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Risk Factors for Delayed Enteral Nutrition in Critically Ill Children

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Abstract

Objective—Delayed enteral nutrition (EN), defined as EN started ≥ 48 hours after admission to the pediatric intensive care unit (PICU) is associated with an inability to achieve full EN and worse outcomes in critically ill children. We reviewed nutritional practices in 6 medical-surgical PICUs and determined risk factors associated with delayed EN in critically ill children.

Design—Retrospective cross-sectional study using medical records as source of data

Setting—Six medical-surgical PICUs in northeastern United States

Patients—Children < 21 years old admitted to the PICU for ≥ 72 hours excluding those awaiting or recovering from abdominal surgery.

Measurements/Main Results—A total of 444 children with a median age of 4.0 years were included in the study. EN was started at a median time of 20 hours after admission to the PICU. There was no significant difference in time to start EN among the PICUs. Of those included, 88 (19.8%) children had delayed EN. Risk factors associated with delayed EN were: non-invasive (odds ratio [OR]: 3.37; 95% CI: 1.69-6.72) and invasive positive pressure ventilation (OR: 2.06; 95% CI: 1.15-3.69), severity of illness, (OR for every 0.1 increase in Pediatric Index of Mortality 2 score: 1.39; 95% CI: 1.14-1.71) as well as procedures (OR 3.33; 95% CI: 1.67-6.64) and; gastrointestinal disturbances (OR: 2.05; 95% CI: 1.14-3.68) within 48 hours after admission to the PICU. Delayed EN was associated with failure to reach full EN while in the PICU (OR 4.09; 95% CI: 1.97-8.53). Nutrition consults were obtained in less than half of the cases and none of the PICUs employed tools to assure the adequacy of energy and protein nutrition.

Conclusions—Institutions in this study initiated EN for a high percentage of patients by 48 hours of admission. Non-invasive positive pressure ventilation was most strongly associated with delay EN. A better understanding of these risk factors and assessments of nutritional requirements should be explored in future prospective studies.

Keywords

nutrition; enteral nutrition; non-invasive positive pressure ventilation (NPPV); vasopressors; procedures; gastrointestinal

Introduction

Providing adequate nutrition to critically ill children is both crucial and challenging. Critically ill children have fewer energy reserves and more variable protein and energy requirements than critically ill adults (1, 2). During a time of profoundly altered metabolism, the afflicted child must satisfy not just current nutritional needs, but also the demands of somatic and neurological development. Malnutrition, which is commonly noted in children admitted to the pediatric intensive care unit (PICU), persists throughout the hospitalization, and has been associated with a complicated PICU course and increased mortality (2-4). Suboptimal nutrition during this period can exacerbate these problems (1).

Enteral nutrition (EN) is the preferred route in children with an intact gut. Compared with parenteral nutrition, EN may be easier to initiate, less costly and associated with lower risk

of infection (5, 6). In addition, EN has been associated with improved nutritional indices and clinical outcomes including a nearly 4-fold decrease in mortality in critically ill, mechanically ventilated children (3, 7, 8).

Early EN, though variably defined by investigators, promotes the achievement of energy and protein nutrition goals and is associated with improved survival in children in the PICU (9-12). In a multicenter retrospective study of 5105 critically ill children, 40% of them had EN delayed beyond 48 hours after admission to the PICU. Those who received early EN had nearly double the rate of survival from the PICU compared with those for whom EN was delayed (10). Morbidity and mortality benefits from early EN have been also been shown across a range of critical illness, including those with severe burn and traumatic brain injury (11, 13, 14). As a result, greater scrutiny is warranted for factors that interfere with both the advancement and initiation of EN.

Much of the current literature relates to barriers to achieving caloric goals for EN in the PICU. These barriers can be divided into patient characteristics (e.g. severity of illness, diagnosis and gastrointestinal intolerance) and treatment factors (e.g. use of neuromuscular blockers, vasoactive medications, mechanical ventilation and procedures) (15-17). Little is known about obstacles to the initiation of EN although it is probable that they would be similar to those associated with the inability to achieve nutritional goals. Since many of the obstacles to achieving nutritional goals may be modifiable, it is possible that barriers to initiation of EN may be modifiable as well (12, 16, 18). The aim of this study was to determine the factors associated with delayed EN in critically ill children.

