Effects of enteral nutrition on clinical outcomes among mechanically ventilated and sedated patients in the pediatric intensive care unit

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ABSTRACT

Objective. To analyze the effects of enteral nutrition on outcomes and complications of critically ill children in the pediatric intensive care unit (PICU).
Design. Retrospective cohort study.
Setting. PICU in a tertiary care academic medical center.
Patients. Patients up to age 17 years who were admitted to the PICU between January 1, 2011, and December 31, 2013.
Interventions. Intubation for more than 48 hours and requiring any sedative medications. Patients with surgical contraindications to feeding were excluded.
Measures and Main Results. A total of 165 patients met inclusion criteria. Both manual review of the electronic health record and automated data capture (whenever technically feasible) were conducted. Data were collected in REDCap software and analyzed using a statistical discovery program. The mean (SD) calorie intake within the first 10 days of PICU admission was 40% (31.9%) of the prescribed calories. Only 67% of the patients had feeding initiated within 48 hours of admission. No significant difference in hospital or PICU length of stay or ventilator-free days was observed in patients who met one-third of their nutritional goals (50.3%) compared with patients who did not (49.7%). Mortality was nonsignificantly higher among patients who did not meet nutritional goals (P=.07). No association was found between higher doses of opioids or benzodiazepines and nutrition tolerance or gastrointestinal complications.
Conclusions. Early adequate enteral nutrition had no statistically significant impact on the short-term clinical outcomes of PICU patients.
Key words: critical illness, deep sedation, energy intake, pediatric intensive care unit, pediatrics, respiration, artificial

INTRODUCTION

Adequate nutrition during critical illness has been shown to favorably affect clinical outcomes in the intensive care or trauma setting. Malnutrition in hospitalized children has been associated with increased physiological instability, which leads to increased resource utilization and potentially affects outcomes. (1) Optimal nutrition in the pediatric intensive care unit (PICU) plays an important role in sustaining organ function, preventing dysfunction of the cardiovascular, respiratory, and immune systems until resolution of the acute illness. (2) Children may also be at risk for morbidity and mortality from cumulative nutrition deficit during the course of a PICU stay. Patients who receive less than one-third of the prescribed energy on average, during the first 10 days after admission to the PICU, have been shown to have substantially higher odds of mortality. (3)
However, recent results from 2 large multicenter studies of adult patients have suggested that it is better to feed less when a patient is admitted to the intensive care unit (ICU). (4,5) A before-and-after study on the implementation of a feeding protocol in the PICU showed a significant improvement in enteral nutrition (EN) delivery but no effect on the length of stay in the PICU or hospital. (6) These findings raised concern that full goal feeds in critically ill patients may not provide benefit and may even cause harm in certain cases. (7) One group of investigators suggests that no forced mandatory feeds should be provided during the first week of hospitalization. (8) The third edition of the Surviving Sepsis Campaign recommends no more than 500 kcal/day over the first week. (9) These recommendations stand in contradiction to many previously published prospective and cohort studies in nutrition and critical care. The Society of Critical Care Medicine, the American Society of Parenteral and Enteral Nutrition, (10) and the Canadian (11) and European (12) nutrition guidelines recommend early initiation of EN (within 48 hours of ICU admission) in patients who are unable to achieve goal oral intake.
Given the recent debates on the value of both early delivery and trophic feeding, we designed a retrospective cohort study to evaluate the nutrition delivery practices in the PICU. The goal of the present study was to identify the differences in clinical outcomes and complications (nosocomial and abdominal) in patients who achieved goal EN compared with those who did not.

