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Original article

Achieving enteral nutrition during the acute phase in critically ill children: Associations with patient characteristics and clinical outcome

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SUMMARY

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

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

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

Conclusions: Several patient and clinical characteristics during the first week of critical illness were associated with EN intake. No independent associations were found between EN intake and clinical outcomes such as mortality, new acquired infection and duration of stay. These data emphasize the

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necessity of adequate multivariable adjustment in nutritional support research and the need for future RCTs investigating optimal EN intake.

1. Introduction

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

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

2. Methods

2.1. Subjects

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

2.2. Nutritional protocol

The local EN protocol, including caloric goal achievement, differed per research centre. The initiation and incline of EN, the type and methods, as well as the use of gastroprokinetics were prescribed via standing orders in each centre and prospectively collected in the study database for each patient [17] Supplemental Table 1 presents the nutritional and fluid practises of the three research centres which were valid during the PEPaNIC trial.

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

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

In Edmonton, Canada, energy expenditure of patients was assessed by indirect calorimetry upon admission to the PICU when

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

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

2.3. Data collection

Data on patient characteristics and gastrointestinal symptoms were prospectively collected and registered in the PEPaNIC RCT database. Characteristics investigated were demographics (early PN randomisation, age, sex, weight or BMI Z-score (defined as weight-for-age Z-score in children <1 year old and BMI-for-age Z-score in children ≥1 year old, as described previously [4]), emergency admission, diagnosis upon admission, centre, STRONGkids, PeLOD score (Paediatric Logistic Organ Dysfunction score), PIM 3 (Paediatric Index of Mortality) and Paediatric Risk of Mortality III (PRISM) score). Prior medical conditions and co-morbidities upon admission were also extracted (syndrome or genetic abnormality, malignancy, chronic disease, mechanical ventilatory or hemodynamic support and infection upon admission). At each day of admission, the nutritional intake, including initiation of EN and the total caloric and protein intake through enteral and parenteral route were recorded. Daily gastrointestinal symptoms recorded were vomiting or aspiration (yes/no), abdominal distension (yes/no), diarrhoea (≥4 times loose stool; defined watery or mushy) and large gastric residual volume (GRV; ≥50% of delivered EN over 24 h). Furthermore, clinical and feeding characteristics and treatment with 12 different medications were also collected daily. Clinical outcomes investigated were mortality, duration of PICU stay, duration of hospital stay, duration of mechanical ventilation, new acquired infections and incidence of hypoglycaemia (plasma glucose <40 mg/dl) during the first 7 days of admission. A complete list of investigated parameters is presented in Supplement File 1.

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

2.4. Statistical analyses

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

For the univariable associations, the main effect of the follow-up time variable was included in the model together with clinical outcome variables. For the multivariable association, in the fixed effects of the linear mixed model we included the main effect of the follow-up time variable, as well as baseline patient characteristics (including PICU site and early PN randomisation), daily admission-level clinical characteristics, feeding characteristics, gastrointestinal symptoms and treatment with medication. A second model included all fixed effect baseline and daily clinical variables and the clinical outcome variable of interest. The duration of stay and duration of mechanical ventilation variables were penalised for mortality as a competitive risk. Data on EN intake and gastrointestinal symptoms needed to be complete, however, multiple imputation has been used to impute missing covariate information using 30 imputed datasets [22–24]. Each imputed dataset has been separately analysed using the two-part mixed model, and the results were pooled using the formulas of multiple imputation. The fit of the model was assessed using scaled simulated residuals. No variable selection has been performed and all models. We hypothesised that patients admitted after gastrointestinal surgery had a different a priori feeding strategy, where EN would be withheld based on the discretion of the surgeons rather than EN intolerance or PICU related reasons. Therefore, sensitivity analyses were performed excluding this patient group (n = 100).

