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Enteral feeding of children on non-invasive respiratory support: a four centre European study

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Enteral feeding of children on non-invasive respiratory support: a four centre European study

Abstract

Objective: To explore enteral feeding practices and the achievement of energy targets in children on Non-invasive respiratory support (NRS), in four European Pediatric Intensive Care Units (PICUs).

Design: A four centre retrospective cohort study

Setting: Four PICUs: Bristol UK, Lyon France, Madrid Spain, Rotterdam the Netherlands.

Patients: Children in PICU who required acute NRS in the first 7 days. The primary outcome was achievement of standardised kcal/goal.

Interventions: Nil

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

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

Keywords: Nutrition; intensive care; critical care; child; infant; non-invasive ventilation

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Conflict of interest declarations

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Tweet: Children on NRS tolerated feeding well, with few complications, but further studies are now required to determine the optimal timing and feeding method during NRS

Introduction

Enteral nutrition (EN) delivery in children on non-invasive respiratory support (high-flow nasal cannula (HFNC), bilevel positive airway pressure (BLPAP) and continuous positive airway pressure (CPAP)) remains challenging. Clinical staff are concerned about the potential need for escalation of treatment and subsequent intubation and of the risk of aspiration. A large study of risk factors for delayed EN in the United States (US) Pediatric Intensive Care Units (PICUs), found non-invasive ventilation was the most significant risk factor for delayed EN [1]. Furthermore, a single centre US study reported enteral feeding was possible in these children, with 64% children receiving EN within 24 hours (54% orally, 30% transpylorically and 7% gastric feeding) [2]. This contrasts with a multicentre adult ICU study in France, which found three-fifths of patients receiving non-invasive ventilation fasted for the first 2 days [3]. The use of non-invasive respiratory support (NRS) is increasing in children worldwide, in efforts to reduce the need for intubation and invasive ventilation [4]. Despite the lack of an accurate and clinically available method of predicting energy expenditure in children on NRS, they are likely to have a higher work of breathing (WOB) (and higher EE) than those on invasive ventilation. As increasing evidence shows associations between inadequate nutrition intake and impaired clinical outcomes in invasively ventilated children [7-10], the impact of this for children on NRS may be worse, particularly in infants and already malnourished children. Efforts to prevent faltering growth occurrence on PICU are recommended in both the ASPEN 2017 and ESPNIC 2020 guidelines. However, these are based on studies in invasively ventilated children, rather than in children on non-invasive ventilation. We lack evidence in this subgroup of critically ill children; thus, we wanted to investigate practices with regards to EN in children receiving NRS across four European PICUs as a first step.

Firstly, we wanted to examine the child’s achievement of energy goals whilst on NRS. Secondly, we wanted to describe the time to initiate EN after NRS commencement; the duration of nil per oral times on NRS**;** the EN site and delivery method and reported gastrointestinal complications on NRS. Then we explored whether any associations existed between main NRS mode, or whether step up or down on EN delivery and percentage of energy targets achieved

Materials and methods

STUDY POPULATION

A retrospective cohort study was undertaken to describe current practices around enteral feeding of all consecutive children who met the study inclusion criteria in four European PICUs receiving some form of acute non-invasive respiratory support: HFNC, CPAP and BLPAP between 2018 – March 2019. We only included children aged 0-17 years receiving acute NRS with no limitation on the duration of NRS and collected data for the first 7 days of NRS and excluded children on chronic long-term respiratory support and preterm infants (<37 weeks gestational age).This period of NRS may have been before or after intubation and it may occur at any time point in the child's PICU stay.

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

Four European centres participated: (Bristol United Kingdom, Lyon France, Madrid Spain and Rotterdam the Netherlands) and collected data on 50 to 100 patients per centre.

Settings: Bristol PICU is an 18-bedded combined general and cardiac PICU, Lyon is a 23-bedded general PICU, Rotterdam is a 24-bedded combined general and cardiac PICU and Madrid is a 11-bedded combined general and cardiac PICU. All units deliver NRS regularly. Supplementary file 1 summarises local unit protocols and practices.

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

OUTCOMES

An important goal of our study was to examine the child's achievement of both their unit derived energy goal and a standardised energy goal (85% Recommended Daily Allowance (RDA) on NRS across the four sites. As no current recommendation exists on how much and how to feed NRS children, we used 85% of RDA as an assumption based on the mean of Schofield (in critically ill intubated sedated children) and RDA (healthy children).This was calculated as: [(total feeds given during NRS in mL, max 7 days) x (feed concentration in kcal/mL)] x 100 / (number of days of NRS in days) / (85% RDA as goal in kcal/d). The definitions for other outcomes were defined and agreed by the four centres (Supplementary File 2).