METHODS

The present study was approved by the Mayo Clinic Institutional Review Board. The PICU at Mayo Clinic, Rochester, Minnesota, is a 16-bed mixed medical-surgical unit (no postoperative cardiac or extracorporeal membrane oxygenation). All decisions regarding nutrition for PICU patients were made by the PICU physician in conjunction with a clinical dietitian. Dietitians regularly attended PICU morning rounds and evaluated all patients, preferably within 24 hours of admission (except weekends). In addition, dietitians wrote a clinical note with recommendations on the type of formula/diet and the goal calorie/protein intake per day.
For the present study, the electronic health records (EHRs) of all patients aged up to 17 years admitted between January 1, 2011, and December 31, 2013, were reviewed. Patients who were on invasive mechanical ventilation for longer than 48 hours and who received any sedative and/or opioid medication were eligible for inclusion in the study. Exclusion criteria were surgical contraindications to feeding (eg, abdomi-

nal surgery in the current admission, intestinal obstruction, intestinal perforation, short gut, congenital gastrointestinal (GI) malformation on chronic total parenteral nutrition) and failure to provide research authorization (figure 1). The EHR at Mayo Clinic was internally developed and is maintained with multiple data repositories, some with built-in search capabilities. For this study, we utilized the following data banks and search resources for automated data capture.

1) The Mayo Clinic Life Sciences System (MCLSS) is a clinical data repository maintained by the enterprise data warehousing section of the institutional information technology department. MCLSS comprises pertinent demographic, diagnosis, laboratory, hospital, flow sheet, clinical notes, and pathology data from clinical and hospital sources within Mayo Clinic. Data in MCLSS can be accessed via the data discovery and query builder tool set, which consists of a web-based graphical user interface (GUI) application and a programmatic application program interface (API). In addition, information in free text can be searched through a Mayo clinical notes search tool.

2) The ICU data mart is a rich data source that contains near real-time copies of pertinent ICU patient information. It includes historical data from 2003 to the present. The ICU data mart utilizes statistical discovery software (JMP based; SAS Institute Inc, Cary, North Carolina) and embedded query-building tools that have the ability to interrogate the database using open database connectivity (ODBC).

An automated query was established to generate a list of PICU patients who were on invasive ventilation for longer than 48 hours. The PICU length of stay, hospital length of stay, number of ventilator days, and hospital mortality were also extracted automatically from the EHR. All data were entered into the specially designed REDCap software. (13) Since our unit does not calculate severity of illness or mortality scores on all admissions, we calculated this risk retrospectively as of the day of admission, utilizing Pediatric Index of Mortality (PIM) software (Virtual PICU Systems LLC, Los Angeles, California). The incidence of nosocomial infections (central line infection, ventilator-associated pneumonia, catheter-associated urinary tract infection, pressure ulcers, Clostridium difficile colitis, surgical wound infections) and the incidence of abdominal, potentially feeds-related, complications (vomiting [>2 times/day], abdominal distension, constipation, feeding intolerance, aspiration pneumonia, necrotizing enterocolitis, GI bleeding) were assessed by utilizing the free text search on all the notes (including but not limited to admission notes, progress notes, administrative, consultations, and procedure notes). The number of goal calories per day for each patient was extracted from the first written dietary note on the PICU admission. Total doses of all the opioids, benzodiazepines, and other sedative medications (both continuous infusions and intermittent administrations) were calculated. The net opioids (morphine equivalent) and benzodiazepines were calculated according to 2 formulas: 1) (fentanyl citrate in mcg/10 + morphine in mg + hydromorphone hydrochloride in mg 10)/body weight in kg and 2) (midazolam in mg + lorazepam in mg + diazepam in mg [by mouth or intravenously])/body weight in kg. These formulas were created on the basis of their equivalent recommended dosing in conjunction with our pediatric clinical pharmacy. We compared and contrasted the patients who received less than one-third of the prescribed calories during the first 10 days (or the duration of their ICU stay, whichever was shorter), with those who received more than one-third of the prescribed calories enterally.

