12-2015 In koelkast bewaren
Glucose 30 % 40 ml
Primene 10% 25 ml
NaCl 100 mg/ml (1.7mmol/ml) 0.6 ml
KCl 150 mg/ml (2.0mmol/ml) 0.6 ml
Ca-gluconat 100 mg/ml 2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml 0.75 ml
Glycophos(fosf.1mmol/ml+na.2mmol/ml 0.5 ml
Peditrace 1 ml
Carnitene 200mg/ml 0.05 ml
CE 0086
LATEX FREE
DEHP
Made in Italy

CHAPTER 7

Early versus late parenteral nutrition in critically ill children

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ABSTRACT

Background

Recent trials have questioned the benefit of early parenteral nutrition in adults. The effect of early parenteral nutrition on clinical outcomes in critically ill children is unclear.

Methods

We conducted a multicenter, randomized, controlled trial involving 1440 critically ill children to investigate whether withholding parenteral nutrition for 1 week (i.e., providing late parenteral nutrition) in the pediatric intensive care unit (ICU) is clinically superior to providing early parenteral nutrition. Fluid loading was similar in the two groups. The two primary end points were new infection acquired during the ICU stay and the adjusted duration of ICU dependency, as assessed by the number of days in the ICU and as time to discharge alive from ICU. For the 723 patients receiving early parenteral nutrition, parenteral nutrition was initiated within 24 hours after ICU admission, whereas for the 717 patients receiving late parenteral nutrition, parenteral nutrition was not provided until the morning of the 8th day in the ICU. In both groups, enteral nutrition was attempted early and intravenous micronutrients were provided.

Results

Although mortality was similar in the two groups, the percentage of patients with a new infection was 10.7% in the group receiving late parenteral nutrition, as compared with 18.5% in the group receiving early parenteral nutrition (adjusted odds ratio, 0.48; 95% confidence interval [CI], 0.35 to 0.66). The mean (±SE) duration of ICU stay was 6.5±0.4 days in the group receiving late parenteral nutrition, as compared with 9.2±0.8 days in the group receiving early parenteral nutrition; there was also a higher likelihood of an earlier live discharge from the ICU at any time in the late-parenteral-nutrition group (adjusted hazard ratio, 1.23; 95% CI, 1.11 to 1.37). Late parenteral nutrition was associated with a shorter duration of mechanical ventilatory support than was early parenteral nutrition (P=0.001), as well as a smaller proportion of patients receiving renal-replacement therapy (P=0.04) and a shorter duration of hospital stay (P=0.001). Late parenteral nutrition was also associated with lower plasma levels of γ-glutamyltransferase and alkaline phosphatase than was early parenteral nutrition (P=0.001 and P=0.04, respectively), as well as higher levels of bilirubin (P=0.004) and C-reactive protein (P=0.006).

Conclusion

In critically ill children, withholding parenteral nutrition for 1 week in the ICU was clinically superior to providing early parenteral nutrition.

INTRODUCTION

Critically ill children cannot normally be fed by mouth, and as a result a pronounced macronutrient deficit often develops after a few days. This macronutrient deficit has been associated with infections, weakness, prolonged mechanical ventilation, and delayed recovery[1-3]. In order to prevent or limit the development of this macronutrient deficit, current guidelines, which are based largely on small studies with surrogate end points and on expert opinion, advise care providers to initiate nutritional support soon after a child's admission to the pediatric intensive care unit (ICU)[4-6]. The preferred route for the administration of nutritional support in the pediatric ICU is the nasogastric tube[7], but enteral nutrition is often delayed or interrupted[8,9]. Since nutrition should equal basic metabolic needs and in children should allow for growth, children require relatively more macronutrients than adults. Hence, the current standard of pediatric intensive care is to meet these requirements early[7,10]. When enteral nutrition fails, parenteral nutrition is advised[5,6], but current nutritional practices in pediatric ICUs vary owing to concerns about the overdosing of parenteral nutrition[8,11].

There is a dearth of adequately powered, randomized, controlled trials that address the effects of parenteral nutrition on clinical outcomes in critically ill children[12]. With respect to critically ill adults, recent large, randomized, controlled trials have questioned the benefit of early parenteral nutrition[13-15].

Therefore, in this international, multicenter, randomized, controlled trial, we investigated whether a strategy of withholding parenteral nutrition up to day 8 (late parenteral nutrition) in the pediatric ICU is clinically superior to the current practice of early parenteral nutrition.

METHODS

Design and oversight

The Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial was a multicenter, prospective, randomized, controlled, parallel-group superiority trial[16]. The institutional review board at each participating site approved the protocol (available with the full text of this article at NEJM.org)[16]. The first and last authors vouch for the fidelity of the study to the protocol and for the accuracy and completeness of the reported data.

From June 18, 2012, through July 27, 2015, all children (from term newborns to children 17 years of age) who were admitted to one of the participating pediatric ICUs were eligible for inclusion if a stay of 24 hours or more in the ICU was expected, if they had a score on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) of 2 or more (with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk)[17], and if none of the criteria for exclusion were met (See Table S1 in the Supplementary Appendix). Written informed consent was requested from parents or legal

guardians before elective admission to the pediatric ICU. For emergency admissions, consent was requested within 24 hours after the child's admission to the pediatric ICU.
At each center, consecutive, eligible patients were randomly assigned to one of the two treatment groups in a 1:1 ratio. Concealment of group assignment was ensured by use of a central computerized randomization system. The randomization was stratified in permuted blocks of 10 according to age (<1 year or ≥1 year) and diagnosis on admission (medical-neurologic, medical-other, surgical-cardiac, or surgical-other). The block size was unknown to the medical and research teams. Outcome assessors and investigators who were not directly involved in ICU patient care were unaware of the treatment assignments.
An independent data and safety monitoring board planned to perform two interim analyses of the safety end points, one after 480 patients had been enrolled and a second after 50% of all patients had been enrolled. The board advised that recruitment could be continued to completion.

Procedures
All participating centers used early parenteral nutrition as the standard of care. Among patients assigned to receive early parenteral nutrition, parenteral nutrition was initiated within 24 hours after admission to the pediatric ICU. The dose and composition varied according to local guidelines (Table S2 in the Supplementary Appendix)[16]; parenteral nutrition was used to supplement any enteral nutrition that was provided, with a goal toward meeting local macronutrient and caloric targets (Table S3 in the Supplementary Appendix).
Among patients assigned to the late-parenteral-nutrition group, parenteral nutrition was withheld up to the morning of day 8 in the pediatric ICU. A mixture of intravenous dextrose (5%) and saline was administered to the late-parenteral-nutrition group to match the amount of intravenous fluid administered in the early-parenteral-nutrition group[16]. When blood glucose levels spontaneously dropped below 50 mg per deciliter (2.8 mmol per liter) in the late-parenteral-nutrition group, the standard 5% dextrose solution was replaced with a 10% dextrose solution until blood glucose exceeded 80 mg per deciliter (4.4 mmol per liter) and remained stable[16].

In both study groups, enteral nutrition was initiated early and was increased in accordance with local guidelines. Both study groups also received intravenous micronutrients (trace elements, minerals, and vitamins) starting from day 2 and continuing until the enteral nutrition provided reached 80% of the caloric targets. Starting from the morning of day 8 in the pediatric ICU, supplementary parenteral nutrition was provided for patients in both groups who were not yet receiving 80% of the caloric target enterally. In Leuven, Belgium, an insulin infusion was started in both groups to target blood glucose levels of 50 to 80 mg per deciliter (2.8 to 4.4 mmol per liter) in infants (<1 year of age) and 70 mg per deciliter (3.9 mmol per liter) to 100 mg per deciliter (5.6 mmol per liter) in children (≥1 year of age). In Rotterdam, The Netherlands, all

patients received an insulin infusion designed to target blood glucose levels of 72 to 145 mg per deciliter (4.0 to 8.0 mmol per liter), with the exception of patients with traumatic brain injury, for whom the target was 108 mg per deciliter (6.0 mmol per liter) to 145 mg per deciliter. In Edmonton, Canada, patients received an insulin infusion when blood glucose levels exceeded 180 mg per deciliter (10.0 mmol per liter). No specific lower boundary was set.

Data collection

All patient data were stored in a logged database that was closed 90 days after enrollment of the last patient. Because the treatment assignment affected the blood glucose level during the first 24 hours after admission, as expected, the Pediatric Risk of Mortality score could not be used to account for the severity of illness at baseline, and the Pediatric Logistic Organ Dysfunction (PELOD) score (which ranges from 0 to 71, with higher scores indicating more severe illness) was used instead. The risk of malnutrition at admission was quantified with use of the STRONGkids score[17]. The determination of the presence of infection on admission to the pediatric ICU or infection acquired after randomization was based on the consensus opinion of two infectious disease specialists, who made their decision on the basis of guidelines in the study protocol (Table S4 in the Supplementary Appendix)[13]; both specialists were unaware of the study-group assignments. During the time patients were in the ICU, daily records were kept regarding all procedures, treatments, nutrition provided, and results of laboratory analyses. Information on vital status at 90 days was obtained from national death registries, hospital information systems, and regional networks of pediatricians and general practitioners.

End points

The two primary end points were new infection acquired during the ICU stay and the duration of ICU dependency, which was adjusted for five prespecified baseline risk factors (diagnostic group, age group, severity of illness, risk of malnutrition, and treatment center)[16]. Among patients with a new infection, the duration of antibiotic treatment was compared between the study groups. The duration of pediatric ICU dependency was quantified as the number of days in the pediatric ICU and as the time to discharge alive from the pediatric ICU, to account for death as a competing risk. Discharge from the pediatric ICU was defined a priori as the moment when a patient was ready for discharge from the pediatric ICU (i.e., no longer required or was no longer at risk for requiring vital organ support)[16].

Secondary safety end points were death during the first 7 days in pediatric ICU, during the total stay in the pediatric ICU, during the stay in the index hospital, and at 90 days after admission to the pediatric ICU and randomization; the number of patients with hypoglycemia (glucose level <40 mg per deciliter [2.2 mmol per liter]); and the number of readmissions to the pediatric ICU within 48 hours after discharge.

Secondary efficacy outcomes were the time to final (live) weaning from mechanical ventilatory support, the duration of pharmacologic or mechanical hemodynamic support, the proportion

of patients receiving renal-replacement therapy, markers of liver dysfunction and inflammation, and the time to (live) discharge from the hospital.

Statistical analysis

We calculated that with a sample of 1440 patients (approximately 720 patients per group), the study would have at least 70% power to detect a 5-percentage-point lower rate of new infection in the late-parenteral-nutrition group than in the early-parenteral-nutrition group, assuming an estimated rate of 20% in the early-parenteral-nutrition group, with the use of a two-tailed test at an alpha error rate of 5%. All analyses were conducted on an intention-to-treat basis.

Variables were summarized as frequencies and percentages, medians and interquartile ranges, or means and standard errors. Univariable comparisons were performed with use of the chi-square test (Fisher's exact test) and the Wilcoxon rank-sum test. Kaplan-Meier plots were used to illustrate time-to-event effects with univariable significance that were analyzed by means of log-rank testing. The time-to-event effect size was estimated with use of Cox proportional-hazards analysis, with data censored at 90 days. To take into account death as a competing risk for outcomes related to duration of care, data for non-survivors were censored at 91 days (i.e., beyond the date for censoring of data for all survivors). These time-to-event outcomes were assessed univariably and with adjustment for the baseline risk factors (diagnostic groups, age group, severity of illness, risk of malnutrition, and treatment center). The adjusted multivariable analysis of the effect of the intervention on dichotomized outcomes was performed with the use of logistic regression.

All P values were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. No corrections were made for multiple comparisons. Because efficacy end points were not assessed in the interim analyses, no adjustment of the P value threshold for significance was required.

To determine whether the effect of the intervention on the primary end points was influenced by baseline risk factors, P values for interaction were calculated with the use of multivariable logistic-regression analyses and multivariable Cox proportional-hazard analyses with a threshold for significance of interaction set at a $P<0.10$.

All analyses were performed with the use of JMP software, version 11.2.0 (SAS Institute).

RESULTS

Patients

A total of 1440 patients underwent randomization and were included in the analysis (Fig.1). At baseline, the characteristics of the patients were similar in the two groups (Table 1). Caloric and macronutrient intake per day up to day 16 in the pediatric ICU, which illustrates adherence

to the protocol, is shown in Figure 2, as well as in Figures S1 and S2 in the Supplementary Appendix.

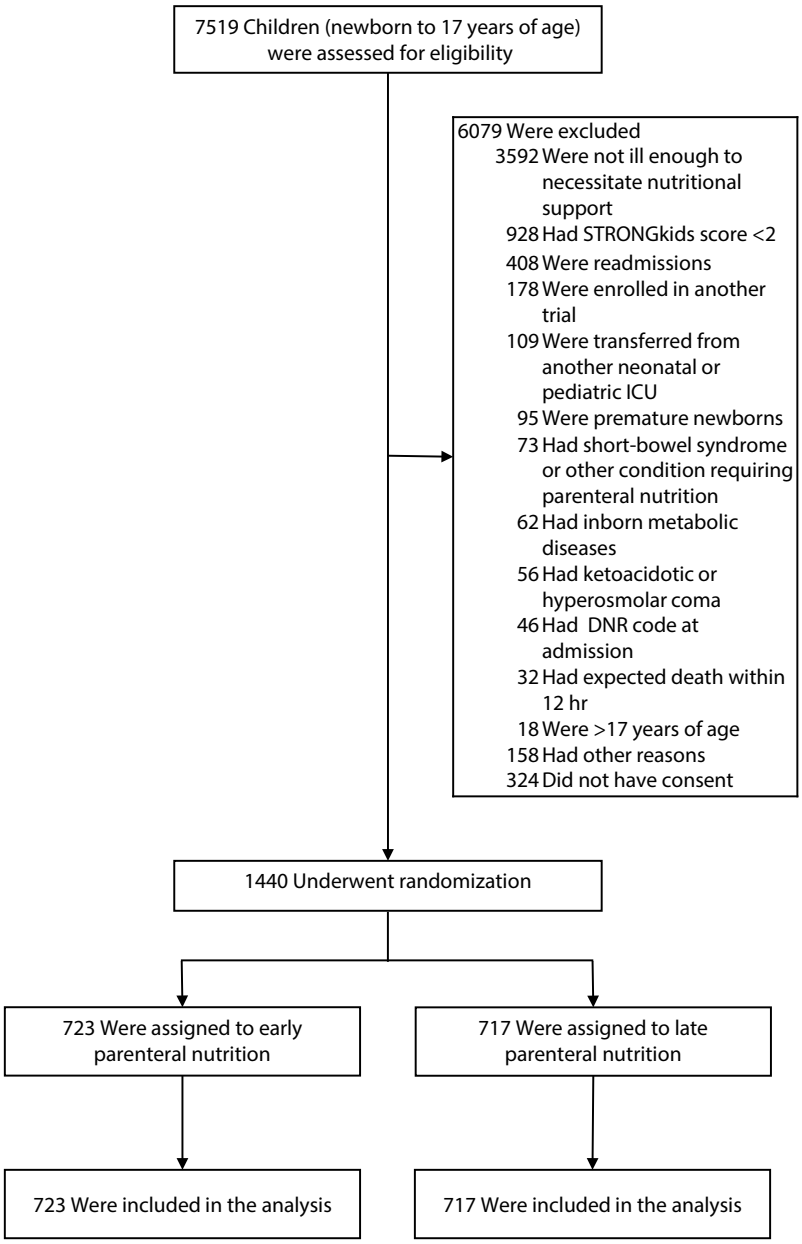

Figure 1. Screening and randomization
The scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk[17]. DNR denotes do not resuscitate, and ICU intensive care unit.

Table 1. *Baseline characteristics**

Characteristic	Early Parenteral Nutrition (N=723)	Late Parenteral Nutrition (N=717)
Median age (IQR) - yr	1.4 (0.3-6.1)	1.5 (0.2-7.2)
Age <1 yr – no. (%)	328 (45.4)	325 (45.3)
Male sex - no. (%)	415 (57.4)	415 (57.9)
Median weight (IQR) - kg	10.0 (4.8-20.0)	10.3 (4.5-21.5)
Median standard deviation score (IQR)†	-0.5 (-1.4-0.5)	-0.4 (-1.4-0.5)
Median height (IQR) - cm	80 (58-113)	80 (56-120)
Median standard deviation score (IQR)†	-0.3 (-1.5-0.8)	-0.3 (-1.4-0.8)
Median BMI (IQR)	15 (14-17)	15 (14-17)
Median standard deviation score (IQR)†	-0.5 (-1.5-0.5)	-0.5 (-1.6-0.6)
STRONGkids risk level - no. (%)‡		
Medium	644 (89.1)	644 (89.8)
High	79 (10.9)	73 (10.2)
Median PELOD score, first 24 hr in pediatric ICU (IQR)§	21 (11-31)	21 (11-31)
Emergency admission - no. (%)	383 (53.0)	400 (55.8)
Diagnostic group - no. (%)		
Surgical		
Abdominal	53 (7.3)	60 (8.4)
Burns	5 (0.7)	5 (0.7)
Cardiac	279 (38.6)	268 (37.3)
Neurosurgery – traumatic brain injury	63 (8.7)	53 (7.3)
Thoracic	34 (4.7)	27 (3.8)
Transplantation	7 (1.0)	17 (2.4)
Orthopedic surgery - trauma	28 (3.9)	26 (3.6)
Other	21 (2.9)	27 (3.8)
Medical		
Cardiac	30 (4.1)	31 (4.3)
Gastrointestinal-hepatic	2 (0.3)	4 (0.6)
Oncologic-hematologic	8 (1.1)	7 (1.0)
Neurologic	51 (7.1)	52 (7.3)
Renal	1 (0.1)	1 (0.1)
Respiratory	99 (13.7)	96 (13.4)
Other	42 (5.8)	43 (6.0)
Condition on admission - no. (%)		
Mechanical ventilation required	639 (88.4)	622 (86.8)
ECMO or other assist device required	19 (2.6)	25 (3.5)
Infection	287 (39.7)	271 (37.8)

* There were no significant differences in characteristics between treatment groups at baseline. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), ECMO extracorporeal membrane oxygenation, and ICU intensive care unit.