STATISTICAL ANALYSIS

Data was collected in Microsoft Excel, checked, anonymised and cleaned before combining into one database, exported directly into IBM SPSS v22 for analysis. Descriptive statistics were summarised by median (IQR) and Mean (SD) if appropriate and numbers (percentages). Data was tested for normality using the Shapiro Wilks test. Non-parametric tests (Spearman's Rho) were used for testing associations between non-normal variables with the primary outcome, and Mann-Whitney or Kruskall Walis to test between categorical variables and the non-normally distributed primary outcome. Stepwise multivariate linear regression analysis was used to identify if any patient or practice variables were associated with percentage of achieved energy targets (% energy intake compared to 85% RDA goal). Investigated variables were age, Paediatric Index Mortality 2 score, NRS initiation, main mode used, Starting Fraction of Inspired Oxygen (FiO2), Inspiratory Positive Airway Pressure (IPAP), Expiratory Positive Airway Pressure (EPAP), highest FiO2, IPAP and EPAP, the child's feeding method and route. Variables were included in the multivariate model if the univariate association with the outcome % achieved energy targets had a significance of $P \leq 0.1$. The multivariate models included the PICU site as a fixed effect to account for. Multicollinearity was assessed using Spearman correlation with a cut-off value of 0.5. The constant, unstandardized beta values with their corresponding standard errors, 95% confidence intervals and P-values were reported for multivariate linear regression model. The normality assumption was not met for the main outcome variable energy achievement, however, due the large cohort group it was considered acceptable under the central limit theorem [5]. Results are reported as standardized beta, standard error, or beta values, and corresponding 95% confidence interval. All P-values were two sided and less than 0.05 were considered as statistically significant.

Results

Three hundred twenty-five children were included (Bristol 104; Lyon 99; Madrid 72; Rotterdam 50). The median (IQR) age and weight were 3 months (1-16) and 5 Kg (4-10) respectively, WAZ score 0.74 (-1.8 -0.39) with 66% children admitted with respiratory failure (Table 1). The patient recruitment number and profile were significantly different between centres (Table 2). The median duration of NRS was 3 days (IQR 2-5) and 190/325 (58.5%) received NRS to prevent intubation and 41.5% as a step down after extubation. Across the four units the main mode of NRS used was High Flow Nasal Cannula (HFNC) 43.7%, Bilevel Positive Airway Pressure (BLPAP) 33.2% and Continuous Positive Airway Pressure (CPAP) 21.2%, with 1.8% patients on Neurally Adjusted Ventilatory Assist (NAVA).

Overall, children received a median of 56% (25-82%) of their energy goals (compared to a standardised 85% RDA) target whilst they were receiving NRS. However, large variability was seen across centres (Table 3). Across all centres the median (IQR) time to first EN after NRS initiation was 4 hours (1-12) but varied between centres. The median percentage of time nil per oral whilst on NRS was 5 hours (IQR 2-14.5). Of the children enterally fed, most children (93.8%) were fed via the gastric route, with 48.4% of these, fed continuously. Only 6.2% were fed post-pyloric. Relatively few (10.8%) received normal oral/bottle and 17 (5.3%) were nil per oral (Table 3). Children receiving continuous feeds achieved significantly more of their energy goals, compared to bolus feeds (mean 70.5% vs 47.8% respectively ($p=<0.001$). Of the 6.2% children fed via the post-pyloric route, they received significantly more of their energy goal (mean 76.8% post-pyloric vs 57.6% $p=0.012$) however, these factors were not significant in the multivariate model.

Overall children receiving HFNC achieved less of their mean energy goal achievement (42.1%) compared to those on BLPAP (68.5%) or CPAP (63.2%) ($p=<0.001$), but this was highly centre dependant and not significant in the multivariate model. Children in whom NRS was initiated as 'step-down' received less than those in whom it was 'step-up' (mean 49% vs 61.9% respectively $p=0.001$) and this was significant only in univariate analysis ($p=<0.001$). In our multivariate analysis a higher age and bolus feeding were associated with lower achievement of standardised target energy goals (Table 4).

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

Discussion

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

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

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

In our study no NRS parameter was significantly associated with a lower achievement of energy targets, whereas Leroue et al [2] found BLPAP itself was a significantly factor for delayed EN with the reported median IPAP at initiation (16cm H20). However, only 18% of children in this US study received HFNC compared to nearly half (44%) of our sample. Surprisingly, in our study, the children receiving HFNC received significantly less of their energy goal compared to children on BLAP and CPAP. There was significant between-centre variation in the use of HFNC however, when corrected for centre there was no significant effect, and in the multivariate analysis mode of NRS was not significant. Two centres (both having a cardiac surgical population) used significantly more HFNC and more step-down HFNC than the other two centres. It may be the impact these fluid restricted post-operative cardiac surgical children may have impacted on this. on this finding of lower energy targets.

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

Few children in our study reached their nutritional targets during NRS: this may be partly due to the centre practices consisting of a progressive increase of enteral nutrition during the first hours / days of PICU stay and ventilation support and impacted also by the severe fluid restriction of children with cardiac failure and post-operative cardiac surgery. However, we did see a significantly higher achievement of energy goal in children continuously fed, compared to those fed by intermittent bolus feeds. However, this practice varied by centre, and future prospective studies are needed investigate this further in children on NRS. In ventilated children, recent recommendations found neither method was superior [16] but this may be different in children on NRS. Similarly, in the few patients receiving post-pyloric feeding (in only two centres), they achieved higher energy goals, but these are small numbers. In the same review [16] they found no difference in energy goals by either method in invasively ventilated children.