Standard summary statistical analysis of categorical and binary data was conducted with JMP statistical software, with results presented as frequency and percentage. Continuous data were summarized with mean (SD), if normally distributed, and as median (interquartile range [IQR]), if skewed. The 2-sided t test was utilized for continuous normally distributed data, and the Wilcoxon rank sum test was used for skewed data. Categorical and binary data were compared using the 2 test. The 2 predefined groups of nutrition delivery were compared after adjustment for the PIM scores using standard statistical modeling. Adjustment for the wide SD of the length of stay (hospital, ICU, and ventilator days) was made using the log of the duration for comparison, including adjustment for PIM. A P value of <.05 was considered statistically significant.

RESULTS

Of the 3,420 patients admitted to the PICU during the 3-year study period, 165 patients met inclusion criteria (figure 1). Most (73 [44%]) were admitted from the emergency department. The rest of the patients were from the pediatric floor (n=39 [24%]), the operating room (n=21 [13%]), external hospitals (n=21 [12%]), outside emergency departments (n=6 [3%]), and the neonatal intensive care unit (n=3 [1%]), or they were admitted directly from home (n=2 [1%]). The mean (SD) age of the patients enrolled in the study was 4.6 years (5.5 years) (median, 2.1 years [IQR, 0.3-7.4 years]), and the mean weight upon admission was 18.7 kg (20 kg) (median, 11 kg [IQR, 5.6-20.5 kg]). The mean PIM

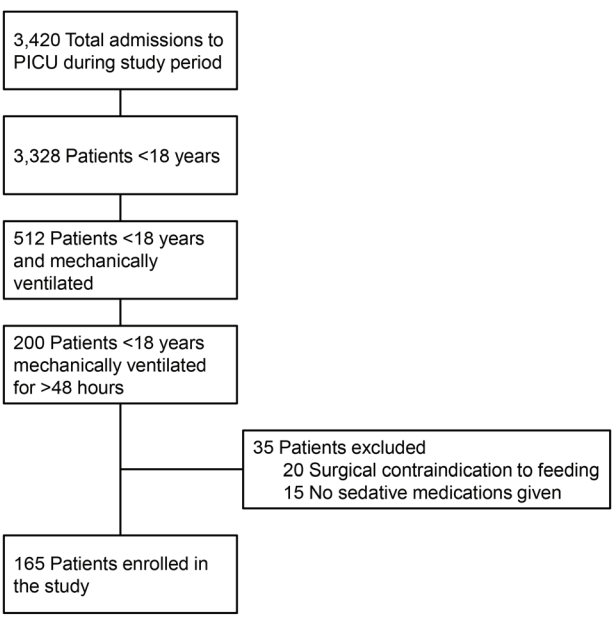

Figure 1. Patient Enrollment Flow Diagram.
PICU,pediatric intensive care unit.

score at admission was 7.6 (13.4) (median, 3.8 [IQR, 1.4-5.7]).The largest diagnostic categories were respiratory (n=75 [45%]), neurology (n=34 [21%]), and surgery (n=17 [10%]). The rest of the diagnostic categories had less than 10% of the patients in the study population (table 1).

Among the study population, all-cause hospital mortality was 7.8%. A total of 35 patients developed a hospital-acquired condition, including central line infection (n=3), catheter-associated urinary tract infection (n=8), pressure ulcer (n=17), and Clostridium difficile colitis (n=7). No patient had ventilator-associated pneumonia or surgical site infection. A total of 98 patients (59%) had some form of GI complication during the first 10 days of their PICU stay. Vomiting was the most frequent EN-related GI complication reported in the study population (n=53 [32%]). Abdominal distension was noted in 46 patients (28%). Other complications included necrotizing enterocolitis (n=5 [3%]), aspiration pneumonia (n=18 [11%]), constipation (n=31 [19%]), GI bleeding (n=4 [2.4%]), and feeding intolerance (n=29, [18%]) (table 2).