† Age- and gender-specific standard deviation scores were calculated with the use of reference data from the World Health Organization[18].

‡ 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.

§ Pediatric Logistic Organ Dysfunction (PELOD) scores range from 0 to 71, with higher scores indicating more severe illness.

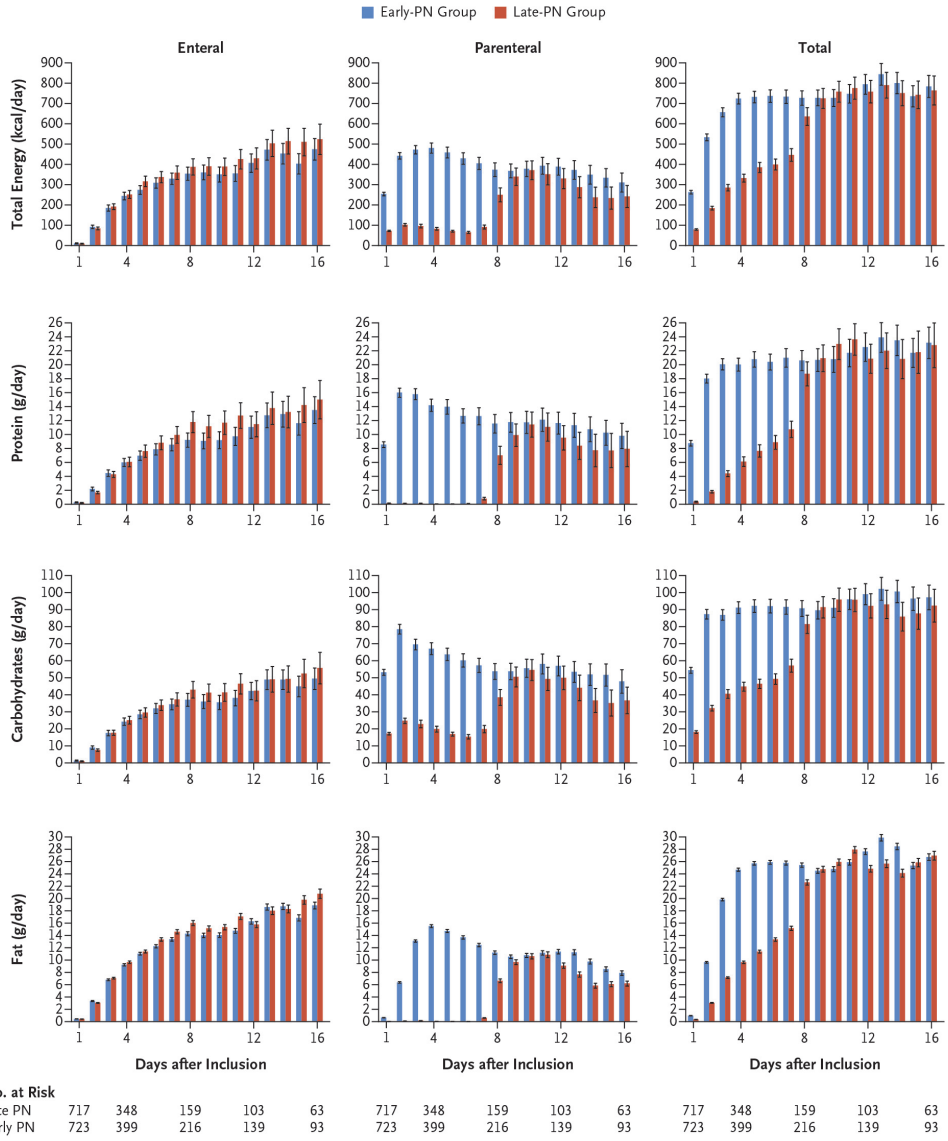

Figure 2. Daily caloric and macronutrient intake
The daily amount of energy (kilocalories per day) and substrate (grams per day) provided by the enteral route, the parenteral route, or both (total) are shown for participants' first 16 days in the pediatric intensive care unit (ICU). Bars indicate the mean, and whiskers indicate the standard error of the mean. PN denotes parenteral nutrition.

Primary outcomes

The rate of acquisition of a new infection was 7.8 percentage points lower (95% confidence Interval [CI], 4.2 to 11.4) among children receiving late parenteral nutrition than among children receiving early parenteral nutrition (adjusted odds ratio, 0.48; 95% CI, 0.35 to 0.66) (Table 2). This result was attributable primarily to the fact that fewer patients in the late-parenteral-nutrition group acquired an airway or blood stream infection (Table 2). Late parenteral nutrition was also associated with a shorter stay in the pediatric ICU by a mean of 2.7 days (95% CI, 1.3 to 4.3) (Table 2), with a higher likelihood of an earlier discharge alive from the pediatric ICU at any time (adjusted hazard ratio, 1.23; 95% CI, 1.11 to 1.37) (Table 2 and Fig. 3, and Fig. S3 and Table S5 in the Supplementary Appendix).

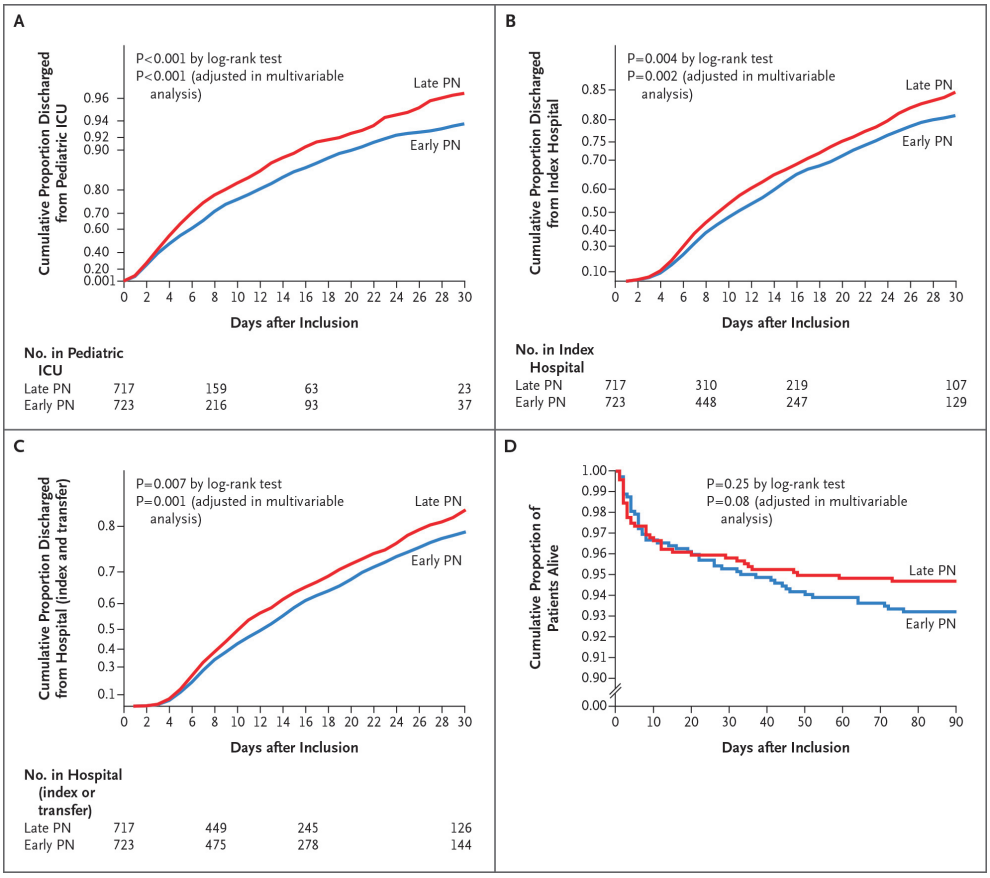

Figure 3. Kaplan-Meier plots for the time to discharge and for survival up to 90 days
Panels A, B, and C show the cumulative proportions of patients discharged from the pediatric ICU, the index hospital, and all hospitals (index and transfer hospitals), respectively. Data for surviving patients were censored at 90 days, whereas data for non-survivors were censored at the time of death. For the sake of clarity, only the first 30 days are shown. Panel D shows the survival rate up to 90 days.
P values were adjusted for diagnostic group, age group, severity of illness, risk of malnutrition, and treatment center.

There were no significant interactions (P<0.10) between treatment assignment and any of the prespecified risk factors (Table S6 in the Supplementary Appendix). However, for the interaction between treatment assignment and risk of malnutrition, the P value was 0.11, with a lower odds of infections with late parenteral nutrition than with early parenteral nutrition among children at high risk of malnutrition (odds ratio, 0.28; 95% CI, 0.10 to 0.70) than among those at medium risk of malnutrition (odds ratio, 0.54; 95% CI, 0.38 to 0.76). There was also a higher likelihood of an earlier discharge alive from pediatric ICU with late parenteral nutrition among the children at high risk of malnutrition (hazard ratio, 1.61; 95% CI, 1.12 to 2.31) than among the children at medium risk of malnutrition (hazard ratio, 1.19; 95% CI, 1.06 to 1.33) (P=0.19 for the interaction).
Similarly, there was no significant interaction between treatment assignment and age group. A post hoc subgroup analysis of the 209 term neonates who were less than 4 weeks of age at the time of study inclusion revealed that the benefits of late parenteral nutrition were similar to or greater than those for children 4 weeks of age or older (odds ratio for new infections, 0.47 [95% CI, 0.22 to 0.95] among neonates and 0.48 [95% CI, 0.33 to 0.69] among older children; P=0.99 for the interaction; hazard ratio for the likelihood of earlier live discharge from the pediatric ICU, 1.73 [95% CI, 1.27 to 2.35] among neonates vs. 1.17 [95% CI 1.04-1.31] among older children; P=0.03 for the interaction).

In addition, the effect of late parenteral nutrition on primary outcomes was unaltered after adjustment for the amount of enteral nutrition provided (Table S7 in the Supplementary Appendix).

Secondary outcomes

Mortality was similar in the two groups at all prespecified time points (Table 2 and Fig. 3). The percentage of patients with an episode of hypoglycemia (glucose level <40 mg per deciliter) was higher in the group receiving late parenteral nutrition than in the group receiving early parenteral nutrition (Table 2). Adjustment for hypoglycemia did not alter the effect size of late parenteral nutrition on the primary outcomes (odds ratio for new infection, 0.45 [95% CI, 0.32 to 0.62] and adjusted hazard ratio for the likelihood of an earlier live discharge from the pediatric ICU, 1.26 [95% CI, 1.13 to 1.41]) (Table S7 in the Supplementary Appendix). Rates of readmission to the pediatric ICU within 48 hours after discharge and of the occurrence of serious adverse events were similar in the two study groups (Table 2).

Table 2. *Outcomes**

Outcome	Early Parenteral Nutrition (N=723)	Late Parenteral Nutrition (N=717)	P Value	Adjusted Odds Ratio or Hazard Ratio (95% CI)†	P Value
Primary					
New infections – no. (%)	134 (18.5)	77 (10.7)	< 0.001	0.48 (0.35-0.66)‡	< 0.001
Airway	59 (8.2)	30 (4.2)	0.002		
Bloodstream	23 (3.2)	10 (1.4)	0.03		
Urinary tract	7 (1.0)	2 (0.3)	0.17		
Central nervous system	3 (0.4)	2 (0.3)	1.00		
Soft tissue	7 (1.0)	4 (0.6)	0.54		
Other focus	5 (0.7)	8 (1.1)	0.42		
No focus identified	30 (4.1)	21 (2.9)	0.25		
Total duration of antibiotic treatment for patients with new infection – days	21.3±3.1	17.4±1.9	0.77		
Total duration of stay in pediatric ICU – days§	9.2±0.8	6.5±0.4	0.002	1.23 (1.11-1.37)	< 0.001
Patients requiring ≥8 days in pediatric ICU - no. (%)	216 (29.9)	159 (22.2)	< 0.001		
Secondary					
Safety					
Death - no. (%)					
Within 8 days of admission to pediatric ICU	21 (2.9)	19 (2.6)	0.87	0.73 (0.34-1.51)‡	0.39
During stay in pediatric ICU	36 (5.0)	32 (4.5)	0.70	0.73 (0.42-1.28)‡	0.27
During hospital stay	44 (6.1)	37 (5.2)	0.49	0.72 (0.43-1.19)‡	0.20
Within 90 days after enrollment	49 (6.8)	38 (5.3)	0.26	0.64 (0.39-1.05)‡	0.08
Hypoglycemia: glucose < 40 mg/dl during first 7 days in pediatric ICU - no. (%)	35 (4.8)	65 (9.1)	0.001		
Hypoglycemia refractory to treatment for ≥ 2 hr - no. (%)	0	1 (0.1)	1.00		
Readmission to pediatric ICU within 48 hr after discharge - no. (%)	9 (1.2)	13 (1.8)	0.39		
Efficacy					
Duration of mechanical ventilatory support - days	6.4±0.7	4.4±0.3	0.01	1.19 (1.07-1.32)	0.001
Duration of hemodynamic support - days	3.0±0.3	2.4±0.2	0.35		

Kidney Failure with renal-replacement therapy - no. (%)	26 (3.6)	18 (2.5)	0.28	0.49 (0.24- 0.96)‡	0.03
Liver dysfunction during first 7 days in pediatric ICU¶					
Highest plasma level of total bilirubin - mg/dl	1.5±0.1	1.7±0.1	0.003		
Highest plasma level of alkaline phosphatase- IU/liter	171±3	171±5	0.04		
Highest plasma level of γ-glutamyltransferase - IU/liter	58±6	45±3	0.001		
Highest plasma level of alanine aminotransferase - IU/liter	72±8	113±20	0.64		
Highest plasma level of aspartate aminotransferase - IU/liter	179±26	262±48	0.76		
Highest plasma level of C-reactive protein during first 7 days in pediatric ICU, as measure of inflammation – mg/liter	79±4	90±4	0.007		
Duration of hospital stay - days					
Index hospital	21.3±1.3	17.2±1.0	0.005	1.19 (1.07-1.33)	0.001
Index and transfer hospital	22.6±1.3	18.6±1.0	0.01	1.21 (1.08-1.34)	< 0.001

* Plus–minus values are means ±SE. No censoring was applied for the unadjusted comparisons of outcomes regarding duration of care. Data for all adjusted outcomes for duration of care were censored at 90 days, and data for nonsurvivors were censored at 91 days. To convert the values for total bilirubin to micromoles per liter, multiply by 17.1.

† Odds ratios and hazard ratios were adjusted for the following risk factors: treatment center, age group, diagnosis group, PELOD score within the first 24 hours after admission, and STRONGkids category.

‡ These values are adjusted odds ratios. All other values in this column are hazard ratios.

§ The duration of stay in the pediatric ICU was defined as the time from admission until the patient was ready for discharge. A patient was considered to be ready for discharge as soon as all clinical conditions for discharge were fulfilled (i.e., the patient no longer required or was no longer at risk for requiring vital-organ support).

¶ Total bilirubin levels were available for 1256 patients, alkaline phosphatase levels for 1234 patients, γ-glutamyltransferase levels for 1222 patients, alanine aminotransferase levels for 1265 patients, aspartate aminotransferase levels for 1264 patients, and C-reactive protein levels for 1301 patients.

The duration of mechanical ventilatory support was shorter and the likelihood of being weaned alive earlier from mechanical ventilation was higher among patients receiving late parenteral nutrition than among those receiving early parenteral nutrition (Table 2, and Table S5 in the Supplementary Appendix), whereas there was no significant between-group difference in the duration of hemodynamic support. After adjustment for prespecified risk factors, late parenteral nutrition was also associated with a lower need for renal-replacement therapy (Table 2, and Table S5 in the Supplementary Appendix). The peak plasma total bilirubin levels were higher in the late-parenteral-nutrition group than in the early-parenteral-nutrition group during the first 7 days in the pediatric ICU (Table 2) and during the duration of the pediatric ICU stay (Table S8 in the Supplementary Appendix), whereas the peak plasma γ-glutamyltransferase and alkaline phosphatase levels were higher with early parenteral nutrition (Table 2). There were no significant between-group differences in the results of other liver tests (Table 2). Although there were fewer new infections with late parenteral nutrition than with early parenteral nutrition, the peak plasma levels of C-reactive protein were higher with late parenteral nutrition during the first 7 days in the pediatric ICU (Table 2).