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

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

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

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

Conclusions

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

Author contributions

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Table and Figure legends

Table 1: Patient demographics by centre

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

Table 3: Variation by centres in Enteral Nutrition Practices

Table 4. Effect of key variables on the achievement of energy targets

Supplementary File 1: Detailed centre nutrition protocols

Supplementary File 2: Outcome definitions

Table 1 Patient demographics variation by centre and overall

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

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

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

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

Table 3: Variation across centres in Enteral Nutrition Practices

Nutrition variable	**Bristol**	**Lyon**	**Madrid**	**Rotterdam**	**Total**	
Feeding tube tip site	N 95	N 99	N55	N 40	N 289	<0.01
Gastric	85(89.5%)	98 (99.0%)	40 (72.7%)	31 (77.5%)	254 (87.9%)	
Post pyloric	0	0	13 (23.6%)	5 (12.5%)	18 (6.2%)	
Gastrostomy	10 (10.5%)	1 (1.0%)	2 (3.6%)	4 (10%)	17 (5.9%)	
Feeding route	N 104	N 99	N 72	N 50	N 325	<0.01
Enteral	89 (85.6%)	99 (100%)	55 (76.4%)	30 (60%)	273 (84.0%)	
Oral	11 (10.6%)	0	16 (22.2%)	8 (16%)	35 (10.8%)	
NBM	4 (3.8%)	0	1 (1.4%)	12 (24%)	17 (5.2%)	
Main enteral feed method during NRS	N 88	N 99	N 55	N 30	272	<0.01
Continuous	2 (2.3%)	96 (97.0%)	46 (83.6%)	12 (40.0%)	156 (57.3%)	
Bolus/Intermittent	86 (97.7%)	3 (3.0%)	9 (16.3%)	18 (60.0%)	116 (42.6%)	
Energy targets used	85% RDA	85% RDA	85% RDA	Individualized*		
Energy goals and fasting	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
0.85% of RDA as energy goal (kcal/d)	497 (297-900)	340 (291-429)	467.5 (377.2-837.3)	817.9 (396.3-1355.8)	425.0 (314.5-850.0)	<0.01
At initiation of NIRS estimated energy requirements (kcal/d)	497 (297-900)	340 (291-429)	467.5 (377.2-837.3)	529.9 (241.3-974.3)	442.0 (320.0-782.0)	<0.01
Time (hours) first EN	3 (2-5)	3 (1-15)	6 (1-14)	11.5 (2.0-21.1)	4 (1-12)	<0.01
NBM hours during NRS	4 (2-6)	5 (1-16)	6 (1-16)	13.5 (4.5-24)	5 (2-14.5)	<0.01
Percentage of hours NBM during total NRS	12.5 (4.1-25)	6.4 (1.2-19.3)	9 (2.0-26.2)	37 (15.4-100)	11.8 (2.9-27.6)	0.02
Energy received compared to centre goal (%)	34.5 (17.6-59)	70.8 (51.9-85.2)	81.9 (50.5-95.8)	22.3 (0-72.7)	56.2 (24.7-79)	<0.01
Energy received compared to 0.85%RDA (%)	34.5 (17.6-59)	70.8 (51.9-85.2)	81.9 (50.5-95.8)	14.4 (0-53.2)	55.9 (24.9-81.8)	<0.01
Gastrointestinal effects						

Any vomiting (yes/no)	13/104 (12.5%)	19/99 (19.2%)	15/72 (20.8%)	7/50 (14.0%)	54/325 (16.6%)	0.4
Any other Gastrointestinal complications?	5/104 (4.8%)	11/99 (11.1%)	14/72 (19.4%)	10/50 (20.0%)	40/325 (12.3%)	<0.01
If Any, other GI complications?	N 5 (4.8%)	N 11 (11.1%)	N 14 (19.4%)	N 10 (20%)	40 (12.3%)	<0.01
Regurgitation	0	11 (100%)	0	0	11 (27.5%)	
Diarrhoea	0/104	0/99	0/72	2 (20.0%)	2 (5.0%)	
High GRV	3 (60%)	0	0	7 (70.0%)	10 (25.0%)	
Abdominal distension	2 (40%)	0	5 (35.5%)	1 (10.0%)	8 (20.0%)	
Constipation	0	0	9 (64.3%)	0	9 (22.5%)	
Aspiration	0/104	5/99 (5.0%)	0/72	0/50	5/325 (1.5%)	<0.01

*: Rotterdam energy goals for enteral nutrition are based on the Schofield equation for weight for the first day of admission and on the Recommended Dietary Allowances (RDA, Dutch Health Council) for the subsequent days

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

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

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

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