Nutrition delivery to the study population

Only 27 patients (16.3%) received full EN (defined as more than 90% of the prescribed calories) on more than 5 days out of the initial 10 days of PICU hospitalization. A total of 67 patients (41%) did not receive full feeds on any of the first 10 days. Only 3 of 165 patients received full EN on all of the first 10 days of their PICU stay (table 3). The mean (SD) enteral calories delivered to all patients was 40% (31.9%) of the prescribed calories, averaged over the duration of their PICU stay or the first 10 days, whichever was shorter. The mean calorie delivered was lowest on day 1 (12.7% [28.8%]) and rose incrementally to 60.1% (45.5%) on day 10 (Table 3). Sixty-seven percent of the patients had their feeds initiated within 48 hours of PICU admission. Of patients meeting inclusion criteria, 8.4% (with no surgical contraindications to feeding) received no EN for the first 5 days of their ICU stay (table 3). Since stool frequency among ICU patients is affected by their relative immobility and the use of opioids and other medications, we reviewed the first day of documented stools in our study population. Only 35% of the patients had stools within the first 48 hours, and 22.6% had no stools within the first 5 days of their ICU stay (table 3).

The EN delivery had a negative correlation with the PIM scores, with average calorie/kg/day decreasing by 3 units for every 10% increase in PIM score, but this did not reach statistical significance (P=.07). We found no statistically significant correlation with nutrition delivery and the total morphine equivalent (P=.38), benzodiazepine equivalent (P=.42), or use of GI medications (P=.17).

Table 1. Demographics of 165 Mechanically Ventilated and Sedated Patients in the Pediatric Intensive Care Unit on Enteral Nutritiona.

Characteristic	Finding
Age, median (IQR), y	2.1 (0.3- 7.4)
Male sex	103 (62)
Weight, median (IQR), kg	11 (5.6-20.5)
PIM score at admission (IQR), %	3.8 (1.4-5.7)
Postoperative	31 (18.7)
Trauma	22 (13.3)
Diagnostic category	
Respiratory	75 (45)
Neurology	34 (21)
Surgical	17 (10)
Trauma	15 (9)
Infection	9 (5.4)
Cardiac	6 (3)
Gastrointestinal	4 (2.4)
Renal	3 (1.8)
Poisoning	1 (0.6)
Other	1 (0.6)
Admission source	
ED	73 (44)
Pediatric floor	39 (23)
Operating room	21 (12)
Transfer from external hospital	21 (12)
Outside ED	6 (3)
NICU	3 (1)
Home	2 (1)

ED, emergency department; IQR, interquartile range; NICU, neonatal intensive care unit; PIM, Pediatric Index of Mortality.

a Values are number (%) unless indicated otherwise.

Comparison of the 2 groups

A total of 83 patients (50.3%) received at least one-third of their prescribed enteral calories. The patients who met their minimum nutrition goals were younger (median age, 1.48 years [IQR, 0.2-3.5 years] vs 3.3 years [IQR, 0.7-11.6 years]; P=.001) and had a lower median weight (8.6 kg [IQR, 4.5-16.3 kg] vs 14.5 kg [6.7-36.7 kg]; P=.004) at admission. However, when adjusted for age, the weight difference between the 2 groups was not statistically significant (P=.09). The 2 groups were similar in terms of mortality risk at admission (P=.43), sex (P=.22), and postoperative status (P=.06). Of 22 patients with trauma who met the study criteria, 19 (86%) did not meet their nutrition goals and 3 (13%) met their goals (P<.001).

The 2 groups received similar amounts of morphine equivalents (unadjusted P value, P=.48; adjusted for PICU length of stay, P=.33); GI medications (unadjusted, P=.13; adjusted for GI complications, P=.11); and vasoactive medications (unadjusted, P=.07; adjusted for PIM scores, P=.08). The group that met the goal of receiving one-third of the desired nutrition received larger amounts of total benzodiazepine (P=.04); however, when adjusted for the PICU length of stay, this difference was not statistically significant (P=.91) (table 4).

Difference in outcomes between the 2 study groups

The group of patients who received at least

Table 2. Outcomes and Complications of 165 PICU Patients on Enteral Nutritiona.