The mean duration of stay in the index hospital was 4.1 days shorter (95% CI, 1.4 to 6.6), and the likelihood of an earlier discharge alive from the hospital was higher (adjusted hazard ratio, 1.19; 95% CI, 1.07 to 1.33) in the late-parenteral-nutrition group than in the early-parenteral-nutrition group (Table 2 and Fig. 3, and Table S5 and Fig. S3 in the Supplementary Appendix). This effect of late parenteral nutrition remained significant when any eventual additional stay in a transfer hospital was taken into account (Table 2 and Fig. 3, and Table S5 and Fig. S3 in the Supplementary Appendix).
Adjustments for hypoglycemia or for the amount of enterally administered nutrition did not alter the effect of late parenteral nutrition on any of the secondary outcomes (Table S7 in the Supplementary Appendix).

DISCUSSION

The results of our trial showed that withholding parenteral nutrition for 1 week in the pediatric ICU was clinically superior to providing early parenteral nutrition; late parenteral nutrition resulted in fewer new infections, a shorter duration of dependency on intensive care, and a shorter hospital stay.

The clinical superiority of late parenteral nutrition was shown irrespective of diagnosis, severity of illness, risk of malnutrition, or age of the child. The observation that critically ill children at the highest risk of malnutrition benefited the most from the withholding of early parenteral nutrition was unexpected. However, this finding was reinforced by the apparently greater

benefit of this strategy for critically ill term neonates than for older children. Indeed, immediate initiation of nutrition is currently advised for neonates because they are considered to have lower metabolic reserve[7].

The benefits of late parenteral nutrition were evident irrespective of the variability in nutritional care and blood-glucose management across participating centers. Late parenteral nutrition resulted in more instances of hypoglycemia than were seen with early parenteral nutrition, but this higher rate did not affect the overall effect of the intervention on the outcome. In addition, in earlier studies, such brief episodes of hypoglycemia in critically ill children or in premature or mature newborns were not shown to have a negative effect on long-term neurocognitive outcomes[19-21].

The finding that the rate of new infections was substantially lower with late parenteral nutrition than with early parenteral nutrition but that the rate of inflammation (as indicated by elevated plasma levels of C-reactive protein) was higher illustrates the limitation of surrogate end points in clinical trials[22-26]. As was seen in a previous study involving adults, plasma levels of γ-glutamyltransferase and alkaline phosphatase were lower in children who received late parenteral nutrition than in those who received early parenteral nutrition, a finding that was suggestive of less cholestasis in children in the late-parenteral-nutrition group[13,27,28]. However, late parenteral nutrition resulted in higher plasma bilirubin levels than did early parenteral nutrition in these critically ill children, as it has in adult patients, which provides further support for the concept that increases in plasma bilirubin levels in response to critical illness may be partially adaptive[29].

The underlying mechanisms of the clinical benefits observed when there is a substantial macronutrient deficit early in critical illness in children remain speculative. Preservation of autophagy may play a role, given its importance for innate immunity and for quality control in cells with a long half-life, such as myofibers[30-32].

A limitation of this study is that the patients, their parents, and the staff providing intensive care were aware of the treatment assignments. However, outcome assessors and caregivers on the pediatric wards were unaware of the treatment assignments. The strength of the study is its external validity, given the multicenter study design.

In conclusion, in critically ill children, withholding parenteral nutrition for 1 week while administering micronutrients intravenously was clinically superior to providing early parenteral nutrition to supplement insufficient enteral nutrition.

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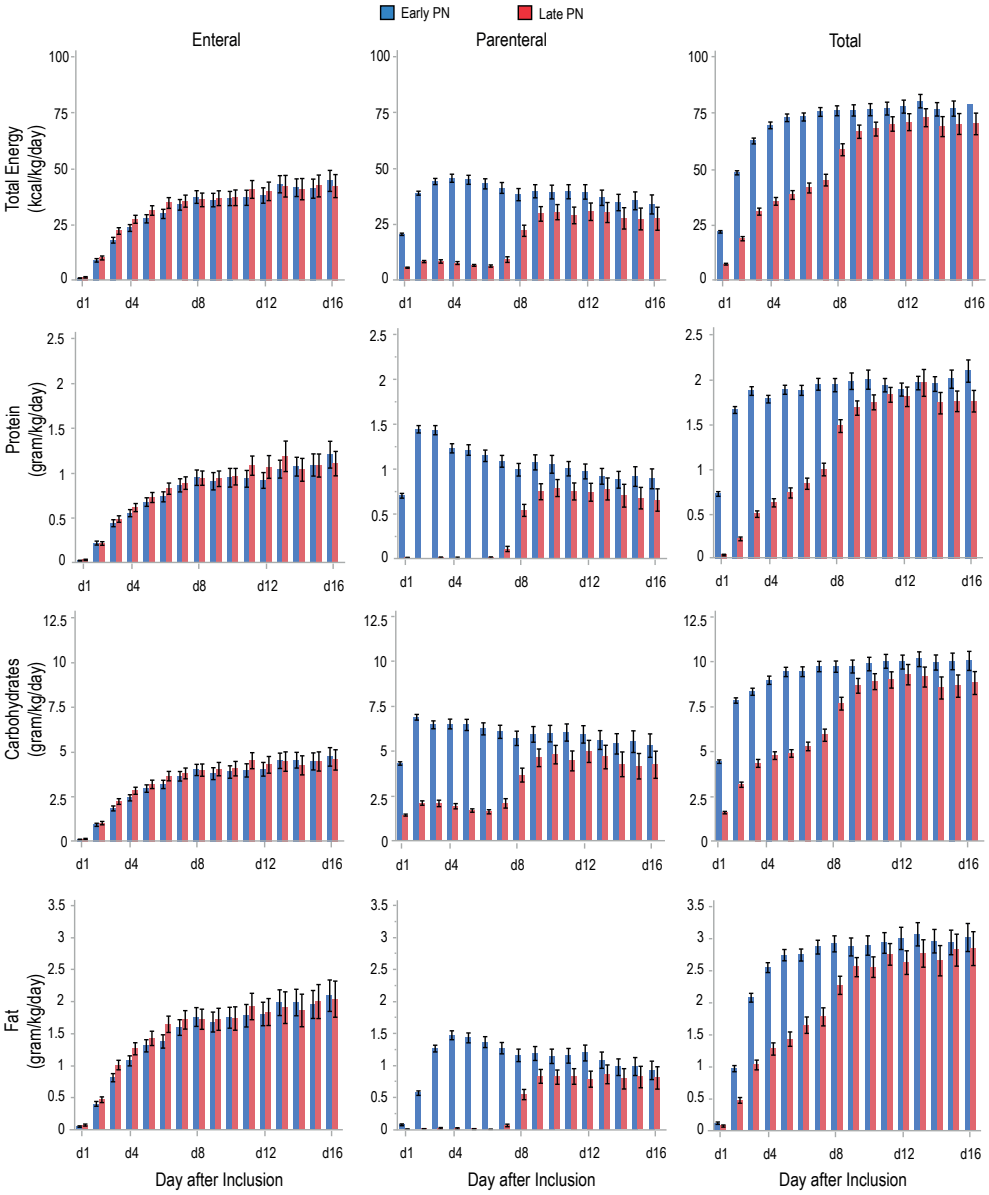
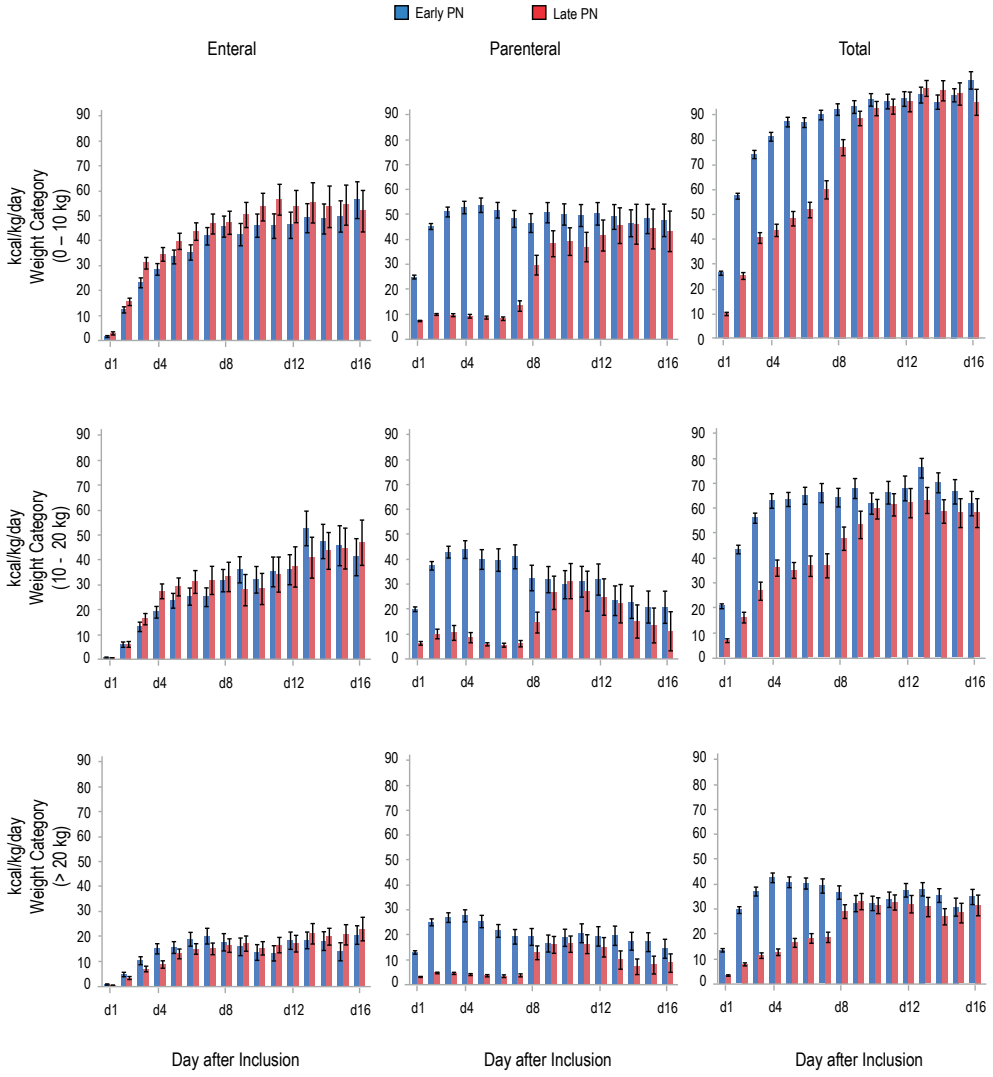
SUPPLEMENTARY FIGURES

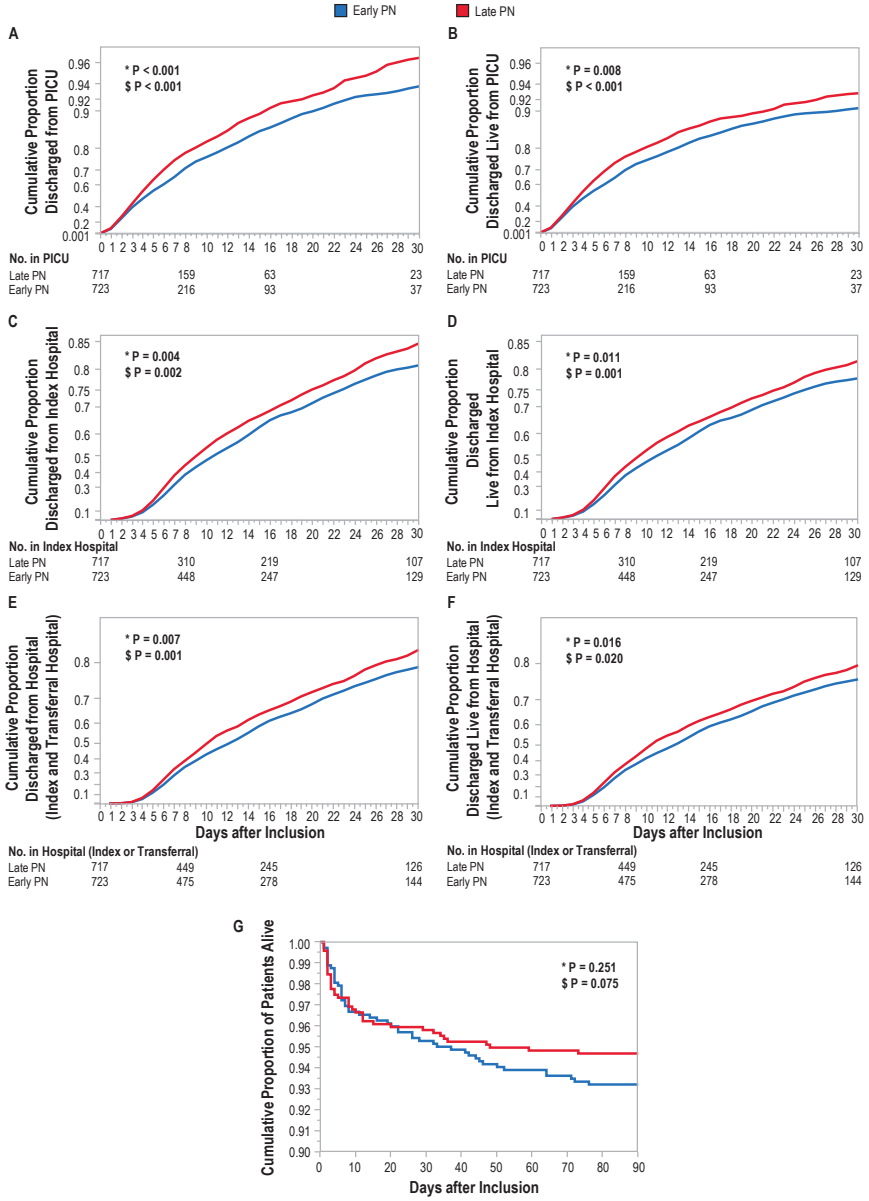


Supplementary Figure 1. Caloric and macronutrient intake per kg
Daily amount of energy in kcal/kg/day, and the daily amounts of substrates in g/kg/day, for the first 16 days of pediatric intensive care unit (PICU) stay provided by the enteral route, the parenteral route or both (total). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the late parenteral nutrition (PN) group; the blue bars represent the early PN group.



No. in PICU															
Late PN	717	348	159	103	63	717	348	159	103	63	717	348	159	103	63
Early PN	723	399	216	139	93	723	399	216	139	93	723	399	216	139	93

Supplementary Figure 2. Caloric intake per kg for weight categories
Daily amount of energy in kcal/kg/day, for three weight categories (<10 kg, 10-20 kg and >20 kg), for the first 16 days of pediatric intensive care unit (PICU) stay provided by the enteral route, the parenteral route or both (total). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the late parenteral nutrition (PN) group; the blue bars represent the early PN group.



Supplementary Figure 3. Kaplan-Meier plots for the time to (live) discharge from the PICU and the hospital and for survival up to 90 days

Panels A to F represent the cumulative proportions of patients discharged from the PICU (A), discharged *live* from the PICU (B), discharged from the hospital [index (C) and total (E)] and discharged *live* from the hospital [index (D) and total (F)]. For the analyses of the time to discharge, data for all patients were censored at 90 days, while non-survivors were censored at time of death. For the analyses of the time to *live* discharge, data were censored at 90 days with non-survivors censored at 91 days to account for death as a competing risk. For sake of clarity, only the first 30 days are shown in panels A-F. Panel G illustrates survival up to 90 days. The red lines represent the late PN group; the blue lines represent the early PN group.

*univariable log-rank P-value; $ P-value adjusted in multivariable analysis.

SUPPLEMENTARY TABLES

Supplementary Table 1. *Exclusion criteria for study participation*

Not critically ill enough to necessitate nutritional support
STRONGkids score lower than 2 on PICU admission[1]
Non-pediatric patients (aged 17 or older)
Premature newborns (<37 weeks gestational age upon admission in the PICU)
'Do not resuscitate' code at the time of PICU admission
Expected death within 12 hours
Readmission to PICU after already having been randomized
Enrollment in another intervention trial
Transfer from another PICU or neonatal ICU after a stay of more than 7 days
Ketoacidotic or hyperosmolar coma
Inborn metabolic diseases requiring specific diet
Short bowel syndrome or other conditions requiring PN for more than 7 days prior to PICU admission

PICU=Pediatric Intensive Care Unit, PN=Parenteral Nutrition

Supplementary Table 2. *Local protocols for initiation of PN in early PN group, in all participating centers EN was attempted as soon as possible*

Center	On admission	Day 2	Day 3	Subsequent Stay
Leuven, Belgium	Mixture of glucose 30% and Vaminolact® (Fresenius)	Addition of lipids (SMOFlipid® Fresenius)	All replaced by mixture of glucose 50% and SMOFlipid® with Vaminolact® or Vamin 18®.	Glucose 50% and SMOFlipid® with Vaminolact® or Vamin 18®
Rotterdam, The Netherlands	Continuous glucose infusion with glucose intake 4-6 mg/kg/min (< 30 kg) or 2-4 mg/kg/min (> 30 kg)	Pharmacy-made PN: mixture of glucose, Primene® (Baxter) and Intralipid® (Fresenius, 50% of final dose). Children >30 kg Olimel® (Baxter, N5 or N4 depending on central or peripheral line)	Increase of lipids to 100%	Pharmacy-made PN: mixture of glucose, Primene® (Baxter) and Intralipid® (Baxter, 100% of final dose). Children >30 kg Olimel® (Baxter, N5 or N4 depending on central or peripheral line)
Edmonton, Canada	Continuous glucose infusion with glucose intake 3-4 mg/kg/min	Addition of 20% IV lipids (50% of final dose)	Increase of lipids to 100% Mixture amino acids and concentrated glucose	Mixture amino acids, concentrated glucose and 20% IV lipids

EN=Enteral Nutrition, IV=Intravenous, PN=Parenteral Nutrition

Supplementary Table 3. *Macronutrient and caloric targets per center*

Center	First day	Subsequent stay
Leuven, Belgium	First 10 kg: 100 kcal/kg 10-20 kg: + 50 kcal/kg >20 kg: + 20 kcal/kg (adjusted downward when fluid restriction required)	
Rotterdam, The Netherlands	EN: basal metabolic rate by Schofield-weight[2] PN: ESPGHAN[3]	EN: Recommended Dietary Allowances[4] PN: ESPGHAN[3]
Edmonton, Canada	Resting energy expenditure by indirect calorimetry If indirect calorimetry impossible: 65% of basal metabolic rate (FAO-WHO[5])	Adjusted daily by the dietitian based on clinical information

EN=Enteral Nutrition, PN=Parenteral Nutrition

Supplementary Table 4. *Protocol for scoring of infections*

1. **Data export**
   All patients receiving antimicrobial agents were identified by the data manager, who provided an export of all patient numbers with all the information on antimicrobial agents given as well as the duration of such treatment.