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

3. Results

Of the total PEPaNIC patient population, 690 patients (58.1% male; 50.7% surgical diagnosis) had a complete recording of gastrointestinal symptoms and nutritional assessment during the first 7 days of admission or until discharge if discharge < 7 days and were included in the analyses. Table 1 presents the baseline patient characteristics. The median age was 1.2 (IQR: 0.1–6.5) year, mean PIM3 score was −2.9 (±1.9) and 76% of the patients had an emergency admission. Nutritional risk, assessed by STRONGkids, was

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

Characteristics upon PICU admission	N = 690
Early PN randomisation	350 (50.7%)
Age, y, median (IQR)	1.2 (0.1–6.5)
Infant (age<1 y)	339 (49.1%)
Male sex	401 (58.1%)
Weight or BMI Z-score, median (IQR)[d]	−0.7 (±1.8)
Acute undernourished	59 (9.1%)
Severe acute undernourished	70 (10.8%)
Emergency admission	535 (77.5%)
Diagnostic group	
Surgical	
Gastrointestinal	100 (14.5%)
Cardiac	111 (16.1%)
Neurosurgery-Traumatic brainInjury	54 (7.8%)
Other	85 (12.3%)
Medical	
Cardiac	45 (6.5%)
Neurologic	64 (9.3%)
Respiratory	161 (23.3%)
Other	70 (10.1%)
Centre	
Leuven	0 (0%)
Rotterdam	593 (85.9%)
Edmonton	97 (14.1%)
STRONGkids risk level[a]	
Medium	577 (83.6%)
High	113 (16.4%)
PeLOD score, first 24 h in PICU, median (IQR)[b]	12 (2–21)
PIM3 score, mean (SD)[c]	−2.9 (±1.9)
PRISM III (IQR)	8 (5–14)
Malignancy	44 (6.4%)
Syndrome or genetic abnormality	
Confirmed	75 (10.9%)
Suspected	29 (4.2%)
Chronic disease	474 (68.7%)
Infection upon PICU admission	368 (53.3%)
Mechanical ventilatory support upon PICU admission	592 (85.8%)
Mechanical hemodynamic support on PICU admission	32 (4.6%)

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

high in 16.4% of patients and medium in 83.6%, whereas the median weight Z-score was −0.5 (IQR: −1.7 to 0.4), with a weight Z-score < -2 in 137 (19.8%) patients. A total of 50.7% was randomised to Early PN, with no differences between baseline patient characteristics (data not shown). Enteral intake and gastro-intestinal symptoms were collected on a total of 3208 admission days (median of 5 (IQR 2–7) days per patient). The presence of at least one gastrointestinal symptom occurred on 631 (19.7%) days, with vomiting or aspiration being the most recorded (7.9%) symptoms followed by diarrhoea (7.4%), large GRV (4.1%) and abdominal distention (2.8%).

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

3.1. Predictors for EN intake

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

3.2. EN intake and outcomes

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

Univariable associations between mean daily enteral intake as % of predicted REE during the first week and clinical outcomes showed that low EN intake was associated with new acquired infection (p < 0.001), incidence of hypoglycaemia (P < 0.001), duration of PICU stay (p = 0.017), duration of hospital stay (p < 0.001) and duration of mechanical ventilation (p = 0.024). EN was not associated with mortality on any of the time-points (Supplement Table 3; Supplement Table 4). However, after multivariable adjustment for confounders and multiple testing, the mixed model analyses did not show any significant associations between lower mean EN intake and duration of PICU or hospital stay, duration of mechanical ventilation or new acquired infection. Patients with an episode of hypoglycaemia during the first 7 days of admission had a 39% lower EN/REE intake as compared with children without hypoglycaemia (p < 0.001) (Table 3). Sensitivity analyses, which excluded patients admitted