Characteristic	Finding
Length of stay, median (IQR), d	
PICU	10.6 (6.0-18.4)
Hospital	15.9 (9.5-36.6)
Ventilator-free days, mean (SD)	20 (8.4)
Vasopressor-free days, mean (SD) (n=74)	6.8 (2.4)
Death	13 (7.8)
Hospital-acquired condition	
CLABSI	3
CAUTI	8
VAP	0
Pressure ulcer	17
Clostridium difficile colitis	7
Surgical wound infection	0
GI complications	
Vomiting	53 (32)
Abdominal distension	46 (28)
Constipation	31 (19)
Feeding intolerance	29 (18)
Aspiration pneumonia	18 (11)
NEC	5 (3)
GI bleeding	4 (2.4)

CAUTI, catheter-associated urinary tract infection; CLABSI, central line associated bloodstream infection; GI, gastrointestinal; IQR, interquartile range; NEC, necrotizing enterocolitis; PICU, pediatric intensive care unit; VAP, ventilator-associated pneumonia.
a Values are number (%) unless indicated otherwise.

one-third of the target EN had a longer length of hospital stay, a longer PICU stay, and fewer ventilator-free days during their first 30 days. This difference was not significant for the mean duration by the Wilcoxon rank sum test for any of the 3 outcome variables, either unadjusted or adjusted for slightly higher PIM scores in the group that did not meet nutrition goals and using log transformation of the mean durations to account for the wide distribution.

However, on linear regression analysis of the average calorie intake with the PICU length of stay, hospital length of stay, and ventilator-free days, we found significant positive correlation. An increase of enteral calorie by 10 kcal/kg/day led to an increase in the PICU length of stay by 1.3 days (P=.01), an increase in hospital length of stay by 2.6 days (P=.02), and a decrease in ventilator-free days by 0.4 days (P=.04). This correlation remained significant even after adjustment for the PIM score (adjusted P values: P=.02, P=.02, and P=.04 for PICU length of stay, hospital length of stay, and ventilator-free days, respectively). After log transformation of the mean PICU length of stay and the hospital length of stay, there was no significant difference between the 2 groups.

There was higher unadjusted mortality in the group that did not meet nutrition goals (12.2% vs 3.6%; P=.048), but this difference was not statistically significant after adjustment for the PIM score (P=.08). The unadjusted odds ratio of increased mortality in the group not meeting nutrition goals was 3.7 (CI, 1.08-16.99; P=.04); after adjustment for the PIM score, the odds ratio was 3.4 (0.8-18.2; P=.08). There was no difference in either unadjusted or adjusted rates of hospital-acquired infections or vasopressor-free days among the 2 groups, but there was a higher rate of GI complications in the group that did not meet the nutrition goals (68.2% vs 50.6%; P=.02). This difference remained statistically significant even after controlling for the PIM score (P=.01). Among the subgroup of types of GI complications, all the complications were more frequently reported in the group that received less EN; however, the difference was not statistically significant except for GI bleeding (4.8% vs 0%; P=.04) (table 5).

GI complications in the study population

The incidence of GI complications was negatively associated with mean enteral calorie intake, with any GI complication leading to a decrease in average calorie intake by 4.3 kcal/kg/day, but the difference was not statistically significant (P=.08). To identify any potentially modifiable characteristics related to the incidence of GI complications, we compared the group of patients with any reported GI complication to those with no reported GI complications. The patients with any GI complication were older, with a median age of 2.6 years (IQR, 0.5-9.5 years) vs 1.3 years (IQR, 0.2-5.2 years) (P=.52), and they had received significantly less mean kcal/kg/day in the first 10 days of their ICU stay (37.0 [31] vs 45.7 [31.5]; P=.04). The 2 groups were not different in terms of PIM scores at the time of PICU admission, postoperative state, amount of opioids or benzodiazepine administered, or use of any vasopressors or any GI medication during the first 10 days (table 6).