2. **Identification of patients with infections**
   The infectious disease specialists, who were blinded for treatment allocation, selected all patients receiving antimicrobial agents for more than 48h, after excluding all patients who received prophylaxis. Each patient who fulfilled the criteria for infection, as well as the type of infection, was identified as such based on thorough review of the medical record[6]. Patients for whom antimicrobials were initiated prior to PICU admission or within the first 48 hours of admission while the criteria for infection were fulfilled, were labeled as "*having an infection upon admission*". When antimicrobial agents were initiated after randomization and beyond the first 48 hours in the PICU, and were given for more than 48 hours while the criteria for infection were fulfilled, the patient was labeled as "*having a new infection*"[6].

Supplementary Table 5. *Logistic regression and Cox proportional hazards analyses*

	OR or HR unadjusted (95% CI) Late PN vs. Early PN	P-value unadjusted	OR or HR adjusted* (95% CI) Late PN vs. Early PN	P-value adjusted
Primary Outcomes				
Odds for New Infection	0.53 (0.39-0.71)	< 0.001	0.48 (0.35-0.66)	< 0.001
Likelihood of Earlier Live Discharge from PICU	1.14 (1.02-1.27)	0.01	1.23 (1.11-1.37)	< 0.001
Safety Outcomes				
Odds for Death				
Within 8 days in PICU	0.91 (0.48-1.71)	0.76	0.73 (0.34-1.51)	0.39
During PICU Stay	0.89 (0.55-1.45)	0.64	0.73 (0.42-1.28)	0.27
During Hospital Stay	0.84 (0.53-1.32)	0.44	0.72 (0.43-1.19)	0.20
Within 90 days after enrollment	0.77 (0.49-1.19)	0.23	0.64 (0.39-1.05)	0.07
Secondary Efficacy Outcomes				
Likelihood of Earlier Live Weaning from Mechanical Ventilatory Support	1.11 (1.00-1.24)	0.04	1.19 (1.07-1.32)	0.001
Odds for Renal Replacement Therapy	0.69 (0.37-1.26)	0.23	0.49 (0.24- 0.96)	0.03
Likelihood of Earlier Live Discharge from Index Hospital	1.14 (1.03-1.27)	0.01	1.19 (1.07-1.33)	0.001
Likelihood of Earlier Live Discharge from Hospital (Index and Transferral Hospital)	1.14 (1.02-1.27)	0.02	1.21 (1.08-1.34)	< 0.001

All duration of care outcomes were censored at 90 days with non-survivors censored at 91 days. OR=Odds Ratio, HR=Hazard Ratio, PN=Parenteral Nutrition, 95% CI= 95% confidence intervals, PICU=Pediatric Intensive Care Unit

* Adjusted for the following risk factors: center, age group, diagnosis group, PELOD score (first 24h)[7] and STRONGkids category[1]

Supplementary Table 6. *P-values for interaction between randomized treatment allocation and the predefined baseline risk factors on the primary outcomes*

	P-value
Patients with New Infections[1]	
PELOD score first 24h in PICU	0.80
Age group	0.55
Diagnostic group	0.25
STRONGkids score[1]	0.11
Center	0.72
Time to live discharge from the PICU[2]	
PELOD score first 24h in PICU	0.80
Age group	0.65
Diagnostic group	0.73
STRONGkids score[1]	0.19
Center	0.56

PELOD=PEdiatric Logistic Organ Dysfunction[7], PICU=Pediatric Intensive Care Unit
[1] Multivariable Logistic Regression Analysis censored at 90 days with non-survivors censored at 91 days
[2] Multivariable Cox Proportional Hazard Analysis censored at 90 days with non-survivors censored at 91 days

Supplementary Table 7. *Adjusted Odds Ratios and Hazard Ratios further corrected for hypoglycemia (plasma concentration glucose < 40 mg/dL) and for the average amount of enteral feeding (kcal/kg/day) during randomisation window*

	OR or HR adjusted* (95% CI) Late PN vs. Early PN (adjusted for hypoglycemia)	P-value	OR or HR adjusted* (95% CI) Late PN vs. Early PN (adjusted for enteral kcal/kg/d)	P-value
Primary Outcomes				
Patients with New Infections	0.45 (0.32-0.62)	< 0.001	0.47 (0.34-0.65)	< 0.001
Likelihood Earlier Live PICU Discharge	1.26 (1.13-1.41)	< 0.001	1.24 (1.12-1.38)	< 0.001
Secondary Efficacy Outcomes				
Likelihood Earlier Live Weaning from Mechanical Ventilatory Support	1.21 (1.09-1.35)	< 0.001	1.19 (1.07-1.32)	0.001
Renal-Replacement Therapy	0.49 (0.24-0.97)	0.03	0.52 (0.25-1.03)	0.06
Likelihood Earlier Live Hospital Discharge	1.22 (1.09-1.36)	< 0.001	1.19 (1.07-1.33)	0.001

All duration of care outcomes were censored at 90 days with non-survivors censored at 91 days. OR=Odds Ratio, HR=Hazard Ratio, PN=Parenteral Nutrition, 95% CI= 95% Confidence Intervals, PICU=Pediatric Intensive Care Unit
* Adjusted for the following risk factors: center, age group, diagnosis group, PELOD score first 24h[7], STRONGkids category[1] and hypoglycemia (plasma concentration glucose < 40 mg/dL) or amount of enterally administered kcal per kg per day.
In both analyses, experiencing hypoglycemia and receiving a higher amount of enterally administered kcal per kg per day were independent risk factors for infections and for a delayed live discharge from PICU (all P-values ≤0.004).

Supplementary Table 8. *Highest plasma concentrations during PICU stay for markers of liver dysfunction and inflammation. Mean plasma glucose concentration during PICU stay*

	Early PN	Late PN	P-value
Highest plasma concentration during PICU stay	N=723	N=717	
Liver dysfunction - mean (SEM)			
Highest plasma bilirubin – mg/dL (N = 1261)	1.6 (0.1)	1.9 (0.2)	0.006
Highest plasma Alkaline Phosphatase (N=1236)	195 (5)	182 (6)	0.001
Highest plasma GGT – IU/L (N = 1225)	85 (7)	64 (5)	0.003
Highest plasma ALT – IU/L (N = 1270)	85 (9)	118 (20)	0.33
Highest plasma AST – IU/L (N = 1268)	202 (28)	271 (48)	0.82
Inflammation - mean (SEM)			
Highest plasma CRP – mg/L (N = 1307)	87 (4)	93 (4)	0.09
Mean plasma glucose – mg/dL (N= 1391)	117 (1.5)	100 (1.2)	< 0.001

PN=Parenteral Nutrition, PICU=Pediatric Intensive Care Unit, SEM= Standard Error of the Mean, GGT= Gamma-Glutamyltransferase, ALT= Alanine Aminotransferase, AST= Aspartate Aminotransferase, CRP= C-reactive protein

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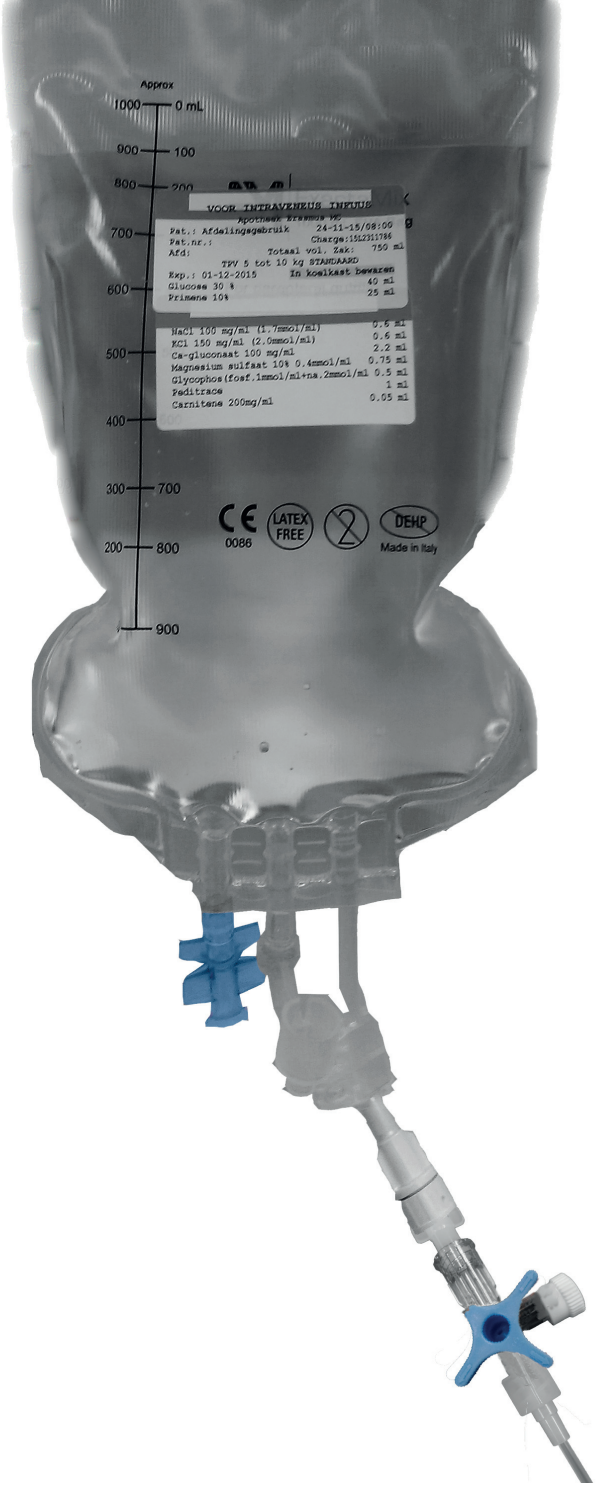
PART V

DISCUSSION AND SUMMARY


Approx
1000 0 mL
900 100
800 200
700
600
500
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300 700
200 800
900
VOOR INTRAVENEUS INFUUS
Apotheek Bremen BV
Pat.: Afdelingsgebruik 24-11-15/08:00
Pat.nr.: Charge:15L2315786
Afd: Totaal vol. Zak: 750 ml
TPV 5 tot 10 kg STANDAARD
Exp.: 01-12-2015 In koelkast bewaren
Glucose 30 % 40 ml
Primene 10% 25 ml
NaCl 100 mg/ml (1.7mmol/ml) 0.6 ml
KCl 150 mg/ml (2.0mmol/ml) 0.6 ml
Ca-gluconaat 100 mg/ml 2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml 0.75 ml
Glycophos(fosf.1mmol/ml+na.2mmol/ml 0.5 ml
Peditrace 1 ml
Carnitene 200mg/ml 0.05 ml
CE 0086
LATEX FREE
DEHP
Made in Italy

CHAPTER 8

General discussion

INTRODUCTION

Understanding the stress response to critical illness is essential for nutritional recommendations in critically ill children. Nutrient restriction early during critical illness might be beneficial for short and long-term outcomes, while inclining caloric and protein requirements allow for a more aggressive feeding approach during the stable and recovery phase. In order to provide the optimal amount of nutrition and prevent the detrimental effects associated with malnutrition, both under- and overfeeding should be identified, but current definitions fail to do this accurately. Although the enteral route is preferred because of its association with improved outcome, (supplemental) parenteral nutrition (PN) is often administered to improve intake adequacy despite potential disadvantages.

This thesis provided insight in the practice and evidence of the timing and goals of PN and thus the development and the subsequent outcome of underfeeding or overfeeding in critically ill children.

CURRENT NUTRITIONAL PRACTICES

Paediatric guidelines

Globally, guidelines for nutritional support have been released by expert committees of non-profit nutritional organisations such as the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), the European Society for Clinical Nutrition and Metabolism (ESPEN), and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) (Chapter 2). Due to a lack of high-level evidence, the consensus-based guidelines offer basic recommendations that are largely driven by expert opinion and extrapolations from studies in adults or noncritically ill children[1,2].

Current guidelines versus clinical practices worldwide

These inconclusive guidelines make clinical implementation in PICUs across the world difficult. This leads to a wide variation of nutritional practices in PICUs, which were quantified by use of an online worldwide survey (Chapter 2). The first survey described local nutritional strategies in 156 PICUs worldwide. Subsequently, a point prevalence study was performed to collect nutritional data from critically ill children on a single day in these same PICUs. By comparing results from the initial survey with the point prevalence data, the deviation between intended and applied nutritional practices was highlighted. Aspects that differed most between PICUs can therefore be presumed to be in greatest need of high-quality evidence to guide future clinical practice. These aspects were identified in both parts of the survey. In chapters 1 and 5 the lack of clinical outcome studies on the use of PN in the PICU has been underlined. Indeed,

according to the survey, a striking lack of consensus was identified on parenteral glucose intake and on the timing and threshold for use of (supplemental) PN (Chapter 2). The limitations of indirect calorimetry (IC) (Chapters 1 and 3), were reflected by a limited availability of IC in only 14% of PICUs. The general inadequacy of predictive equations to determine resting energy expenditure (REE) in absence of IC (Chapter 4) combined with conflicting evidence on the effect of patient- and disease-related factors on REE (Chapter 1), resulted in adoption of at least 10 different equations for energy expenditure, adjusted for a wide variety of correction factors (Chapter 2).

Early initiation of enteral nutrition is preferred

The most consistent finding between PICUs was the preference for enteral nutrition (EN) as route of nutrient delivery and its early initiation within 24 hours after admission (Chapter 2). This is in line with the general acceptance of the benefits of early EN, as shown in previous studies in critically ill adults and children[3-8] and recommendations by current guidelines for critically ill adults[9-11]. However, the beneficial physiologic effects from early provision of EN, established in many laboratory and animal models, do not automatically reflect improvement of clinical outcome. In chapter 1 it was shown that studies that claimed an improved clinical outcome with early EN in critically ill children were all observational in design. Their conclusions should be interpreted cautiously because patients who are more tolerant for EN, are usually more likely to be less severely ill. Only for critically ill children with burns, superiority of early EN has been proven by a randomised study design[12], but recommendations for other PICU patients cannot be derived directly from this data. Despite the circumstantial evidence on the benefits of early provision of EN, there is a general consensus that EN should be initiated within 24-48 hours after PICU admission, if possible (Chapter 2)[1].

In contrast, the optimal amount of early EN remains a topic of debate. Several studies found an association between higher enteral intake in critically ill children and improved outcome[8]. This perception was reflected in the survey by the intention to meet caloric targets by the enteral route within 3 days in the majority of PICUs (Chapter 2). However, higher enteral intake is predominantly defined as a higher percentage of caloric targets achieved by the enteral route. As shown in chapter 2 and 4, caloric targets vary widely between PICUs, so an equal amount of EN provided in these PICUs might be reflected by different percentages of caloric target achieved. Careful interpretation of these data is therefore warranted.

What to do with current guidelines

With grade C as the maximum level of evidence, recommendations in current guidelines for nutrition support in critically ill children are based on insufficient data (Chapter 1 and 5). Many of the studies on which the guidelines are based are limited by sample size, patient heterogeneity, variability in disease severity and lack of baseline nutritional status (Chapter 5). The guidelines also do not cover every aspect of nutritional support; the A.S.P.E.N. guideline

does not provide recommendations on macronutrient intake, whereas the ESPEN/ESPGHAN only has a guideline on adult EN, not on EN in children. Moreover, the PN guidelines of the ESPEN/ESPGHAN are targeted at children in general, and information on critically ill children is limited to specific and generally small sections. Finally, the phase of critical illness (Chapter 1 and 4) is not taken into account in any of the recommendations for critically ill children, while a large proportion of nutritional studies are limited to the (semi)acute phase.

Even after a highly needed update of current guidelines, recommendations guided by high-level evidence remain scarce. However, as alternatives are lacking, they reflect the best available evidence. Furthermore, since availability of a nutritional protocol, even if based on low-grade evidence[8], is associated with improved outcome, clinical implementation of these recommendations is useful. The judgment of the clinician based on individual circumstances of the patient must always take precedence over these guidelines[10].