Subjects and Methods

Study Design

We conducted a retrospective cross-sectional study of nutritional practices across 6 PICUs in northeastern United States: Baystate Children's Hospital, Connecticut Children's Medical Center (CCMC), Maria Fareri Children's Hospital (MFCH), University of Massachusetts Memorial Children's Medical Center, Women and Children's Hospital of Buffalo and Yale-New Haven Children's Hospital (YNHCH) in 4 discontinuous months in 2011 to capture the seasonal variation of diagnoses in critically ill children. All participating PICUs admit medical-surgical children while 3 of them also care for post-operative cardiac children (CCMC, MFCH and YNHCH). When combined, the 6 PICUs represent an annual admission rate of nearly 6,000 children and a total of 91 beds. The Institutional Review Board of each institution approved the study and granted waivers of consent.

Subjects

The study included all children <21 years old who were admitted to the participating PICUs for ≥ 72 hours. This period was selected to exclude children with low severity of illness or those who were moribund on admission. Children who were admitted for abdominal surgery were excluded as they are typically not fed during the initial days before and after the surgery. We identified eligible subjects using cost-accounting databases maintained at each

participating institutions. Each patient's medical records were reviewed to confirm eligibility.

Data Collection

All data were collected from the patient's medical records. We abstracted the patient's age, weight, z score of weight for age, gender, severity of illness expressed as pediatric index of mortality 2 (PIM 2) score and diagnosis on admission. At 48 hours after admission, we recorded whether the patient was receiving respiratory support (none, non-invasive or invasive positive pressure ventilation), neuromuscular blockade, vasopressors or fluid restriction, and whether procedures, gastrointestinal disturbances or nutrition consult had occurred. From admission, the following times were calculated: start of EN, achievement of full EN, nutrition consult (a registered hospital dietician), and discharge from the PICU. If performed, we collected data on studies used to assess the adequacy of nutrition (e.g., nitrogen balance calculation, indirect calorimetry, albumin, and prealbumin), urinalysis, and daily energy and protein intake calculation.

These data points were defined as follows:

Non-invasive positive pressure ventilation (NPPV) — bi-level (BiPAP) or continuous positive airway pressure (CPAP) ventilation via mask or nasal prongs, or high flow nasal cannula (HFNC)

Invasive positive pressure ventilation — respiratory support with mechanical ventilator via endotracheal tube or tracheostomy

Vasopressors — dopamine, dobutamine, epinephrine, norepinephrine or phenylephrine

Fluid restriction — intravenous fluids maintained at less than full maintenance

Procedures — included, but were not limited to endotracheal intubation, placement of a Central venous catheter or chest tube, surgical or radiologic interventions

Gastrointestinal disturbances — “excessive” gastric residual volumes as arbitrarily defined in each PICU, vomiting, abdominal distension, constipation and diarrhea

Early EN – enteral nutrition begun by 48 hours of admission with the intent to advance feeds regardless of mode of delivery (i.e., oral, nasogastric, nasojejunal or via gastrostomy)

Full EN — 100% of the volume prescribed by the nutrition or care team

Statistical Analysis

We divided the children into 2 groups based on the time to start EN. EN was started <48 hours from PICU admission in children in the early EN group and ≥48 hours in those in the delayed EN group. Continuous, categorical and time to event data were compared using Mann-Whitney U, chi-square and log-rank tests, respectively. We performed logistic regression with backward elimination at a threshold of $p > 0.10$ to identify potential risk factors for delayed EN. Based on prior literature and discussion among investigators, we hypothesized *a priori* that age, severity of illness, cardiac surgery, traumatic brain injury,

cancer, higher levels of respiratory support, use of vasopressors, fluid restriction, procedures, gastrointestinal disturbances, or absence of nutritional consultation may be associated with delayed EN (18, 19).

We conservatively estimated that 40% of the children in the PICU would have delayed EN (1, 7, 16). We would need a minimum of 300 children to have sufficient statistical power for the regression model. This sample size would provide us with 10 children with delayed EN for each covariate in the model. Data is presented as median (inter-quartile range [IQR]) and counts (percentage), where appropriate. Magnitudes of association are presented as odds ratios (OR) with 95% confidence interval (CI). All statistical analyses were evaluated at a 2-tailed level of significance of 0.05 and were performed using Stata 13 (StataCorp, College Station, TX).

Results

During the 4 study months, there were 444 children who fulfilled our eligibility criteria (Table 1). The median age was 4.0 years (IQR: 0.5-11.9 years) and 58.3% of them were males. The median PIM 2 score was 0.011 (IQR: 0.004-0.035). The most common diagnoses were respiratory (45.1%), neurologic (16.7%) and cardiovascular (12.4%).