DISCUSSION

In evaluating nutrition delivery and its impact on outcomes and complications of PICU patients, we selected patients who required intubation for longer than 48 hours because of the severity of illness and the potential positive role of nutrition as it pertains to clinical outcomes. As a result of prolonged intubation, patients were more likely to receive sedation, which may affect GI motility and feeding tolerance. Mechanical ventilation has been shown to affect GI motility in up to 50% of patients. (14) Prior studies on nutrition delivery have also included patients requiring mechanical ventilation for longer than 48 hours (3) or patients who required admission for longer than 24 hours. (2) To our knowledge, this is one of the first studies to assess the risks of GI complications and the effects of sedative/opioid medications on tolerance of EN.

In the present study, only 16.3% of patients received adequate nutrition for more than 5 of the first 10 days, and 40% did not receive full nutrition any day during the study period. These findings are similar to those of prior reports. In the first of these studies, the mean calorie goal for 84 children in the PICU was reached by day 5 after admission, and the children were underfed on 50% of patient days. (15) A subsequent prospective observational study of 47 patients reported that more than 55%

Table 3. Nutrition Delivery in PICU Patients.

	PICU Day											
Variable	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**None**
Days with full enteral delivery, No. (%)	67 (41)	29 (17)	19 (11)	15 (9)	8 (4.8)	8 (4.8)	4 (2.4)	3 (1.8)	4 (2.4)	5 (3)	3 (1.8)	NA
Percentage of feeds by day, mean (SD)	NA	(n=165) 12.7 (28.8)	(n=165) 27.5 (40.5)	(n=164) 38.5 (43.7)	(n=163) 46.9 (45.2)	(n=156) 47.4 (42.9)	(n=149) 44.7 (42.1)	(n=136) 46.4 (44.0)	(n=129) 53.4 (45.3)	(n=121) 54.6 (42.7)	(n=112) 60.1 (45.5)	NA
Day of initiation of feeds, No. (%)	NA	53 (32)	59 (35)	21 (12)	9 (5.4)	7 (4.2)	6 (3.6)	2 (1.2)	2 (1.2)	2 (1.2)	2 (1.2)	2 (1.2)
Day of first stool, No. (%)	NA	40 (24)	19 (11)	30 (18)	15 (9)	20 (12)	12 (7)	13 (7)	7 (4)	4 (2)	1 (0.6)	4 (2)

NA, not applicable; PICU, pediatric intensive care unit.

Table 4. Comparison of the 2 Groups of PICU Patients.

Variable	Met One-third of Nutrition Goal (n=83)	Did Not Meet One-third of Nutrition Goal (n=82)	P Value	Adjusted P Value
Male patients, No. (%)	48 (57.8)	55 (67.1)	.22	
Age, median (IQR), y	1.48 (0.2-3.5)	3.3 (0.7-11.6)	.001	
Weight, median (IQR), kg	8.6 (4.5-16.3)	14.5 (6.7-36.7)	.004	.09[a]
PIM score at admission, median (IQR)	3.1 (1.4-5.7)	4.1 (1.4-5.9)	.43	
Postoperative, No. (%)	11 (13)	20 (24.3)	.06	
Posttrauma, No. (%)	11 (3.6)	19 (23.1)	<.001	
Total morphine equivalent, median (IQR), mg/kg	1.5 (0.1-4.3)	0.7 (0.2-2.9)	.48	.33[b]
Total benzodiazepine equivalent in mg/kg, median (IQR)	11.2 (2.8-28.8)	7.9 (1.1-16.6)	.04	.91[b]
Any GI medication, No. (%)	54 (65)	44 (53)	.13	.11[c]
Any vasoactive medication, No. (%)	32 (38)	43 (52)	.07	.08[d]

GI, gastrointestinal; IQR, interquartile range; PICU, pediatric intensive care unit; PIM, Pediatric Index of Mortality.
a Adjusted for age.
b Adjusted for PICU length of stay.
c Adjusted for GI complication.
d Adjusted for PIM score.