ENERGY EXPENDITURE

Measurement of REE

Current guidelines advise to match REE by caloric intake to limit caloric deficit[1]. In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using IC is desirable[1]. This practice is challenging however, due to the limited availability of IC (Chapter 2) and the inaccuracy of predictive equations (Chapter 4) to calculate REE. Ventilator-derived VCO_2 measurements are a promising alternative method to determine REE in mechanically ventilated children weighing 15 kg or more because of its increased precision compared to the current predictive equations (Chapter 3). However, these results should mainly be regarded as a proof of concept, mainly due to the small study population. Further validation of this method to improve accuracy of the measurements and to detect sources of error in a larger cohort of critically ill children is needed before implementation in clinical practice is possible. This could be done by collecting and comparing REE values derived from IC and the ventilator whenever IC is performed (Chapter 3), and ultimately by investigating whether adjustment of nutrition based on ventilator-derived VCO_2 measurements improves clinical outcome of critically ill children.

Since this method appears to be valid only in children weighing ≥15 kg, around 60% of PICU patients at risk will still need to rely on inadequate predictive equations to determine REE in absence of IC. The inadequacy of the ventilator-derived method in children <15 kg, presumably caused by sampling specifications, is not likely to be resolved in the near future. However, this method should again be investigated in smaller children, when the technical performance of the CO_2 sensor is improved (by an increased accuracy and sampling frequency), and an improved version of the airway adapter causes less increase of dead space and turbulence. Moreover, even in children weighing ≥15 kg, this method cannot be validated using regular IC.

In children with tube leak and children on HFO and ECMO, measurement of expiratory VCO_2 is inherently meaningless. In children with a supplied oxygen level of more than 60%, validation is restricted by the limitations of IC, so other validation techniques (e.g. double-labelled water) can be used to study this method in these children.

Although limited to a selected group of patients, clinical implementation of the ventilator-derived method will provide a more reliable determination of REE. Continuous provision of values will help to visualise the course of REE values during PICU stay and thereby allow early detection of changes in REE, as can be expected in septic neonates, children with fever and neonates after surgery (Chapter 1). In order to do so, VCO_2 values from the ventilator need to be automatically registered by the patient data management system and recalculated into REE based on the previously validated metabolic equation[13]. Measurements with more than 10% fluctuation in VCO_2 will need to be discarded automatically. Based on the remaining steady-state VCO_2 measurements, mean REE values can be provided to the attending clinicians to guide nutritional therapy. Although repeated measurements of REE improved outcome in geriatric patients following surgery[14] and showed a trend towards improved hospital mortality in mechanically ventilated adults[15], a single determination of REE is sufficient to guide nutrition in the majority of critically ill children. Repeated measurements may be useful only in children with suspected metabolic alterations or malnutrition[16].

Use of REE to guide nutritional support

In contrast with the paediatric guidelines, results from recent large RCTs in the adult ICU question the need for matching REE by the enteral route during the acute phase of critical illness. No differences in mortality or other clinical outcome measures were found between permissive underfeeding and planned delivery of a full amount of nonprotein calories in critically ill adults[17,18]. Moreover, no faster recovery was observed in critically ill adults receiving more than 30% of the caloric goal by the enteral route compared to adults receiving less than 30% during the first week of the adult version of the PEPaNIC trial (EPaNIC trial)[19]. Finally, endogenous energy production during the acute phase of critical illness limits the use of exogenous provided energy. The optimal amount of required energy to supplement this endogenous production cannot be measured by IC.

Therefore, emphasis on measurement of REE to guide nutritional therapy is likely to shift to subsequent phases of critical illness, aimed at restoration of lean body mass while synthesis of excess fat mass should be avoided. This is already practiced in the NICU, where longitudinal IC measurements are mainly used to guarantee appropriate growth for this population[20,21]. However, these phases are characterised by weaning or even absence of ventilatory support (Chapter 1), limiting the use of IC or ventilator-derived values. Moreover, independently of the phase, application of IC in preterm infants is extremely challenging and therefore hardly practiced outside research settings. In absence of REE measurements, early initiation of nutrition is aspired in all preterm infants (Chapter 5), irrespective of severity of illness[22].

The use of REE to identify overfeeding is also presumed to be limited to the stable and recovery phase. Overfeeding in the most general sense is defined by a worsening of outcome due to an excess of nutrients. Despite the current lack of outcome-based definitions, detrimental effects from overfeeding have been identified (Chapter 1 and 4). Different concepts of overfeeding, such as excessive amounts of caloric intake or separate macronutrients (glucose, amino acids or lipids) can occur isolated or simultaneously, and are associated with specific disadvantages. Early caloric overfeeding is associated with increased mortality in critically ill adults[23], and with liver dysfunction and hepatobiliary complications in children[24,25]. Current definitions of caloric overfeeding based on IC measurements are inaccurate and show a varying specificity. Depending on the definition used, up to 61% of children on the PICU were identified as being overfed[26]. The risk of caloric overfeeding and its complications are presumed to be influenced by age and nutritional status of the child (Chapter 4), the phase of critical illness (Chapter 1 and 4), and by the route of nutrition. In order to prevent the adverse effects of overfeeding during these phases, a new definition of overfeeding needs to be identified (Chapter 4) and should preferably be calibrated on clinical outcome measures.

Since overfeeding and underfeeding both depend on the same requirements, it can be presumed that underfeeding is influenced by similar patient- and disease related factors. Therefore, IC-derived definitions to identify underfeeding[27] are likely to be just as inaccurate as those for overfeeding (Chapter 4). Whereas full nutrition in the acute phase will easily result in overfeeding, the risk of underfeeding is highest during the stable and recovery phase due to increasing requirements (Chapter 1). If requirements are not met during these last two phases, recovery and (catch-up) growth are hampered, thereby affecting outcome.

SUPPLEMENTAL PARENTERAL NUTRITION

The beneficial effect of withholding PN up to day 8 after PICU admission

The use of EN exclusively puts the patient at risk for the development of substantial macronutrient deficits during PICU stay. Despite the aim of most PICUs to meet caloric targets within 3 days by the enteral route, the point prevalence measurement showed that 40% of PICUs failed to achieve this (Chapter 2). Although solid evidence for use of PN in the PICU is lacking (Chapter 5), the survey showed that in 40% of PICUs PN is already started when EN fails to meet 80% of caloric targets (Chapter 2). These specific PICUs represent approximately 36.000 admissions per year. As 16% of PICUs was estimated to participate in the survey, this means that each year at least 200.000 critically ill children receive a medical treatment with only very limited clinical evidence. This is in line with the estimation that 30-50% of critically ill children in Europe and the United States receive this therapy, representing 118.000-196.000 children, based on the number of PICU beds and average length of stay in the United States[28].

In contrast with this current practice and the findings of previous observational studies[8,29], the PEPaNIC trial (Chapter 6 and 7) showed that withholding PN during the first week of PICU stay is clinically superior to the early initiation of (supplemental) PN, with fewer new infections, shorter duration of intensive care dependency and a shorter hospital stay. This trial was conducted in 1440 critically ill children at nutritional risk (Chapter 6). Non-critically ill children were excluded, because the lower severity of stress enabled them to be monitored without any form of organ support and/or to be discharged from the PICU within 24 hours. This group mainly consisted of patients after heart catheterisation, endoscopy, surgical corrections of atrial and septum ventricular defects, inguinal hernia and craniotomy. Also children with asthma exacerbations or congenital heart disease without cardiac failure were excluded. Children at low nutritional risk (STRONGkids score <2) were excluded, since the need for artificial nutrition in this population is low. By doing so, the application of the study results are reserved for at-risk patients, with pre-existent malnourishment, increased energy requirements and/or gastro-intestinal losses who are likely to benefit most from withholding PN.
However, underlying mechanisms for the observed benefits with late PN remain speculative. Several aspects may have played a role:

- Amplification of the acute catabolic stress response
- Preservation of autophagy (fasting response)
- Maintenance of muscle integrity and function
- Prevention of PN-related complications

Amplification of the acute catabolic stress response
An increase in the acute inflammatory response was found with late initiation of PN, as indicated by the plasma CRP (Chapter 7), confirming the findings of the EPaNIC trial[30]. It might be speculated that this increase is caused by the expected increased use of insulin in the early PN group, rather than by nutrient restriction in the late PN group[31]. An increase in CRP has been associated with enhanced catabolism by reducing protein synthesis and increasing protein breakdown[32].
Also, a rise in total bilirubin was detected (Chapter 7), possibly reflecting amplification of the metabolic component of the stress response with omitting PN up to day 8. Caloric restriction early during critical illness might increase the redirection of conjugated bilirubin from the hepatocyte back into the bloodstream, instead of transporting it against the concentration gradient into the bile, resulting in preservation of energy[33].
Inactivation of thyroid hormone, possibly also reflecting an adaptive beneficial response[32,33], is enhanced in response to nutrient restriction during the acute phase[34] and associated with a better outcome[34,35] (Chapter 1). Possible alterations of the neuro-endocrine axes with late PN, and its association with acute and long-term clinical outcomes, will be investigated in a mechanistic study of PEPaNIC data. This will be combined with the current data and an

evaluation of functional, physical and neurocognitive outcome 2 and 4 years after admission to the PICU (Chapter 6).

Although amplification of these presumed adaptive processes appear to be beneficial during the acute phase, they may become maladaptive with prolonged critical illness[36,37]. As reflected by an early discharge (before the fourth day of PICU stay) of almost 50% of PEPaNIC patients (Chapter 7), this acute phase is likely to last only for a short period of time in the majority of critically ill children.

Preservation of autophagy (fasting response)

Preservation of autophagy by parenteral nutrient restriction in the acute phase may have contributed to the observed beneficial effects, given its importance for innate immunity and for quality control in cells with a long half-life[38-40]. The exact role of autophagy in the PEPaNIC study will be investigated with analyses of leukocyte samples (Chapter 6). Nutrients provided by the enteral route also affect the severity of starvation, and therefore possibly suppress autophagy as well. Long before activation of autophagy was suggested as a possible underlying mechanism for benefits of withholding artificial nutrition early in critical illness, studies showed that forced EN in septic mice decreased survival time, whereas starvation decreased mortality and promoted pathogen clearance[41,42]. Strikingly, the greatest survival was observed in mice who lost the most weight, whereas in many nutritional studies weight gain is considered a primary beneficial outcome in critically ill children.

Maintenance of muscle integrity and function

In the EPaNIC trial, preservation of autophagy in skeletal muscle explained the reduced ICU-acquired weakness and enhanced recovery observed with late PN[40]. Due to ethical considerations, no tissue biopsies were performed in the critically ill children participating in PEPaNIC. Alternatively, early detection of muscle mass wasting is challenging, due to unreliability of ultrasonography[43], and does not automatically reflect loss of muscle function[44]. Muscle function can be quantified by measurements of muscle strength, most easily performed by use of a dynamometer to measure hand grip strength. This method is however not generally applicable to the PICU population, since baseline values are often lacking due to clinical instability or sedation. These factors also limit use of hand dynamometry later during PICU stay in children with prolonged critical illness that are most at risk for loss of muscle function. Investigation of the effect of late PN and critical illness on muscle function will therefore remain reserved to the long-term follow-up and will be quantified by measurements of hand grip strength, a 6-minute walk test, the timed up and go test and preferably also by use of a physical activity monitor. Results from the PEPaNIC patients at planned follow-up visits will be compared with reference values and healthy volunteers, and can be correlated to patient- and disease related factors during PICU stay, such as length of stay, duration of ventilation and nutritional data.

Prevention of PN-related complications

By withholding PN, complications associated with central venous access[45] and composition of PN solutions[46] might be prevented. Despite these additional complications of PN administration, only 3.5% of PICUs would withhold PN for at least 7 days (Chapter 2). Also, after the first week of PICU stay, a large proportion (38%) of the PEPaNIC children depended on PN with its added risk. The complications associated with central venous access devices are not likely to have contributed to the beneficial effects of late PN, since the percentage of central venous lines is expected to be similar between the two treatment groups. Moreover, the reduced proportion of patients with a new infection in the late PN group was not only attributable to fewer patients acquiring a blood stream infection, but also to fewer airway infections. Clinical implementation of the late PN strategy will most likely decrease the number of venous access devices and associated complications in the future, although venous access remains essential for different reasons than provision of PN in the large proportion of children with multi-organ failure and/or underlying chronic diseases.

Use of PN has also been identified as a risk factor for caloric overfeeding[47,48]. Furthermore, patients with the lowest cumulative caloric intake (lowest dose intervals) showed a similar or better outcome than any of the higher doses in post-hoc analyses of adult RCTs[19,49]. By reducing the total caloric intake with late initiation of PN (Chapter 7), the prevalence of caloric overfeeding and its complications are likely to decrease. However, it is difficult to investigate the prevalence of overfeeding and its contribution to the unfavourable outcome in the early PN group. Endogenous glucose production is presumed to match 50-75% of REE the first days after admission[50], resulting in an uncertainty of actual energy requirements when endogenous sources are used for energy. Current definitions of overfeeding are considered inadequate because they fail to take this and several other essential patient and disease related factors into account, and even identify patients with an intake below the threshold to equilibrate nitrogen balance as overfed (Chapter 4).

On the other hand, one might state that recommendations by current guidelines reflect overfeeding in the acute phase of critical illness, because providing early PN in agreement with these guidelines is clinically inferior to withholding PN during this phase.

In summary, despite the lack of adequate definitions, macronutrient intake should be reduced during the acute phase, since introduction of (supplemental) PN will easily result in overfeeding[51] (Chapter 1).

The role of macronutrient dose

Strategies of early and late initiation of PN differed in parenteral macronutrient intake, with no provision of amino acids and lipids and reduced intake of glucose in the late PN group (Chapter 6). High parenteral intake of glucose and amino acids are known to cause multiple, mostly metabolic, side effects in children[23,52-59].

Protein

Recent large prospective studies have particularly stressed the importance of a high total (but predominantly enteral) protein intake in critically ill children and adults due to its association with decreased mortality and reduced length of stay, independently of caloric intake[23,60,61]. However, co-occurrence of high protein intake and improved outcome does not imply causation. Also, as with the association between higher caloric intake and improved outcome, protein intake goals vary widely between PICUs (Chapter 2). Administration of protein enriched enteral formulas in critically ill children consistently increases total protein synthesis/balance and levels of amino acids[62-66]. However, relations between these surrogate endpoints and clinically relevant outcomes are often non-existent or weak. Sometimes surrogate endpoints even suggest a benefit whereas the clinical outcomes indicate harm (Chapter 5 and 7). Cumulative amino acid dose early during ICU stay was associated with delayed recovery in a post-hoc analysis of the EPaNIC trial[19]. Some amino acids, such as leucine, exert a primary anabolic effect in skeletal muscle and inhibit the initiating step of autophagy[67] by activation of mTOR (mammalian target of rapamycin)[68], thereby reducing tolerance to oxidative stress, increasing risk for organ failure (especially liver and kidney) and cell death, eventually resulting in worse clinical outcome[69].

Lipids

Due to a lack of evidence, the optimal amount of lipid administration in critically ill children remains unclear, reflected by a wide range in parenteral lipid targets (from below 1.5 to above 3.5 g/kg/day) (Chapter 2). Provision of saturated fatty acids is known to provoke more endoplasmatic reticulum (ER) stress and inflammation in liver and adipose tissue of rats than provision of unsaturated fatty acids[70], resulting in catabolism and ultimately in apoptosis[71]. Intravenous lipid emulsions provided in critically ill children are traditionally rich in n-6 fatty acids impacting neural development, growth, immune function and outcome after surgery[72]. The alternative lipid emulsions, enriched with n-3 fatty acids, are safe and effective in reducing the infection rate and length of stay of adult ICU patients[73] and might promote the resolution of the inflammatory process in children post-surgically[74]. However, evidence for the use of these emulsions in critically ill children is solely based on surrogate endpoints (Chapter 5) and therefore differs between PICUs (Chapter 2).

Also in the PEPaNIC study, different types of lipid emulsions were used (predominantly SMOFlipid® in Leuven and Intralipid® in Rotterdam). A more detailed analysis is needed to investigate the relation between type of lipid emulsion and clinical outcomes, such as PICU dependency and incidence of new infections.

With the current lacking and conflicting evidence, the macronutrient dose dependency analysis of PEPaNIC is eagerly awaited. The optimal timing for the initiation of PN should be marked by the moment in which its benefits on clinical outcomes by providing essential

nutrients exceed the adverse effects of its provision. This moment is likely to depend on the age and clinical status of the child (Chapter 4) and also on the phase of critical illness (Chapter 1 and 4). With the PEPaNIC trial, the most optimal timing so far for initiation of PN in critically ill children is determined at 8 days after PICU admission. Since the majority of patients will have left the PICU by that time, they will not receive any PN during their stay on the PICU.

Effect of early parenteral nutrient restriction in children at nutritional risk

The clinical superiority of late PN was present irrespective of the admission diagnosis, the severity of illness and the STRONGkids category. Certain populations within the PICU, such as neonates and malnourished children, are presumed to have less metabolic reserve[75]. Other children are at greater nutritional risk[76] due to higher requirements, decreased intake or increased losses[77-79]. Especially for these groups of 'at-risk' patients, fear for profound cumulative macronutrient deficits exists. Indeed, malnourishment was frequently mentioned as condition for early initiation of PN in the survey (Chapter 2, data not shown). The PEPaNIC trial did not stratify for different nutritional risk categories a priori. Planned subgroup analyses of this trial will investigate differences in effect size of withholding PN between certain patient groups, and may generate new hypotheses.