Nutrition services were consulted for 48.9% of the children. The consults occurred at a median of 39 hours (IQR: 20-67 hours) after admission to the PICU. Multiple tools, including the World Health Organization, Seashore and Schofield equations and Dietary Reference Intakes, Mifflin-St. Jeor and Ireton-Jones formulas, were used to estimate energy requirements. Daily energy calculation occurred in 57.0% of children. Serum albumin was measured in 41.0% of the children, whereas prealbumin was assessed in only 3.8% of the children. None of the PICUs used indirect calorimetry to measure resting energy expenditure nor calculated protein balance. Only one of 6 PICUs had a formal nutrition protocol in place and only one had a clearly defined and enforced policy on gastric residual volumes and one PICU proscribed its measurement.

EN was started at a median time of 20 hours (IQR: 6-42 hours) after admission to the PICU (Figure 1). There was no significant difference in the time to start EN among the 6 PICUs ($p=0.59$). A total of 356 (80.2%) and 88 (19.8%) children were included in the early and delayed EN groups, respectively (Table 1). In the unadjusted analyses, children with delayed EN were more severely ill than those who had early EN. The distribution of diagnoses on admission was also different between groups with trauma ($p=0.03$) and toxic ingestion ($p=0.02$) more common in the delayed EN group. At 48 hours after admission, children with delayed EN had higher levels of respiratory support, were more likely to be receiving neuromuscular blockade or vasopressors, and more likely to have had a procedure. The median times to full EN in the early and delayed EN groups were 30 hours (IQR: 13-56 hours) and 96 hours (IQR: 67-144 hours), respectively ($p<0.001$) (Figure 2). While in the PICU, 93.3% of children with early EN and 78.4% with delayed EN received full EN ($p<0.001$). Compared with the delayed EN group, the OR of achieving full EN in the early group was 3.81 (95% CI 1.98-7.34). The association remained significant after adjusting for

severity of illness, length of stay in the PICU and site (OR: 4.09; 95% CI: 1.97-8.53). The lengths of stay in the PICU were similar between the 2 groups.

The level of respiratory support at 48 hours was associated with delayed EN. Compared with no support, the OR of delayed EN in children with NPPV and invasive positive pressure ventilation were 3.37 (95% CI: 1.69-6.72) and 2.06 (95% CI: 1.15-3.69), respectively. Other factors associated with delayed EN were severity of illness (OR for every 0.1 increase in PIM2 score: 1.39; 95% CI: 1.14-1.71), procedures (OR: 3.33; 95% CI: 1.67-6.64) and gastrointestinal disturbances (OR 2.05; 95% CI: 1.14-3.68) within 48 hours of admission to the PICU (Table 2). Neuromuscular blockade at 48 hours, which was significant in the unadjusted analysis but was not pre-specified, was not associated with delayed EN in the full model (OR 1.35; 95% CI: 0.56-3.23) and was eliminated.

Discussion

This study presents a snapshot of current nutritional practices in 6 medical-surgical PICUs in northeastern United States. We found that higher levels of respiratory support, increased severity of illness, procedures, and gastrointestinal disturbances were associated with delayed EN. NPPV has not been previously associated with delayed EN. Our review of PICU management at the participating institutions also revealed a broad commitment to early EN, but there was significant variance in practice when compared with current consensus guidelines and recent research.

A total of 80.2% of our patients received early EN. This level was higher than anticipated, but a wide range has been described (1, 10, 12, 17). Consistent with previous reports, early EN increased the odds of reaching goals feeds in our cohort (20). Yet even more important than this advantage may be the association that has been described between early EN and clinical outcomes such as mortality (10, 11). Since there are few absolute contraindications to its use, it is reasonable to examine perceived obstacles to initiating EN in critically ill children.

Prior investigation has associated invasive mechanical ventilation with both the promotion and delay of EN, yet the influence of NPPV in this context has not been evaluated (10, 17). The practice has been safely performed in very low birth weight premature infants but there is limited data on its safety when used in older children (21). This is an issue of growing relevance as the use of NPPV is increasingly employed as definitive, rather than “bridging” therapy. Our results are more consistent with the historic reluctance to enterally feed critically ill children on NPPV than attitudes expressed recently by pediatric intensivists. Of 81 intensivists surveyed, 91% did not view NPPV as a contraindication to starting EN (22). If one assumes similar advantages from EN in children on NPPV compared with other critically ill children, attention should be paid to the discordance between attitude and practice. Future efforts could more clearly define the risks of EN, such as aspiration, in children on NPPV and explore methods (e.g. post-pyloric feeding tubes) to attenuate them (23, 24).