Table 5. Difference in Clinical Outcomes for the 2 Groups of PICU Patients.

Variable	Met One-third of Nutrition Goal	Did Not Meet One-third of Nutrition Goal	P Value	Adjusted P Value
PICU length of stay, mean (SD), d	19.2 (25.2)	16.1 (19.7)	.14	.24[a,b]
Hospital length of stay, mean (SD), d	37.7 (5.2)	30.2 (5.3)	.64	.94[a,b]
Ventilator-free days, mean (SD)	19.9 (8.5)	21.0 (8.3)	.15	.38[a]
Vasopressor-free days, mean (SD)	(n=32) 7.5 (1.9)	(n=42) 6.3 (2.7)	.07	.11[a]
Mortality, No. (%)	3 (3.6)	10 (12.2)	.048	.08[a]
HAC rate, No. (%)	14 (16.8)	16 (19.5)	.65	.66[a]
GI complication rate, No. (%)	42 (50.6)	56 (68.2)	.02	.01[a]

GI, gastrointestinal; HAC, hospital-acquired conditions; PICU, pediatric intensive care unit; PIM, Pediatric Index of Mortality.
a Adjusted for PIM score.
b Log adjusted.

Table 6. Gastrointestinal Complications.

Variable	GI Complication	No GI Complication	P Value
Age, median (IQR), y	2.6 (0.5-9.5)	1.3 (0.2-5.2)	.05
PIM score, mean (SD)	6.7 (10.0)	8.8 (17.2)	.84
Calorie intake, mean (SD), kcal/kg/d	37.0 (31)	45.7 (31.5)	.04
Postoperative, No. (%)	22 (22.4)	9 (13.4)	.15
Vasoactive medication, No. (%)	43 (43.8)	32 (47)	.62
Days on vasopressors, mean (SD)	3.3 (2.5)	2.8 (2.3)	.38
Morphine equivalent, median (IQR), mg/kg	1.2 (0.2-3.3)	0.8 (0.05-4.2)	.39
Benzodiazepine equivalent, median (IQR), mg/kg	9.3 (1.7-22.4)	8.0 (1.3-23.6)	.87
Any GI medication, No. (%)	59 (60)	39 (58)	.79

GI, gastrointestinal; IQR, interquartile range; PIM, Pediatric Index of Mortality.

received less than 50% of their estimated calorie requirements. (2) In our study, the mean calorie intake exceeded 50% only by day 8 in the PICU, a finding that may be related to relatively less utilization of postpyloric feeding tubes at our institution. The mean calorie intake of 40% (31.9%) was similar to that reported by other authors. In the multicenter study by Mehta et al., (3) mean daily nutritional intake compared to the prescribed goals was 38% (34%) for energy and 43% (44%) for protein. They also reported initiation within 48 hours of admission in 60% of the patients. (3) In the Tume et al. (2) study, the mean time to initiation of enteral feeding was 11.9 hours (range, 1.5-79.0 hours); with protocol-driven nutrition therapy, they were able to initiate enteral feeds within 6 hours of PICU admission in 46% of the children. In the present study, 67% of our patients had EN initiation within 48 hours.

We did not observe any correlation of a decrease in nutrition tolerance with an increase in sedation, in contrast to previous findings. (16) We were also not able to find a validated score to calculate the total sedative medication use. To create a formula for cumulative dosing, we utilized equivalent morphine dosing, as previously described. (17) We did not take into consideration the use of oral opioids in the PICU because they were used infrequently. Since opiate-induced delay in gastric emptying is mediated peripherally by the interaction with the GI μ-receptors, it is also possible that oral opioids have a larger effect on feeding tolerance than intravenous opioids, due to their preferential attachment to opioid receptors in the gut.