STRONGkids score

The beneficial effect size observed in children in the highest STRONGkids risk category was larger than in children in the medium STRONGkids risk category (Chapter 7), even after correction for diagnosis, age and severity of illness. The STRONGkids screening tool was initially developed and validated to identify hospitalised children at nutritional risk[76]. We successfully used this tool to also identify critically ill children at nutritional risk. Clinically, the highest STRONGkids scores were mainly reserved for critically ill children with malignancies, severe cardiac disease (cardiomyopathy, hypoplastic heart syndrome) or after surgical correction of gastro-intestinal tract anomalies.

In order to implement the strategy of withholding PN during the first week of PICU stay in children at nutritional risk and to identify children that will possibly benefit most from this strategy, determination of the STRONGkids or another nutritional risk score in every child upon admission to the PICU is recommended.

The distinct effect in children at higher nutritional risk, questions the reservation of early PN for children at-risk, as often applied in North American PICUs. The effect of late PN on clinical outcomes in children that are malnourished (SD-score for BMI <-2) and on children with a contra-indication for EN will be investigated in planned sub-group analyses. Possible underlying explanations for the enhanced effect in these children at higher nutritional risk will also be studied by comparing the amount of PN provided and macro- and micronutrient status upon admission.

Hypoglycaemia with parenteral nutrient restriction

Despite the clinical benefits, late PN increased the incidence of hypoglycaemia from 4.8% to 9.1% (Chapter 7). However, experiencing hypoglycaemia with late PN did not reduce its impact on any of the primary or secondary outcomes (Supplementary appendix, chapter 7). Previous studies have shown that brief episodes of hypoglycaemia, either during paediatric critical illness or in premature/mature newborns, did not negatively affect long-term neurocognitive outcomes[80,81]. A follow-up study of all PEPaNIC patients is currently conducted to evaluate functional, physical and neurocognitive outcome 2 and 4 years after admission to the PICU (Chapter 6). Data will be compared between the two treatment groups, but also between PEPaNIC patients and matched healthy controls. Results from this study will provide more insight in the long-term effects of critical illness in general and nutritional support in the PICU in particular.

FUTURE PERSPECTIVES

Future research

The results described in this thesis have provided some important answers, but also raised questions. The PEPaNIC trial has provided the long awaited evidence for use of (supplemental) PN in critically ill children of all age groups and diagnoses during the first week of PICU stay. The rigid study protocol, although practical for large clinical trials, is unlikely to have represented an optimal nutritional strategy for every individual patient, but has provided a strategy that is generally applicable with a risk of being unfocused.

Pre-planned subgroup analyses from the PEPaNIC trial might support specific evidence-based guidelines in respect to disease and settings, in order to individualise nutritional support on the PICU. The following subgroups will be investigated: cardiac patients, patients with sepsis, malnourished patients and children with contra-indication for EN on admission. Also, the enhanced beneficial effect of late PN in neonates (Chapter 7) will be further analysed.

Pre-planned mechanistic studies on endocrine, inflammatory and genetic markers and a dose- and macronutrient dependency analysis might unravel underlying mechanisms of the beneficial effect of early parenteral nutrient restriction.

In order to translate nutritional recommendations to clinical practice, it is essential to make a distinction between the phases of critical illness (Chapter 1). For the PEPaNIC trial, the acute phase was defined as the first 7 days after PICU admission. However, in the majority of the children the acute phase was shorter because they had left the PICU within the first 7 days (Chapter 7) or because enteral caloric intake was already sufficient to meet caloric goals on day 8 (60% of children present at day 8).

To further individualise and thereby optimise nutritional support, (bio)markers involved in the neuro-endocrine, immunologic/inflammatory and metabolic part of the stress response, could be used to identify the onset of the different phases within each child. Due to the insufficient sensitivity, specificity or availability of most (bio)markers, integration of several markers combined with clinical characteristics might be most promising to optimise individualised nutritional therapy in the PICU.
To investigate the effect of such a patient-tailored approach on short-, and preferably also long-term clinical outcomes, clinical trials are needed to compare a strategy of marker-targeted feeding with the current generally applied nutritional practices.

This information will add valuable evidence to current guidelines, that as of now do not distinguish between phase of critical illness, severity of illness and diagnoses. Recommendations derived from the high-level evidence provided by the PEPaNIC trial are also generally applicable, but provide specific recommendations on provision of PN in respect to phase of illness. Because recommendations on other aspects of nutritional support, such as enteral caloric and macronutrient goals, should take these phases into account as well[51,82] (Chapter 1), an update of current guidelines is urgently needed. Until other studies have provided evidence to individualise nutritional support to disease and settings, these updated guidelines should be used as a foundation for nutritional therapy, whilst considering the physiology of the individual patient.

In the PEPaNIC trial, the strategy of withholding PN was limited to the period following PICU admission. One might question if deterioration of clinical status beyond this period might evoke a similar acute stress response and therefore if the child might benefit from parenteral nutrient restriction as well. When more insight can be provided into the relation between the stress response and the beneficial effects of late PN based on the PEPaNIC trial, application of this strategy later during PICU stay might need to be investigated.

Finally, since we have shown that permissive parenteral underfeeding is beneficial early in critical illness, avoidance of overfeeding has become even more significant. In order to improve its detection, a new definition of overfeeding is urgently needed and should take into account the age and nutritional status of the child, the phase of critical illness, and possibly also the route of nutrition. However, to develop such a phase-dependent definition, adequate identification of these phases is essential. In a subset of PEPaNIC patients, results from REE measurements by IC will be analysed to gain more insight in the concept of overfeeding on the PICU.

Other nutritional aspects in critically ill children that were beyond the scope of this thesis, but in profound need of high-level evidence, are the optimal amount of EN early in critical illness

and the optimal macronutrient and micronutrient composition of both enteral and parenteral formulas.

Suggestions for clinical implementation

Protocol adherence in a research setting mainly depends on the effectiveness of the research team. Successful clinical implementation of study results on the other hand, depends on the personal adherence of the involved clinicians and other health care workers. This process could be improved by modification of a protocol to local context while considering current practice, resources and costs. Nonetheless, extensive education of all involved clinicians remains essential. Continuous evaluation on the execution of the new strategy is needed to detect the challenges and pitfalls of this practice when carried out in a in a clinical setting.

In order to implement the PEPaNIC strategy in the PICU of the Sophia Children's Hospital–Erasmus MC in Rotterdam, several concessions to the study protocol have been made to comply with the availability and compatibility of local PN components and the current infrastructure of the local pharmacy.

Based on the results presented in this thesis and the available literature, the following nutritional strategies in critically ill children are recommended:

1. Critically ill children at nutritional risk should be identified in order to decide which type of nutritional support should be given
2. Use of a nutritional risk score such as the STRONGkids is recommended
3. In critically ill children at nutritional risk, parenteral amino acids and lipids should be withheld and parenteral glucose intake should be reduced during the first week of PICU stay (Fig 1. and Table 1)
4. Electrolytes, minerals, trace elements and vitamins should be provided as recommended by the guidelines[2] in an age-dependent manner from day 2 onwards. Parenteral supplementation should be stopped as soon as enteral nutrition provides ≥80% of caloric goal (Fig. 1)
5. Enteral macronutrient intake in the first week of PICU stay depends on the route of nutrition, weight of the child and phase of critical illness (Table 1)
6. Enteral nutrition should ideally be initiated within 24-48 hours after admission
7. Increase of macronutrient intake after 1 week in the PICU depends on the phase of critical illness and can be classified as follows:
    a. acute phase: requirement of (escalating) vital organ support
    b. stable phase: stabilisation or weaning of vital organ support
    c. recovery phase: clinical mobilisation of the child, that is no longer in need of vital organ support

8. Children receiving <80% of caloric goals by the enteral route after one week of PICU stay can be provided with supplemental PN (Fig. 1)
9. Macronutrient intake after the acute phase should ideally be guided by REE, preferably by IC- or ventilator-derived measurements, or, in absence of such a device, by use of predictive equations without use of correction factors. The upper limit of caloric intake varies with the route of nutrition and phase of critical illness (Table 1)

In conclusion, while enteral nutrition should ideally be initiated early during PICU stay, during the acute phase of critical illness **less** parenteral nutrition **is more!**

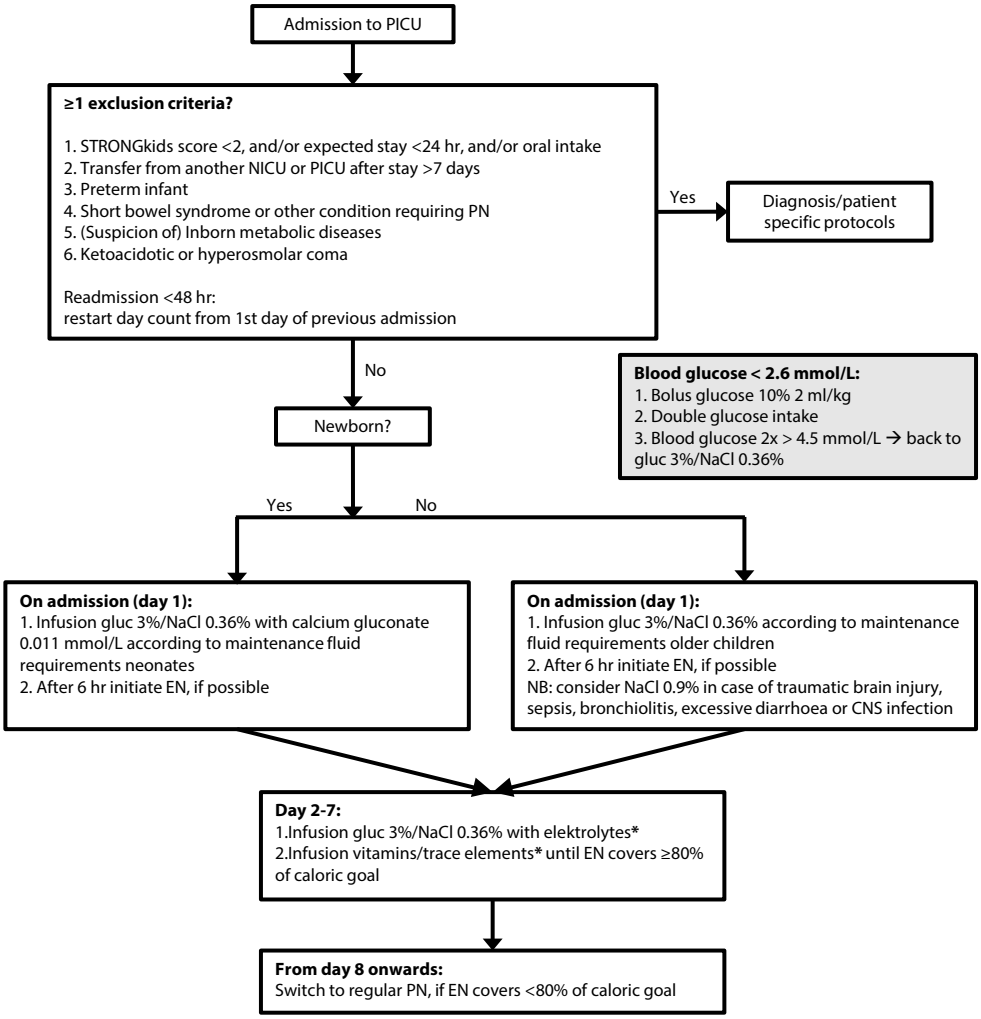

Figure 1. Flowchart for nutritional support in critically ill children after admission to the PICU
*Composition age-dependent, based on ESPEN/ESPGHAN guidelines[2]

Critically ill children at nutritional risk (STRONGkids score≥2)[76], with an expected PICU stay of at least 24 hours without oral intake, and not fulfilling any of the exclusion criteria[84], will be provided with an infusion of glucose 3% /NaCl 0.36% upon admission. For newborns, this infusion will be supplemented with extra calcium to meet the higher requirements in this population.

If possible, enteral nutrition (EN) is initiated after 6 hours, preferably by post-pyloric tube, using commercially available formulas. If placement of a post-pyloric tube fails, gastric feedings should be attempted. The aim of EN administration is to reach caloric and protein goals by day 3: use of caloric and protein enriched formulas may be necessary to achieve this. Details of the local EN protocol have been described previously[85].

From the morning following admission (day 2) up to day 8, pharmacy-made parenteral nutrition (PN) solutions for different weight categories, containing glucose 3%/NaCl 0.36% and electrolytes, are provided at rates based on maintenance fluid requirements proposed by Holliday-Segar[86], or lower in case of fluid restriction or concomitant enteral nutrient administration, according to the judgement of the attending physician. No parenteral lipids or amino acids are to be administered during the first week of PICU stay. Vitamins and trace elements are provided by a continuous parenteral infusion (neonates-children 30 kg)

or as a bolus once a day (children >30 kg), until EN provides ≥80% of preset caloric goals, PICU discharge, or up to day 8 of PICU stay, whichever comes first.
On the morning of day 8 after admission, if still present in the PICU, children receiving <80% of caloric goals by the enteral route, will be switched to regular PN solutions containing lipids and amino acids with a composition based on the ESPEN/ESPGHAN guidelines[2]. After discharge from the PICU, the nutritional management is at the discretion of the physicians on the regular wards.

Table 1. *Suggested energy and macronutrient intake during the different phases of critical illness*

	Acute phase	**Stable phase**	**Recovery phase**
		Enteral nutrition (Preferred route)	
Energy	Start as soon as possible to match REE and gradually increase if tolerated		2xREE and higher if necessary to enable growth
Protein (g/kg/day)	1-2	2-3	3-4
		Parenteral nutrition	
Energy	<REE	1.3-1.5xREE	2xREE
Carbohydrates (mg/kg/min)			
Newborn	2.5-5	5-10	5-10
28d-10 kg	2-4	4-6	6-10
11-30 kg	1.5-2.5	2-4	3-6
31-45 kg	1-1.5	1.5-3	3-4
>45 kg	0.5-1	1-2	2-3
Protein (g/kg/day)	0	1-2	2-3
Lipids (g/kg/day)	0	1-1.5	1.5-3

REE= Resting Energy Expenditure
From: Nutritional support and the role of the stress response in critically ill children, K. Joosten, D. Kerklaan, S. Verbruggen. Curr Opin Clin Nutr Metab Care 2016[83]. Copyright©. Reprinted with permission.

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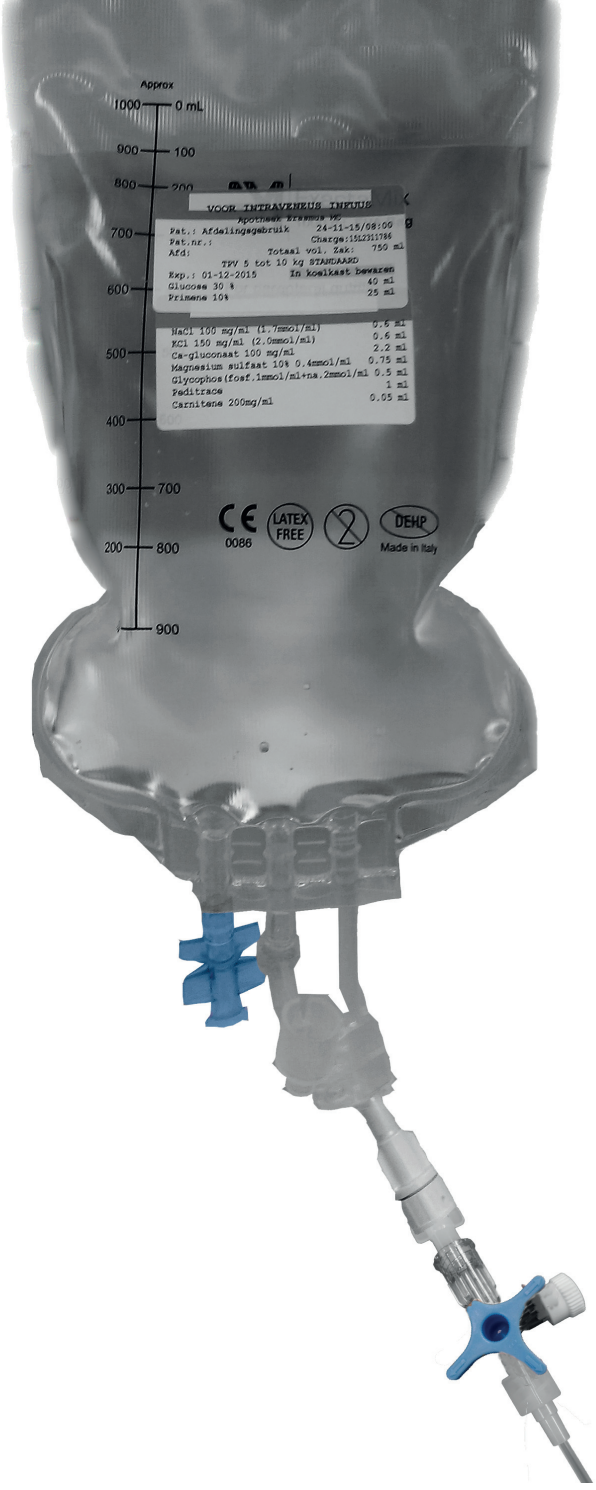
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Exp.: 01-12-2015 In koelkast bewaren
Glucose 30 % 40 ml
Primene 10% 25 ml
NaCl 100 mg/ml (1.7mmol/ml) 0.6 ml
KCl 150 mg/ml (2.0mmol/ml) 0.6 ml
Ca-gluconat 100 mg/ml 2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml 0.75 ml
Glycophos(fosf.1mmol/ml+na.2mmol/ml 0.5 ml
Peditrace 1 ml
Carnitene 200mg/ml 0.05 ml
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LATEX FREE
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Made in Italy

CHAPTER 9

Summary of the thesis

Samenvatting

The main findings of this thesis are summarised in Table 1.