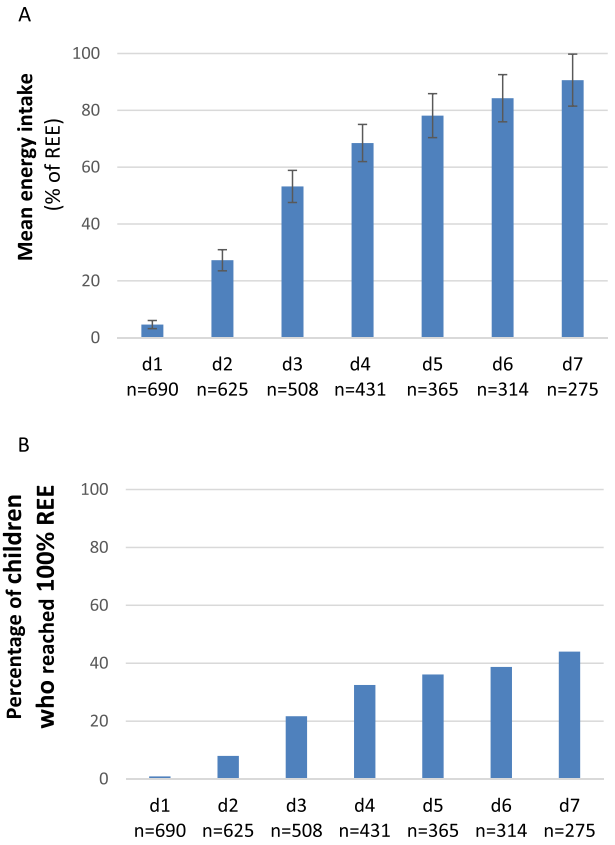

Fig. 1. A. Daily mean enteral energy intake (expressed as % of predicted resting energy expenditure (REE)) of critically ill children during first week of paediatric intensive care unit (PICU) admission. Bars represent the mean and the whiskers represent the 95% confidence interval (CI); B. Percentage of critically ill children who reached a daily mean enteral energy intake (expressed as % of predicted REE) of 100% during first week of PICU admission. Bars represent the percentage of children who reached 100% REE.

after gastrointestinal surgery, did not result in different results (Supplement Table 5).