For assessment of the impact of EN on outcomes, we selected those patients who received at least one-third of their prescribed calories and compared them with patients who received less than one-third. The cut-off of one-third of the calorie intake was based on the work of Mehta et al., (3) who observed significantly higher odds of mortality in patients receiving less than one-third of the prescribed energy on average during the first 10 days in the hospital. They found that an increase in energy intake by 1 tertile (33%-66%) significantly decreased the odds of death. (3) It has also been suggested that 25% of goal calories may be sufficient to achieve the outcome benefits of EN. (18) In adult ICU patients, the failure to deliver at least 25% of the predicted requirement was associated with significantly increased infections and mortality. (19)

In our study, patients who received adequate EN were younger than those who did not. This finding may be related to a higher awareness of the requirement for nutrition in younger patients. The risk of death was higher, but it was not statistically significant. Although only 22 of our patients that met the inclusion criteria had trauma, there was significantly less nutrition delivery in this group. Although this finding may be multifactorial, these patients are cared for in our PICU by surgeons rather than by the pediatricians who care for the rest of the patients and these surgeons may be less cognizant of the importance of EN. The total morphine equivalent administration and benzodiazepine equivalent was not significantly different between the 2 groups. This finding may be related to a complex interaction of the severity of illness, more awareness on the part of physicians, and difference in the use of GI medications in the 2 groups.

We were unable to detect any significant difference in outcomes, including length of PICU stay, length of hospital stay, ventilator-free days, or risk-adjusted mortality. These findings contrast with those of previously reported pediatric and adult studies. A meta-analysis of 6 small trials involving 234 adult patients showed a survival benefit with immediate initiation of EN compared to delayed nutrition. (20) A large multicenter trial of 31 PICUs in academic hospitals in 8 countries showed that a higher percentage of goal energy intake via EN was significantly associated with lower 60-day mortality. (3) However, more recently, large adult randomized trials have failed to show a beneficial effect. The EDEN trial (Trophic vs Full Energy Enteral Nutrition in Mechanically Ventilated Patients with Acute Lung Injury), (4) showed that those patients who received trophic feeding for 1 week had a substantially worse nutritional deficit than did patients who received full enteral feeding, but with no difference in acute or long-term function. These findings were in agreement with those from a smaller single-center trial of 240 patients, in which no difference was found in outcomes of adult ICU patients with lower calorie intake. (21)

Lower EN supplemented by parenteral nutrition has also not been shown to be helpful. In the EPaNIC trial (Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients), another large, randomized controlled trial, patients who received insufficient EN were discharged earlier from the ICU and the hospital. They also had a lower incidence of new ICU-related infections and ICU-acquired weakness, compared to patients who received parenteral nutrition to supplement EN. (5)

Because of sedation and mechanical ventilation, the calorie needs of PICU patients may be less than estimated, and overfeeding can increase the need for mechanical ventilation, the risk of infection, and the length of the PICU stay. (22,23) Early nutrition has been suggested to suppress autophagy, (24,25) which is an important protective mechanism of cells in situations of increasing oxidative stress and inflammation. However, this response may even-

tually fail, with the patient progressing to malnutrition. (26) Short-term recovery from critical illness may not be completely relevant to the pediatric population, as the long-term impact of acute illness and starvation on growth and development has not been well studied.

The comparison of patients with any GI complication with those who had no such complications is novel to our study. We found no difference in the use of opioids or benzodiazepine on GI complications. The use of vasoactive medications was also no different between the 2 groups, despite the practice in the ICUs of stopping feeds while patients are on vasopressor drips because of concern about possible GI complications. These beliefs are based on the anecdotal reports of mesenteric ischemia in patients receiving vasopressors. (27) However, a growing body of medical literature now suggests that EN actually increases the blood flow to the gut and protects against bowel ischemia. (28-30) Limitations of our study are its retrospective nature and insufficient power; thus, these findings are at best hypothesis-generating results that emphasize the need for further study.

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