Chapter 1

Nutritional support affects recovery and outcome in critically ill children, but its application is supported by a scarcity of high-level evidence. For that reason, the optimal timing, amount and route of nutrition in the Paediatric Intensive Care Unit (PICU) remain debatable. This results in a wide variation in clinical practice, which impacts outcome of critically ill children.

In the introduction of this thesis an overview is provided of the different aspects of nutritional support in critically ill children in relation to the different phases of the stress response. The characteristics of the different phases of critical illness are described, followed by an elaboration on the optimal nutrition strategy for each phase.

Finally, an overview is given on the use of energy expenditure to guide nutritional therapy throughout the course of critical illness. Chapter 1 ends with the aims and outline of this thesis.

Chapter 2

International consensus-based guidelines on nutritional support in critically ill children generally rely on expert opinions and studies in adults or non-critically ill children, and provide rather non-specific recommendations. To identify local strategies and guidelines, we distributed a two-part online survey to PICUs across the world. In addition we compared the local guidelines with nutritional data collected in all patients present on a single day in a subgroup of the responding PICUs. We observed that, due to the limited guidelines, current nutritional practices vary widely between PICUs worldwide. Most variation was observed in macronutrient targets, the estimation of energy requirements and the threshold for the use of (supplemental) parenteral nutrition (PN). Subsequently, we found that applied nutritional practice deviated from local protocols or strategies on multiple occasions. The only wide-spread consensus appeared to be on the preference for the enteral route and its early initiation. These results highlight the need for sound clinical studies to develop evidence-based guidelines on nutritional support for critical ill children, since inconclusive and low-level evidence appears to represent a barrier to clinical implementation.

Chapter 3

Measurement of resting energy expenditure (REE) through indirect calorimetry (IC) is the preferred method to determine energy requirements in critically ill children. Since availability of IC is limited worldwide, most PICUs rely on predictive equations to determine REE. However, these equations cannot accurately predict REE in critical illness, because they are derived from measurements in healthy children. Fortunately, VCO_2 values to calculate REE can also be automatically subtracted from a ventilator.

In chapter 3 we have shown that VCO_2 measurements by the Servo-I® ventilator are more precise in determination of REE than the frequently used predictive equations in mechanically ventilated children weighing more than 15 kg. This provides a promising alternative to the limited available IC. However, for the large proportion of PICU patients weighing less than 15 kg this method is not sufficiently accurate due to the technical specifications of the sampling method.

Chapter 4

Energy overfeeding is associated with worse outcome and is frequently observed in critically ill children. In a cohort of mechanically ventilated children, we found that the number of children identified as overfed ranged widely depending on the definition used. Even children with an energy intake below the presumed threshold to equilibrate nitrogen balance were identified as overfed, indicating inaccuracy of current definitions.

The maximum caloric intake is likely to depend on the age and nutritional status of the child and the phase of critical illness. However, current definitions of overfeeding fail to take these factors into account, and are therefore not generally applicable to the PICU population. To prevent the detrimental effects of overfeeding, an age- and phase dependent definition of overfeeding is warranted, preferably based on hard clinical outcomes.

Chapter 5

Provision of enteral nutrition (EN) in critically ill children often results in a pronounced caloric deficit, which is associated with poor outcomes and impaired growth. Use of (supplemental) PN helps reaching preset goals, but with the added risk of metabolic disturbances and an increased nosocomial infection rate.

Chapter 5 reviews the available evidence from RCTs supporting the use of PN in critically ill children. Only six small RCTs were identified, showing a beneficial effect of increased or altered PN. However, these studies focused only on surrogate endpoints, such as nitrogen balance or inflammatory markers, underlining the lack of high-level evidence on clinical outcomes in critically ill children regarding the effect of timing, amount and composition of PN.

Chapter 6 and 7

Evidence from high-quality RCTs in critically adults no longer supports early initiation of (supplemental) PN. To determine if a pronounced macronutrient deficit could also be tolerated in critically ill children, we performed an international multicentre RCT in 1440 critically ill children at nutritional risk.

We found that withholding PN for one week in the PICU was clinically superior to early provision of PN, with fewer new infections, shorter duration of intensive care dependency and shorter hospital stay. This beneficial effect was detected irrespective of the treatment centre, severity of illness, STRONGkids category, age and diagnosis on admission. The effect was even larger in children with the highest nutritional risk and in critically ill neonates.

Therefore this approach should be implemented in current nutritional practice on PICUs worldwide.

Chapter 8

This chapter provides a general discussion in which the main findings of this thesis are evaluated and substantiated by speculations on underlying mechanisms. Based on the findings and available literature, current gaps in knowledge of nutritional support in critically ill children are highlighted and are followed by future perspectives on clinical practice and nutritional research.

Table 1. *Main findings of this thesis*

	Findings
Chapter 1 Introduction	Understanding the stress response of critical illness and its phases is essential to provide recommendations on amount, timing and route of nutrition in critically ill children
Chapter 2 Worldwide survey of nutritional practices in PICUs	Current nutritional practices vary widely between PICUs worldwide, especially on macronutrient targets, estimation of energy requirements and threshold for the use of (supplemental) PN. Applied nutritional practice deviated from local protocols or strategies on multiple occasions. There appears to be wide-spread consensus on the preference for the enteral route and its early initiation
Chapter 3 Ventilator-derived VCO_2 measurements to determine REE	Use of VCO_2 measurements by the Servo-I® ventilator is a feasible and more precise method to determine REE in mechanically ventilated children >15 kg than predictive equations. It may be a promising method to compensate for the limited availability of indirect calorimetry in the future
Chapter 4 Use of indirect calorimetry to detect overfeeding	The number of children identified as overfed ranges widely depending on the definition used. Current definitions of overfeeding fail to take into account several factors associated with critical illness and are therefore not generally applicable to the PICU population
Chapter 5 Evidence for the use of PN in the PICU	There is currently no evidence to support any of the current PN practices for critically ill children. Available RCTs focus on surrogate outcome measures instead of hard clinical outcomes. The evidence from high quality RCTs in critically ill adults no longer supports the early use of PN
Chapter 6 and 7 PEPaNIC trial	Withholding PN for one week in the PICU is clinically superior to early provision of PN, with fewer new infections, shorter duration of intensive care dependency and a shorter hospital stay

PICU= Paediatric Intensive Care Unit, REE= Resting Energy Expenditure, PN= Parenteral Nutrition, RCT= Randomised Controlled Trial

SAMENVATTING

Inleiding (Hoofdstuk 1)

Kritisch zieke kinderen, die opgenomen zijn op de intensive care afdeling, kunnen meestal niet zelf eten. Als onderdeel van de behandeling wordt daarom al vroeg gestart met het toedienen van kunstmatige voeding. Dit gebeurt, afhankelijk van de diagnose en ernst van ziekte, middels een voedingssonde in het maag-darmstelsel (enterale voeding) of via een infuus (parenterale voeding). Uit beschouwend onderzoek is bekend dat deze voedingsstrategieën het beloop en herstel van de ziekte kunnen beïnvloeden, maar tot nu toe is er weinig kwalitatief hoogstaand wetenschappelijk bewijs geleverd op dit gebied. Er is dan ook nog veel discussie over de optimale timing, hoeveelheid en toegangsweg van kunstmatige voeding bij kritisch zieke kinderen. Dit leidt ook tot veel variatie bij het geven van voeding op de kinder-intensive-care afdeling (PICU).

Het doel van dit proefschrift is om meer inzicht te verschaffen in huidige voedingsstrategieën in kritisch zieke kinderen.

De inleiding van dit proefschrift bevat een overzicht van de verschillende aspecten die een rol spelen bij het toedienen van kunstmatige voeding aan kritisch zieke kinderen. Deze aspecten worden weergegeven in relatie tot de fase van de zogeheten stress respons van kritieke ziekte. Deze evolutionaire respons op schade door ernstige ziekte, trauma of een operatie bestaat uit complexe veranderingen in de hormoonhuishouding en stofwisseling met als doel de kritieke ziekte te overleven.

Er kunnen 3 verschillende fasen worden onderscheiden in kinderen: de acute, de stabiele en de herstelfase. Zowel de duur als de intensiteit van elke fase is afhankelijk van de leeftijd van het kind en de ernst van de ziekte. De optimale voedingsstrategie verschilt per fase: in de acute fase lijkt het beperken van voeding, en dan met name parenterale voeding, beter te zijn (op basis van studies in volwassenen), terwijl het tijdens de stabiele en herstelfase beter lijkt te zijn om de inname van voedingsstoffen te verhogen om te voldoen aan de toename van de energiebehoefte.

Omdat de energiebehoefte per kind kan wisselen, wordt de hoeveelheid voeding meestal gebaseerd op het individuele rust energieverbruik (REE) per kind. REE kan worden berekend met formules, maar de waarde is het meest betrouwbaar wanneer die gemeten wordt. Deze meting bestaat uit het bepalen van het zuurstofverbruik en de koolstofdioxideproductie met behulp van de uitademingslucht, wat indirecte calorimetrie wordt genoemd. Indirecte calorimetrie is echter kostbaar, tijdsintensief en alleen toepasbaar in een selecte groep kinderen en wordt in een minderheid van de PICUs gebruikt. Daarom hebben we in hoofdstuk 2 met behulp van een online vragenlijst onder andere onderzocht op welke manier PICUs REE bepalen. In hoofdstuk 3 hebben we een alternatieve methode getest om het REE te meten, zodat indirecte calorimetrie niet langer noodzakelijk is.

De nadruk van dit proefschrift ligt op calorische overvoeding en parenterale voeding. Wanneer er sprake is van overvoeding is niet altijd duidelijk gedefinieerd; de problemen en uitdagingen die hiermee verbonden zijn worden besproken in hoofdstuk 4. De voorkeur voor parenterale voeding om gestelde doelen gemakkelijker te bereiken wordt onderzocht in hoofdstuk 5, ook hier blijkt de associatie of verwachting sterker dan het klinisch bewijs. Er is dus hoogstaand wetenschappelijk onderzoek nodig naar de timing, hoeveelheid en samenstelling van voeding bij kritische zieke kinderen.
Om meer inzicht te krijgen in hoe we de voeding bij deze groep kinderen het beste kunnen reguleren en toedienen hebben we een grootschalig onderzoek opgezet in samenwerking met Leuven en Edmonton. De resultaten van deze studie, die we hebben uitgevoerd bij 1440 kinderen verspreid over drie ziekenhuizen, worden besproken in hoofdstuk 6 en 7. In hoofdstuk 8 worden onze resultaten in perspectief geplaatst en wordt de huidige stand van zaken beschouwd.

Hoofdstuk 2
Verschillende internationale voedingsorganisaties hebben richtlijnen uitgebracht over het voorschrijven van voeding aan kritisch zieke kinderen. Door het tekort aan solide studies over het effect van voeding op kritisch zieke kinderen, zijn deze richtlijnen voornamelijk gebaseerd op de mening van experts op dit gebied, en afgeleid van studies die gedaan zijn bij volwassenen in plaats van kinderen. De adviezen in deze richtlijnen zijn daarom niet altijd even concreet.
Om te onderzoeken welke voedingsstrategieën er op verschillende PICUs gehanteerd worden, hebben we een online vragenlijst verstuurd naar PICUs over de hele wereld. De vragenlijst bestond uit twee delen. In het eerste deel werd gevraagd naar de lokale protocollen op het gebied van voeding bij kinderen. In het tweede deel werd gevraagd om de voedingsgegevens te noteren van alle kinderen die op één en dezelfde dag aanwezig waren in de PICU. De vragenlijst werd ingevuld voor 156 PICUs in 52 verschillende landen en 6 continenten.
Uit de resultaten van deze vragenlijst bleek er veel variatie te zijn in de gehanteerde voedingsstrategieën bij de verschillende PICUs. De strategieën varieerden vooral wat betreft het bepalen van de macronutriënt- (koolhydraat, eiwit en vet) en energiebehoefte, en de drempel voor het gebruik van parenterale voeding. Een van de weinige overeenkomsten tussen de PICUs was de intentie om vroeg te starten met enterale voeding. Bij het vergelijken van het eerste met het tweede deel van de vragenlijst bleek tevens dat de werkelijke uitvoering van de voedingsstrategieën vaak verschilt van de lokale protocollen (zoals genoemd in het eerste deel). Deze resultaten geven aan dat er solide klinische studies nodig zijn naar voeding bij kritisch zieke kinderen, omdat het tekort aan bewijs een duidelijke barrière vormt voor het implementeren van de protocollen op de PICU.

Hoofdstuk 3

Om de energiebehoefte van kritisch zieke kinderen te bepalen heeft het meten van het rust energieverbruik (REE) middels indirecte calorimetrie de voorkeur. Helaas is deze methode slechts beperkt beschikbaar en wordt de energiebehoefte in veel PICUs berekend met behulp van formules. De meest gebruikte formules zijn echter afgeleid van metingen bij gezonde kinderen, en zijn minder betrouwbaar in gebruik bij kritisch zieke kinderen. Een alternatieve mogelijkheid om de energiebehoefte te bepalen is om REE te berekenen op basis van de koolstofdioxideproductie per minuut (VCO_2), een waarde die direct kan worden afgelezen van de beademingsmachine.

Wij hebben deze methode getest bij 41 kinderen die aan de beademing lagen. De methode was veilig en praktisch goed uit te voeren. Bij kinderen met een gewicht vanaf 15 kg kwamen de uitslagen van deze methode goed overeen met die van indirecte calorimetrie. De methode bleek ook betrouwbaarder in het bepalen van de energiebehoefte dan het gebruik van de standaardformules. Helaas was de methode bij kinderen met een gewicht onder de 15 kg onvoldoende betrouwbaar, waarschijnlijk doordat de meting niet precies genoeg was voor de kleinere luchtwegen en hogere ademsnelheid in deze groep.
Het gebruik van de beademingsmachine is een veelbelovende methode om REE te bepalen bij kritisch zieke kinderen vanaf 15 kg die zijn opgenomen op PICUs die niet beschikken over indirecte calorimetrie en nu nog afhankelijk zijn van het gebruik van formules.

Hoofdstuk 4

Kritisch zieke kinderen worden regelmatig calorisch overvoed, doordat ze meer energie binnen krijgen dan ze verbruiken. Calorische overvoeding op de intensive care wordt geassocieerd met leverfalen, langere beademingsduur, en een grotere kans op overlijden en op infecties, maar een eenduidige definitie van overvoeding ontbreekt. Wij hebben de verschillende definities van calorische overvoeding, gebaseerd op metingen met indirecte calorimetrie, vergeleken bij 78 kinderen met mechanische beademing. Het aantal kinderen dat geïdentificeerd werd als overvoed varieerde, afhankelijk van de gebruikte definitie, van 23% tot 50%. Sommige kinderen kregen minder calorieën dan de minimale hoeveelheid die nodig lijkt te zijn om eiwitafbraak te kunnen compenseren, maar werden wel geïdentificeerd als overvoed. Huidige definities van calorische overvoeding zijn dus ontoereikend.
De energiebehoefte is logischerwijs afhankelijk van de leeftijd en de voedingsstatus van het kind. Ook de fase van kritieke ziekte heeft invloed op de energiebehoefte. Met deze factoren wordt geen rekening gehouden in de huidige definities van calorische overvoeding, waardoor deze definities niet consequent toegepast kunnen worden in de gehele populatie van kritisch zieke kinderen. Om de nadelige effecten van calorische overvoeding te voorkomen is een nieuwe definitie nodig die leeftijds-, voedingsstatus- en fase-afhankelijk is.

Hoofdstuk 5

Het toedienen van enterale voeding aan kritisch zieke kinderen wordt vaak uitgesteld of onderbroken, waardoor er ten opzichte van de gestelde voedingsdoelen een tekort aan energie en/of macronutriënten ontstaat. Het toevoegen van parenterale voeding zorgt ervoor dat de gestelde doelen gemakkelijker behaald kunnen worden, maar kan ook tot verschillende bijwerkingen leiden.

Hoofdstuk 5 geeft een overzicht van het wetenschappelijk bewijs voor het gebruik van parenterale voeding bij kritisch zieke kinderen. Van de 584 artikelen over dit onderwerp, werden slechts 6 kleine studies geïdentificeerd die dit onderwerp hadden onderzocht in kritisch zieke kinderen met behulp van gerandomiseerde studies. Deze studies lieten een positief effect zien van het ophogen of aanpassen van parenterale voeding, maar enkel op surrogaat uitkomstparameters (eiwitbalans, ontsteking). Een positief effect op surrogaat uitkomstparameters reflecteert echter niet altijd een positief effect op klinische uitkomstmaten, zoals duur van de beademing of verblijf op de PICU, die veel belangrijker zijn om te bepalen of een behandeling nut heeft. Hoogstaande wetenschappelijke studies naar het effect van timing, hoeveelheid en samenstelling van parenterale voeding bij kritisch zieke kinderen op klinische uitkomstmaten zijn dus nog hard nodig.