4. Discussion

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

4.1. Predictors

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

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

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

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

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

	Coefficient[d]	% EN/REE	95% CI	p-value[e]
(Intercept)	2.961			<0.001
Baseline characteristics				
Randomisation to late vs early initiation of PN	0.043	+4.4%	−6.0; +16.0%	0.418
Day of admission	0.190	+21.0%	+18.2; +23.8%	**<0.001***
Age in years	−0.018	−1.8%	−3.1; −0.7%	**0.010**
Female vs male sex	0.078	+8.1%	−2.6; +20.0%	0.145
Malnourishment[a] (as compared with normal)				
Acute malnourished	0.147	+15.8%	−2.4; +37.5%	0.093
Severe acute malnourished	0.165	+17.9%	−2.2; +40.6%	0.067
Urgent vs elective admission	−0.143	−13.3%	−28.8; +5.6%	0.156
Diagnostic category (as compared with cardiac surgery)				
Surgical − Neurosurgery	0.169	+18.4%	−12.8; +60.9%	0.279
Surgical − Gastrointestinal	−0.672	−48.9%	−63.1; −29.3%	**<0.001***
Surgical − Other	−0.044	−4.3%	−22.5; +18.1%	0.680
Medical − Cardiac	0.069	+7.2%	−16.8; +38.1%	0.592
Medical − Neurologic	0.371	+45.0%	+10.3; +90.7%	**0.008**
Medical − Respiratory	0.328	+38.8%	+9.7; +75.7%	**0.006**
Medical − Other	0.114	+12.0%	−16.5; +50.3%	0.448
Centre Edmonton vs Rotterdam	−0.456	−36.6%	−48.4; −22.2%	**<0.001***
STRONGkids score high risk vs medium risk	0.179	+19.6%	+2.7; +39.2%	**0.021**
PIM3 score (per point added)	−0.071	−6.8%	−10.9; −2.6%	**0.002**
PRISM score (per point added)	−0.000	+0.0%	−1.0; +1.0%	0.925
Malignancy vs no malignancy	−0.027	−2.7%	−24.3; +25.0%	0.831
Syndrome or genetic abnormality vs no syndrome	0.148	+15.9%	−2.2; +37.4%	0.088
Suspicion or genetic abnormality for syndrome vs no syndrome	−0.019	−1.9%	−21.6; +22.7%	0.865
Chronic disease vs no chronic disease	0.010	+1.0%	−11.9; +15.8%	0.883
Admitted with infection	−0.047	−4.6%	−17.4%; +10.2%	0.522
Admitted with mechanical ventilation support	0.222	+24.9%	+2.0%; +52.9%	**0.032**
Admitted with hemodynamic support	−0.185	−16.9%	−36.5%; +8.8%	0.178
Daily clinical characteristics				
PeLOD score (per point added)	−0.007	−0.7%	−1.2%; −0.3%	**0.002**
Maximum CRP in mg/L (per point added)	−0.000	+0.0%	−0.1%; +0.0%	0.150
Maximum WBC in 10^9/L (per point added)	−0.005	−0.5%	−1.0%; +0.0%	**0.044**
Maximum Lactate in mmol/L (per point added)	−0.001	−0.1%	−2.3%; +2.1%	0.909
Daily feeding characteristics				
Location Tube (as compared with nasogastric tube)				
post-pyloric tube	0.269	+30.9%	+16.5; +47.0%	**<0.001***
No tube	−0.175	−16.1%	−35.6; +9.9%	0.202
Main type of feeding (as compared with no Standard formula)				
Human Milk	0.012	+01.2%	−12.3; +16.8%	0.866
Energy enriched formula	0.220	+24.6%	+7.7; +44.2%	**0.003**
Peptide formula	0.287	+33.2%	+5.5; +68.3%	**0.016**
Oral intake	−0.249	−22.0%	−37.7; −2.5%	**0.029**
No formula	−1.284	−72.3%	−84.9; −49.3%	**<0.001***
Daily gastro-intestinal symptoms				
Large Gastric residual volume[b] (>50% of EN intake)	−1.032	−64.4%	−71.7; −55.2%	**<0.001***
Presence of diarrhoea[c]	0.096	+10.1%	−8.3; +32.1%	0.302
Presence of vomit and/or aspiration	0.124	+13.2%	−10.2; +42.7%	0.293
Presence of abdominal distention	−0.314	−27.0%	−48.7; +3.9%	0.081
Presence of ≥ EN intolerance parameter	−0.053	−5.2%	0.784; +14.7%	0.584
Daily treatment with medication				
Treatment with anti-emetics	−0.119	−11.2%	−24.3; +4.2%	0.144
Treatment with oral laxation	0.175	+19.1%	+4.9; +35.3%	**0.007**
Treatment with acid suppression	−0.057	−5.5%	−15.4; +5.5%	0.313
Treatment with rectal enema	0.086	+8.9%	−7.2; +27.8%	0.294
Treatment with corticosteroids	−0.084	−8.0%	−17.9; +3.0%	0.147
Treatment with antibiotics	−0.114	−10.8%	−20.2; −0.3%	**0.045**
Treatment with benzodiazepines	−0.110	−10.4%	−19.6; −0.2%	**0.045**
Treatment with opiates	−0.097	−9.2%	−18.5; +1.2%	0.081
Treatment with vasopressors	−0.217	−19.5%	−30.6; −6.7%	**0.004**
Treatment with inotropic agents	−0.242	−21.5%	−31.6; −9.9%	**<0.001***
Treatment with hypnotics and/or barbiturates	−0.005	−0.5%	−9.9; +9.8%	0.922
Treatment with Alpha-2 antagonist	−0.055	−5.3%	−18.2; +9.6%	0.465

Abbreviations: CRP: C-reactive protein; EN: enteral nutrition; GRV: gastric residual volume; PeLOD: Paediatric Logistic Organ Dysfunction; PIM: paediatric index of mortality; PN: parenteral nutrition; PRISM: Paediatric Risk of Mortality; REE: resting energy expenditure; WBC: white blood count.
Bold: Statistically significant before correction for multiple comparisons using Holms method.