Severity of illness was associated with delayed EN in our study, suggesting that EN was often withheld from the “sickest” patients. It is interesting that this risk factor is not consistently described as a threat to achieving full EN (12, 18). In fact, PICU caregivers have acknowledged a greater reluctance to start EN for patients who are “too ill” than those frankly “hemodynamically unstable” (25). This attitude is reflected in our study in which severity of illness, but not vasopressor use, was associated with delayed EN. Interestingly, severity of illness scores have not been shown to predict the safety and tolerance of EN and there is no recognized risk of mortality above which EN is contraindicated (26, 27). In addition, observational studies have described the safety and benefits of EN in children on vasopressors and threats posed by these agents may be related to the particular vasopressor/s or doses employed (28-30)

The performance of procedures is frequently described as delaying EN. Many of these procedures may be unavoidable in the course of providing care. Nonetheless, anticipating or grouping these interruptions may lead to a more rapid, predictable initiation or advancement of EN (17, 18).

Gastrointestinal disturbances represent a range of perturbations, the severity and clinical relevance of which is highly variable and largely speculative. For example, lack of agreement as to what constitutes significant residual volumes or abdominal distension has made it difficult to assess the true impact each has on EN. Recently published protocols defining these common disturbances could promote a more consistent--and testable--approach to managing EN (16, 17, 31).. It is worth noting that even in extreme cases (very low birth weight, premature infants at risk for necrotizing enterocolitis), the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends the initiation of EN by 48 hours (32).

Early EN was widely practiced at our institutions even in the absence of nutrition consults for nearly half of the patients and formal feeding protocols in only 1 of the 6 PICUs, both of which have been shown to encourage EN (17, 31). The heterogeneity of tools used to estimate energy requirements among the PICUs is consistent with the variability noted in the literature (33, 34). This variability may be related to the lack of superiority of any one of these tools over the others in estimating actual energy requirements in critically ill children (17, 35). In recognition of this limitation, ASPEN recommends the judicious use of indirect calorimetry (36). This tool was used in approximately 17% of PICUs surveyed in Europe, but none in our group. Prealbumin, a marker for adequate nutrition, was rarely measured. Finally, none of the PICUs in our study measured protein balance in spite of mounting data supporting the importance protein metabolism in the management of critically ill children (1, 9, 16, 37).

The main strength of our study is that it was conducted in settings where most critically ill children in the US receive their care (i.e., medical-surgical PICUs with less than 20 beds), and with a group of children whose breadth of diagnosis is similar to that described in other reports (31, 38). In addition, the severity of illness as represented by a rate of mechanical ventilation of 35% at 48 hours is comparable to that described in other PICU nutrition studies (10). By excluding children who were admitted to the PICU for <72 hours, our

patient population is likely representative of children who would most benefit from EN; i.e., those who died soon after admission and those who were relatively well, were eliminated.

There were a number of limitations to acknowledge. Our study is retrospective and relied on the interpretation of medical records as the source of data. Although we provided definitions for data collection, clinicians may have documented differently across the 6 PICUs. It is also not possible to discern the providers' rationale and intent regarding the initiation or delay of EN. Based on prior studies, we anticipated the frequency of delayed EN to be approximately 40%, which was double that of our study. Sample size estimates based on this assumption may have led us to miss other important risk factors for delayed EN. This study was not designed to look at clinical outcomes such as mortality or PICU length of stay. Interestingly, early EN was associated with longer PICU stays in a recent study (10). We did not distinguish between enteral and post-pyloric feeds. This prevented us from analyzing the association between mode of delivery of EN and delay in its initiation. We censored the observations upon discharge from the PICU after which children may have achieved full EN rapidly. However, this is unlikely based on the data we presented.

In conclusion, the 6 medical-surgical PICUs participating in this study demonstrated a consistent commitment to providing early EN. Increased levels of respiratory support, severity of illness, procedures and gastrointestinal disturbances were associated with delayed EN. These risk factors could be more clearly defined and possibly modified by future prospective studies. Finally, we have described deficiencies and areas in which our PICUs could more accurately determine and satisfy nutritional needs.

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Figure 1. Time to Start Enteral Nutrition (in hours)

Figure 2. Time to Full Enteral Nutrition (in hours)