Hoofdstuk 6 en 7

Het idee dat vroeg starten van (aanvullende) parenterale voeding bij kritisch zieke volwassenen om de gestelde macronutriënt- en energie doelen te behalen de voorkeur heeft, wordt op basis van de resultaten van recente grote klinische studies niet langer ondersteund.

Samen met het UZ Leuven (België) en het Stollery Kinderziekenhuis in Edmonton (Canada) hebben wij een gerandomiseerde studie uitgevoerd onder 1440 kritisch zieke kinderen, om te onderzoeken of het later starten van parenterale voeding ook in deze populatie voordelig kan zijn. Kritisch zieke kinderen met risico op ondervoeding (bepaald aan de hand van een risicoscore) werden gerandomiseerd voor het vroeg (binnen 24 uur) of laat (op dag 8 van PICU opname) starten van parenterale voeding op het moment dat er onvoldoende enterale voeding kon worden gegeven. In beide groepen werd dezelfde hoeveelheid vocht, micronutriënten en enterale voeding toegediend.

Kinderen die de eerste week op de PICU geen parenterale voeding kregen toegediend, bleken inderdaad minder vatbaar voor nieuwe infecties, verbleven korter op de PICU en in het ziekenhuis, en waren een kortere periode afhankelijk van de beademing, dan kinderen waar parenterale voeding binnen 24 uur was gestart.

Dit positieve effect van het onthouden van parenterale voeding was onafhankelijk van het ziekenhuis waar de studie werd uitgevoerd, de ernst van ziekte, de leeftijd, de diagnose en het risico op ondervoeding. Bij kritisch zieke neonaten (kinderen < 1 maand oud) en bij kinderen met het hoogste risico op ondervoeding was het positieve effect nog groter. Deze resultaten tonen aan dat het doorvoeren van de late voedingsstrategie in alle PICUs wenselijk is bij deze groepen kritisch zieke kinderen.

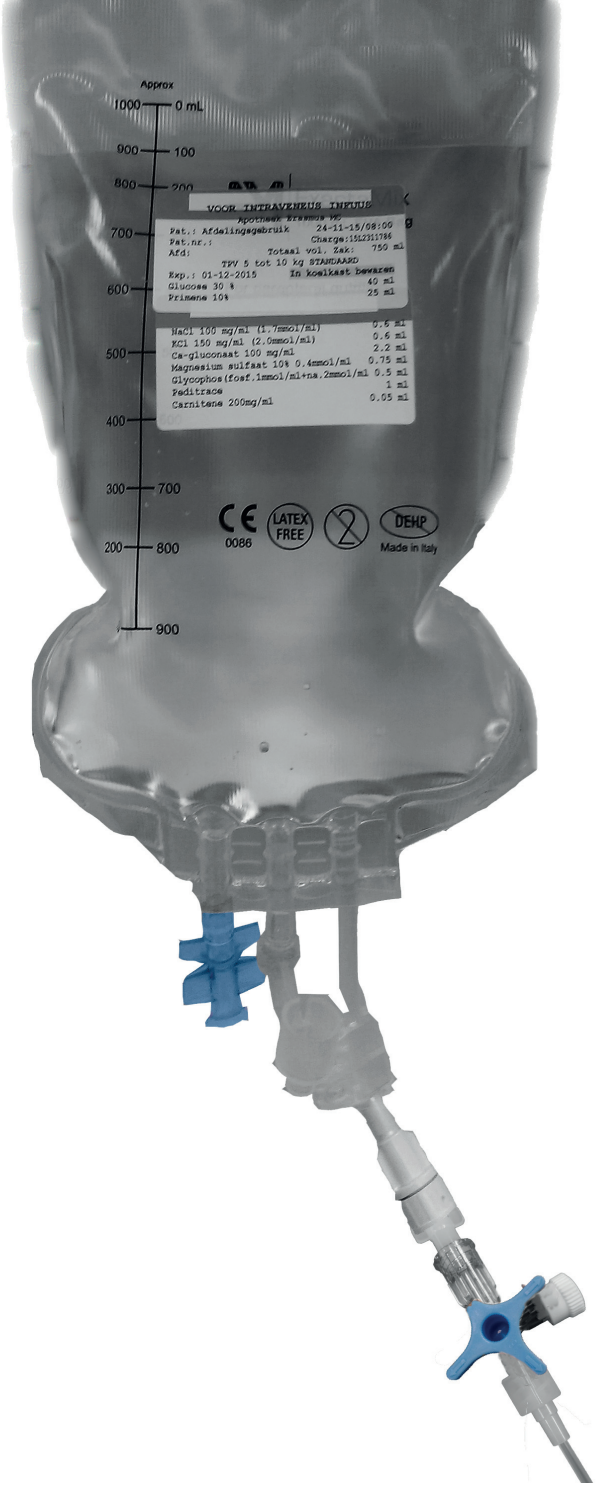
Discussie (Hoofdstuk 8)

In hoofdstuk 8 zijn de belangrijkste bevindingen van dit proefschrift gecombineerd, geanalyseerd en verder onderbouwd. Met behulp van de nieuwe bevindingen en de beschikbare literatuur, wordt de huidige stand van zaken op het gebied van voedingsstrategieën bij kritisch zieke kinderen uitvoerig beschouwd. Er worden verschillende mechanismen besproken die het positieve effect van het onthouden van parenterale voeding kunnen verklaren.

Omdat het onwaarschijnlijk is dat de optimale timing voor het starten van (aanvullende) parenterale voeding voor alle kinderen gelijk is, is meer onderzoek nodig om de timing te kunnen individualiseren. Door groepen met verschillende patiëntkenmerken te vergelijken, zowel binnen de huidige studie, als in toekomstige studies, en door meer inzicht te verkrijgen in de onderliggende mechanismen, kunnen voedingsstrategieën in de toekomst geïndividualiseerd worden om de best mogelijke uitkomst te bewerkstelligen, zowel op korte als op langere termijn. Naast deze toekomstperspectieven op het gebied van voedingsonderzoek worden er in dit hoofdstuk adviezen geven voor implementatie van de bevindingen van dit proefschrift in de dagelijkse praktijk.

PART VI

APPENDICES


Approx
1000 0 mL
900 100
800 200
700
600
500
400
300 700
200 800
900
VOOR INTRAVENEUS INFUUS
Pat.: Afdelingsgebruik 24-11-15/08:00
Pat.nr.: Charge:15L2315786
Afd: Totaal vol. Zak: 750 ml
TPV 5 tot 10 kg STANDAARD
Exp.: 01-12-2015 In koelkast bewaren
Glucose 30 % 40 ml
Primene 10% 25 ml
NaCl 100 mg/ml (1.7mmol/ml) 0.6 ml
KCl 150 mg/ml (2.0mmol/ml) 0.6 ml
Ca-gluconat 100 mg/ml 2.2 ml
Magnesium sulfaat 10% 0.4mmol/ml 0.75 ml
Glycophos(fosf.1mmol/ml+na.2mmol/ml 0.5 ml
Peditrace 1 ml
Carnitene 200mg/ml 0.05 ml
CE 0086
LATEX FREE
DEHP
Made in Italy

APPENDICES

List of abbreviations

About the author

List of publications

PhD portfolio

Dankwoord

LIST OF ABBREVIATIONS

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
A.S.P.E.N.	American Society for Parenteral and Enteral Nutrition
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CI	Confidence Interval
CRP	C-Reactive Protein
DSMB	Data Safety Monitoring Board
DNR	Do Not Resuscitate
eCRF	electronic Case Record Form
EN	Enteral Nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
ESPNIC	European Society of Paediatric and Neonatal Intensive Care
GGT	Gamma-Glutamyltransferase
GRV	Gastric Residual Volume
HR	Hazard Ratio
IC	Indirect Calorimetry
ICU	Intensive Care Unit
IQR	Interquartile Ranges
IV	Intravenous
LOS	Length Of Stay
LCT	Long Chain Triglycerides
MCT	Medium Chain Triglycerides
MREE	Measured Resting Energy Expenditure
NST	Nutrition Support Team
OR	Odds Ratio
PELOD	PEdiatric Logistic Organ Dysfunction
PEPaNIC	Pediatric Early versus Late Parenteral Nutrition In Critical Illness
PICU	Pediatric Intensive Care Unit
PN	Parenteral Nutrition
PREE	Predicted Resting Energy Expenditure
PRISM	Pediatric Risk of Mortality
RACHS	Risk-Adjustment in Congenital Heart Surgery
RCT	Randomized Controlled Trial
RDA	Recommended Dietary Allowances
REE	Resting Energy Expenditure

RQ	Respiratory Quotient
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	Standard Error of the Mean
SPN	Supplemental Parenteral Nutrition
TEE	Total Energy Expenditure
TPN	Total Parenteral Nutrition
VCO_2	CO_2 production per minute
WFPICCS	World Federation of Pediatric Intensive and Critical Care Societies
WHO	World Health Organization

ABOUT THE AUTHOR

Dorian Kerklaan was born on the 8th of April 1986 in Leiden, The Netherlands. She completed her high school (Gymnasium, cum laude) at the 'Stedelijk Gymnasium Leiden' in 2004. In the same year she moved to Maastricht to start her medical training at the Faculty of Health Medicine and Life Sciences of Maastricht University. As part of her clinical rotations, she did a clinical elective in paediatrics in the Mater Dei Hospital in Malta. After finishing her senior clinical elective in paediatrics in the Atrium Medical Centre in Heerlen, she obtained her master's degree in 2010.

In January 2011 she started working as a resident in the Erasmus MC - Sophia Children's Hospital in Rotterdam, both on the peadiatric medium care and intensive care unit. In 2012 she started her dissertation on nutritional support in critically ill children at the paediatric intensive care unit (promotor prof.dr. D. Tibboel, supervisors dr. K.F.M. Joosten, dr. S.C.A.T. Verbruggen). During this period she was a board member of the Sophia Researchers Association and organised the Theme Sophia Research Days in 2014 and 2015.

In June 2016 Dorian will start her paediatrics residency at the University Medical Centre Utrecht – Wilhelmina Children's Hospital in Utrecht and the Gelre Ziekenhuizen in Apeldoorn. Dorian currently lives in Utrecht, together with Anton van Rooij.

LIST OF PUBLICATIONS

1. **Kerklaan D*,** Fivez T*, Verbruggen S, Vanhorebeek I, Verstraete S, Tibboel D, Guerra GG, Wouters PJ, Joffe A, Joosten K, Mesotten D, Van den Berghe G. *contributed equally. Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial. Trials 2015;16:202.

2. **Kerklaan D*,** Fivez T*, Mehta NM, D. Mesotten D, van Rosmalen J, Hulst JM, Van den Berghe G, Joosten KF, Verbruggen SC. *contributed equally. Worldwide survey of nutritional practices in PICUs**.** Pediatr Crit Care Med 2016;17(1):10-18

3. **Kerklaan D*,** Fivez T*, Mesotten D, Verbruggen S, Joosten K, Van den Berghe G. *contributed equally. Evidence for the use of parenteral nutrition in the pediatric intensive care unit. Clin Nutr 2016; Nov 23 [Epub ahead of print].

4. **Kerklaan D**, Augustus ME, Hulst JM, van Rosmalen J, Verbruggen SC, Joosten KF. Validation of ventilator-derived VCO_2 measurements to determine energy expenditure in ventilated critically ill children. Clin Nutr 2016; Jan 7 [Epub ahead of print].

5. Joosten KF, **Kerklaan D,** Verbruggen SC. Nutritional support and the role of the stress response in critically ill children. Curr Opin Clin Nutr Metab Care 2016;19(3):226-233.

6. **Kerklaan D*,** Fivez T*, Mesotten D*, Verbruggen S*, Wouters PJ, Vanhorebeek I, Debaveye Y, Vlasselaers D, Desmet L, Garcia Guerra G, Hanot J, Joffe A, Tibboel D, Joosten K, Van den Berghe G. *contributed equally. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374(12):1111-22.

7. **Kerklaan D**, Hulst JM, Verhoeven JJ, Verbruggen SC, Joosten KF. Use of indirect calorimetry to detect overfeeding in critically ill children; finding the appropriate definition. J Pediatr Gastroenterol Nutr 2016; Mar 18 [Epub ahead of print].

AWARDS

Young investigators award for oral presentation. Theme Sophia Research Day 2016, Rotterdam: Early versus late parenteral nutrition in critically ill children

PhD PORTFOLIO

Name PhD student:	D. Kerklaan
Erasmus MC department:	Intensive Care and Department of Paediatric Surgery
PhD period:	July 2012 – June 2016
Promotor:	Prof.dr. D. Tibboel
Copromotors:	Dr. K.F.M. Joosten
	Dr. S.C.A.T. Verbruggen

	Year	Workload (ECTS)
General academic skills		
BROK (Basiscursus Regelgeving Klinisch Onderzoek) Erasmus University Rotterdam	2012	1.0
CPO mini course	2013-2014	0.6
Biomedical English writing and communication	2014	3.0
Integrity in scientific research	2015	2.0
Research skills		
MolMed - Basic Introduction Course on SPSS	2013	1.0
Nihes - Biostatistical Methods 1: basic principles	2014	5.7
Nihes - Regression Analysis for Clinicians	2015	1.4
Seminars and workshops		
Theme Sophia Research Days	2013-2016	1.2
2nd Erasmus Critical Care Day	2013	0.3
24th annual meeting of ESPNIC: *postgraduate course Nutrition*	2013	0.3
Fresenius Kabi Advanced Nutrition Conference on Pediatrics (FRANC Ped), Bad Homburg, Germany	2014	0.6
Young Investigator Days (Tulips)	2014-2015	0.6
(Inter)national conferences and presentations		
24th annual meeting of the ESPNIC, Rotterdam, The Netherlands: *poster presentation*	2013	1.0
7th World Congress on Pediatric Intensive and Critical Care, Istanbul, Turkey: *invited speaker & oral presentation*	2014	3.0
7th and 9th 'Nationale Voedingscongres', Arnhem, The Netherlands: *invited speaker*	2014-2016	4.0
36th ESPEN Congress, Geneva, Switzerland: *oral presentation & poster presentation*	2014	2.0
26th annual meeting of the ESPNIC, Vilnius, Lithuania: *oral presentation*	2015	2.0
ESPGHAN Young Investigators Platform: *oral presentation*	2015	2.0

	Year	Workload (ECTS)
Symposium Research group Metabolism, Endocrinology and Nutrition: *invited speaker*	2015	1.3
36th International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium	2016	0.2
Theme Sophia Research Day, Rotterdam, The Netherlands: *oral presentation*	2016	2.0
Symposium 'Sectie Intensive Care Kinderen', The Netherlands: *oral presentation*	2016	2.0
Teaching activities		
Tutoring 1st year medical students	2013	1.5
Tutoring 'Getting acquainted with the medical profession'	2014	0.5
Supervising 3 students in their research project	2014-2015	1.6
Other		
Board member Sophia Researchers Association (SOV)	2013-2015	3.0
Organisation Theme Sophia Research days	2013-2015	4.0
Research meeting Metabolism, Endocrinology and Nutrition	2013-2016	1.5
SCCM practical application of nutrition/immunonutrition	2013	0.3
ESPEN Life Long Learning in Clinical Nutrition and Metabolism	2013-2016	0.5

ECTS = European Credit Transfer and Accumulation System (1 ECTS represents 28 hours)

DANKWOORD

Het bereiken van de top van de Kilimanjaro was dan wel mijn letterlijke hoogtepunt van de afgelopen vier jaar, de inspanning die daarvoor nodig was valt volledig in het niet bij al het werk dat is geleverd voor dit proefschrift. Dat werk heb ik niet alleen gedaan, en had ik ook niet alleen kunnen doen. Daarom wil ik graag alle mensen bedanken die hebben meegewerkt om PEPaNIC en dit proefschrift tot een succes te maken.

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Het uitvoeren van de studie was ook onmogelijk geweest zonder de medewerking van alle artsen, verpleegkundigen, zorgassistenten, secretaresses en overige medewerkers van de IC Kinderen, en zonder hulp van de apothekers, apothekersassistenten en het PDMS team.
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Daarnaast wil ik een aantal personen in het bijzonder bedanken.

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werkte. Onze discussies prikkelden me elke keer om het nog net een stapje beter te doen. En wie zegt dat empathie niet aan te leren is… Ik had me geen betere aanvoerder kunnen wensen, het is een eer jouw eerste promovenda te zijn!

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Lieve Tom, het is misschien geen officiële duo-promotie, maar ik had me geen betere promotiepartner kunnen wensen. Onze samenwerking scheelde niet alleen in de grote hoeveelheid werk en stress, maar heeft het promoveren vooral een stuk leuker gemaakt!

Alle coauteurs wil ik bedanken voor de prettige samenwerking. Jessie, speciaal bedankt voor je kritische blik en uitgebreide statistische hulp. De studenten die ik de afgelopen jaren heb begeleid: Neelke, Bregje, Emma, dank voor jullie inzet voor de database, topdokters worden jullie!

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Dorian

Approx
1000 0 mL
900 100
800 200
700 300