[a] Children younger than 1 year: weight-for-age Z-score; children 1 year or older: body mass index−for-age Z-score.

[b] Large gastric residual volume was defined as volume in ml more than 50% of prescribed EN feeding per 24 h.

[c] Diarrhoea was defined as four or more loose stools per 24 h.

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

[e] *Statistically significant after correction for multiple comparisons using Holms method.

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

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

Abbreviations: PICU: paediatric intensive care unit. REE: Resting energy expenditure.
Bold: Statistically significant before correction for multiple comparisons using Holms method.
[a] The reported coefficients, and the corresponding 95% confidence intervals and p-values are for the marginalized mean of enteral nutrition intake. The exponent of the coefficients quantifies the multiplicative increase in the average of the main outcome. Hence, an exponent of the coefficients of 0.90 reflect a 10% lower mean enteral intake expressed as a % of REE.
[b] *Statistically significant after adjusting for multiple comparisons using Holms method. Supplement File 1 presents the complete list of included baseline and daily parameters for multivariate correction.

indicating the robustness of the predictors. Lastly, centre was also associated with the amount of EN intake, with a higher EN intake in Rotterdam. This is most likely the result of differences in local enteral feeding protocols and thereby differences in caloric targets during the acute phase of illness.

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

4.2. Outcomes

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

Methodological differences between the PIN studies and our study could explain the differences in results. Most importantly, the availability of extensive prospectively collected detailed daily characteristics and the large number of children enabled us to perform methodologically sound multivariable analyses adjusting for 40 baseline and daily clinical parameters with a potential mediating effect on clinical outcomes. Selecting only a small number of variables into the model based on the univariable coefficient quantities can provide misleading conclusions due to inappropriate adjustment of variables needed for control in the model [40]. Univariable analyses from our study showed indeed the frequently referenced association between higher achievement of EN and improved outcome [1,5]. However, multivariable adjustment without pre-selection deemed imperative due to raised concerns on the potential influence of predictors on the amount of energy and protein intake as well as on clinical outcome. The PIN studies used pre-selection methods and included only a small number of confounders in their model. As such, EN intake could directly be related to outcome or indirectly reflect one or more underlying predictors, such as illness severity, resulting in worsened feeding intolerance and subsequently lower intake in the sickest children. Second, in both PIN studies data collection was not complete with illness severity scores reported to be missing in up to 31% of the participants [1,5]. Additionally, illness severity was found to be a significant confounder between the association of protein intake and 60-day mortality [5]. Hence, the influence of the severity of illness or other possible predictors cannot be ruled out in the observational PIN studies. A third important difference is the categorisation of essential continuous variables. For instance, the variable EN intake was categorized into three groups (energy/goal <33%, 33–67% and >67% or protein/goal <20%, 20–60% and >60%). Also, illness severity was categorised due to different scores used in different research centres in the PIN studies.

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

on timing and/or amount of EN where a trophic feeding strategy deserves to be taken into account.

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

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

5. Conclusions

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

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Availability of data and materials

The datasets and analyses used for the current study are available from the corresponding author on reasonable request.

Authors' contributions

RE, JH, BdK, KJ and SV designed the protocol for this subanalysis of the PEPaNIC study. RE, DR, JH, BdK, KJ and SV designed the statistical analysis plan, and RE and DR performed the statistical analyses. All authors interpreted the data, drafted and revised the manuscript; All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the study.

Conflict of interest

The authors declare that they have no competing interest.

Abbreviations

BMI	body mass index
CI	confidence interval
EN	enteral nutrition
GRV	gastric residual volume
IQR	interquartile range
PeLOD	paediatric logistic organ dysfunction score
PICU	paediatric intensive care unit
PIM 3	paediatric index of mortality 3
PINS	paediatric international nutrition study
PRISM III	paediatric risk of mortality III
RCT	randomized controlled trial
REE	resting energy expenditure
SD	standard deviation
WFA	weight-for-age

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.09.005.

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