Table 1
Characteristics of Children Included in this Study

	All Children (n=444)	Early Enteral Nutrition (n=356)	Delayed Enteral Nutrition (n=88)	p value*
Site of admission (% of total/by site)				0.53
PICU A	60 (13.5)	45 (12.6/75)	15 (17.1/25)	
PICU B	81 (18.2)	62 (17.4/76)	19 (21.6/24)	
PICU C	64 (14.4)	50 (14.0/78)	14 (15.9/22)	
PICU D	97 (21.9)	83 (23.3/86)	14 (15.9/14)	
PICU E	22 (5.0)	17 (4.8/77)	5 (5.7/23)	
PICU F	120 (27.0)	99 (27.8/83)	21 (23.9/17)	
Age in years	4.0 (0.5-11.9)	4.1 (0.5-12.3)	4.2 (0.8-11.1)	0.73
Weight in kg	15.0 (6.5-35.8)	15.0 (6.5-35.1)	17.2 (7.9-40.9)	0.57
z-score of weight for age	-0.4 (-1.9–1.0)	-0.3 (-2.0–1.0)	-0.5 (-1.6–0.8)	0.96
Male	259 (58.3)	205 (57.6)	54 (61.4)	0.52
PIM2 score	0.011 (0.004-0.035)	0.010 (0.004-0.031)	0.015 (0.008-0.068)	0.001
Diagnosis on admission				0.02
Trauma/Surgical	21 (4.7)	13 (3.7)	8 (9.1)	
Cardiovascular	55 (12.4)	42 (11.8)	13 (14.8)	
Respiratory	200 (45.1)	165 (46.4)	35 (39.8)	
Neurologic	74 (16.7)	63 (17.7)	11 (12.5)	
Toxic/Metabolic	42 (9.5)	28 (7.9)	14 (15.9)	
Hematologic/Oncologic	21 (4.7)	20 (5.6)	1 (1.1)	
Others	31 (7.0)	25 (7.0)	6 (6.8)	
Respiratory support				<0.001
None	222 (50.0)	196 (55.1)	26 (29.6)	
Non-invasive	68 (15.3)	48 (13.5)	20 (22.7)	
Invasive	154 (34.7)	112 (31.5)	42 (47.7)	
Neuromuscular blockade	44 (9.9)	29 (8.2)	15 (17.1)	0.01
Vasopressors	37 (8.3)	23 (6.5)	14 (15.9)	0.004
Fluid restriction	29 (6.5)	22 (6.2)	7 (8.0)	0.55
Procedures	154 (34.7)	114 (32.0)	40 (45.5)	0.02
Gastrointestinal disturbance	138 (31.1)	104 (29.2)	34 (38.6)	0.09
Nutrition consult	217 (48.9)	174 (48.9)	43 (48.9)	1.00
Full enteral nutrition while in the PICU	401 (90.3)	332 (93.3)	69 (78.4)	<0.001

	All Children (n=444)	Early Enteral Nutrition (n=356)	Delayed Enteral Nutrition (n=88)	p value *
Full enteral nutrition within 5 days in the PICU	377 (84.9)	325 (91.3)	52 (59.1)	<0.001
Length of stay in the PICU in days	6.0 (3.8-10.1)	5.8 (3.8-10.0)	6.4 (3.9-10.5)	0.72

* Comparisons were made between early vs. delayed enteral nutrition. Data presented as counts (percentage) for categorical variables or median (interquartile range) for continuous variables. PICU – pediatric intensive care unit; PIM2 – pediatric index of mortality 2

Table 2
Multivariable analysis showing the risk factors associated with delayed enteral nutrition

Risk factor	Full Model			Final Model*		
	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Site of admission			0.62			
	PICU A	Referent				
	PICU B	1.80	0.74-4.39	0.20		
	PICU C	0.91	0.37-2.23	0.83		
	PICU D	0.92	0.37-2.30	0.86		
	PICU E	0.81	0.21-3.08	0.76		
	PICU F	1.10	0.47-2.60	0.83		
Age (per 1 year increase)	1.01	0.97-1.05	0.58			
PIM2 score (per 0.1 increase)	1.33	1.07-1.65	0.01	1.39	1.14-1.71	0.001
Cardiac surgery	1.61	0.47-5.45	0.45			
Traumatic brain injury	2.33	0.81-6.73	0.12			
Cancer	0.55	0.18-1.69	0.30			
Respiratory support at 48 hours			<0.001			0.002
	None	Referent		Referent		
	Non-invasive	4.32	2.02-9.20	<0.001	3.37	1.69-6.72
	Invasive	2.21	1.15-4.27	0.02	2.06	1.15-3.69
Vasopressor at 48 hours	1.20	0.50-2.85	0.68			0.02
Fluid restriction	1.18	0.41-3.39	0.76			
Procedures	1.74	0.99-3.08	0.06	3.33	1.67-6.64	0.001
Gastrointestinal disturbance	1.94	1.13-3.32	0.02	2.05	1.14-3.68	0.02
Nutrition consult at 48 hours	0.72	0.41-1.26	0.25			

* Risk factors for final model were selected using backward stepwise selection at a threshold $p < 0.10$. PICU – pediatric intensive care unit; PIM2 – pediatric index of mortality 2