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Association Between Enteral Feeding, Weight Status, and Mortality in a Medical Intensive Care Unit

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Abstract

Background—Clinical practice guidelines recommend enteral nutrition for most patients receiving mechanical ventilation. However, recently published evidence on the effect of enteral nutrition on mortality, particularly for patients who are well nourished, is conflicting.

Objectives—To examine the association between enteral feeding and hospital mortality in critically ill patients receiving mechanical ventilation and to determine if body mass index mediates this relationship.

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Methods—A retrospective cohort study of patients receiving mechanical ventilation admitted to a medical intensive care unit in 2013. Demographic and clinical variables were collected. Cox proportional hazards regression was used to examine the relationship between an enteral feeding order and hospital mortality and to determine if the relationship was mediated by body mass index.

Results—Of 777 patients who had 811 hospitalizations requiring mechanical ventilation, 182 (23.4%) died in the hospital. A total of 478 patients (61.5%) received an order for enteral tube feeding, which was associated with a lower risk of death (hazard ratio, 0.41; 95% CI, 0.29-0.59). Body mass index did not mediate the relationship between mortality and receipt of an order for enteral feeding. Median stay in the unit was 3.6 days. Most deaths (72.0%) occurred more than 48 hours after admission.

Conclusion—The finding of a positive association between an order for enteral feeding and survival supports enteral feeding of patients in medical intensive care units. Furthermore, the beneficial effect of enteral feeding appears to apply to patients regardless of body mass index.

It seems intuitive that providing energy to a patient who is unable to eat is advantageous to avoid muscle catabolism and to ensure adequate nutrient intake. Enteral nutrition is beneficial because it helps to maintain mucosal integrity, impede bacterial translocation, and reduce infection, most likely by decreasing permeability of the gut mucosa.[1-3] Enteral feeding has been associated with improved outcomes such as reduced mortality and shorter stay in some observational studies.[4,5] Aspiration, gut ischemia, and metabolic abnormalities are complications associated with enteral feeding that may reduce or eliminate its beneficial effects in some patients.[6] However, failure to provide adequate nutrition to hospitalized patients is a common problem.[7,8] Although many published studies have examined the merits of enteral versus parenteral and early versus later enteral feeding, the impact of enteral feeding on mortality and the effect of weight status on this relationship remain unknown.

Despite the lack of data on the impact of feeding versus not feeding, we can make some inferences on the basis of the growing literature on the timing and amount of enteral feeding. A meta-analysis of 15 randomized trials of early enteral nutrition reported a benefit when all trials were included in the analysis but no benefit when only studies deemed of high quality were included, leaving authors to attribute some reported benefits to methodologic flaws.[9]

Several trials have challenged commonly held beliefs regarding the benefits of enteral nutrition. In a study of 130 critically ill patients, researchers compared using indirect calorimetry to target an energy intake goal with feeding to a calorie goal set by a formula. Feeding to a goal set by indirect calorimetry resulted in higher caloric intake and was associated with a trend toward reduced hospital mortality. However, the indirect calorimetry group had more infections and longer stays in the intensive care unit (ICU).[10]

In another investigation, a cluster randomized trial,[11] researchers compared usual care with the use of a protocol for enteral nutrition aimed at starting feeding within 24 hours of admission and reaching 80% or more of nutritional requirements by 72 hours after admission. Receipt of recommended feeding was started earlier (0.75 versus 1.37 days) and caloric goals were achieved more often in the protocol group. However, the protocol intervention was not associated with any improvement in mortality.[11] It is also worth noting that both the usual-care and protocol were fed within the time frame recommended by current guidelines from the American Society for Parenteral and Enteral Nutrition.

In a randomized controlled trial of patients with acute respiratory distress syndrome, researchers compared trophic feeding with enteral feeding to goal during the first week of critical illness. The results indicated no differences in ventilator-free days, mortality, or infections between the groups.[12] Of note, the trophic-feeding group received an average of 25% of a caloric goal determined by a weight-based formula and the feeding-to-goal group received an average of 80% of the goal. Additionally, although nutritional risk was not assessed in this study, the average body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) in both groups was around 30.

The most recent clinical practice guidelines for critically ill adult patients emphasize nutritional assessment with validated tools to identify those patients most likely to benefit from nutritional therapy.[2] However, these recommendations are based primarily on expert opinion. The purpose of this study was to examine the association between enteral nutrition and hospital mortality in critically ill patients receiving mechanical ventilation and to determine if BMI mediates this relationship. We hypothesized that the benefits of enteral feeding would be most pronounced in underweight patients.

Methods

We conducted a retrospective cohort study of all patients receiving invasive ventilation who were admitted to our medical ICU in 2013. Patients with ICU stays of less than 2 hours were excluded from our study population. Our medical ICU is a 24-bed closed unit staffed by rotating internal medicine residents and physician assistants supervised by critical care attending physicians. Data from electronic health records (EHRs) are stored in a data warehouse and are accessible for research purposes. We also obtained data on the number of patients in the medical ICU treated with total parenteral nutrition (TPN) from records of the nutrition support team. This project was approved by our institutional review board.

We identified all patients receiving mechanical ventilation in the medical ICU by using EHR data. We also obtained the following variables from the EHRs: sex, race (black, white, other), age, duration of mechanical ventilation, positive end-expiratory pressure used on ventilator, comorbidities as defined by Elixhauser,[13] Pao_2, fraction of inspired oxygen, length of stay, and BMI. We defined obesity as a BMI of 30 or greater. Because height and weight were typically recorded multiple times during a patient’s stay, we used the hospital stay average BMI for each patient. We used “order for enteral feeding” as a proxy for enteral feeding. To validate this assumption, we conducted a chart review of 50 admissions for patients who had this order. We obtained date and time of admission and discharge from EHR data. For patients who died, we calculated survival time as death date/time minus admission date/time.

We used Cox proportional hazards regression models to examine the association of enteral feeding and hospital mortality after adjusting for the variables listed in the preceding paragraph. We first examined the independent association of an enteral feeding order and mortality without the BMI variable after adjusting for age, race, comorbid conditions, admitting diagnosis, duration of ICU stay, degree of hypoxemia, and duration of mechanical ventilation. We subsequently added BMI to determine whether BMI was a mediator of this association and to examine the interaction between BMI and a tube feeding order. We conducted a series of sensitivity analyses to assess the robustness of our results. First, we repeated the analysis after excluding patients who received TPN to ensure that adverse effects from TPN were not significantly influencing results. Second, we replaced the mean BMI values for each patient by the minimum BMI values to determine if fluid retention might be influencing results. Third, we excluded patients who stayed in the ICU less than 24 hours to address the indication bias because these patients are less likely to receive enteral nutrition. Fourth, we kept in the model only the patients who survived the first 24 hours of the ICU stay to again address the indication bias because these patients are less likely to receive enteral nutrition. We created survival curves from Cox proportional hazards regression models to compare in-hospital mortality over time in patients with and without an order for enteral nutrition. We analyzed the data with Stata version 13 (StataCorp).

Results

We identified 892 hospitalizations for 857 patients who received mechanical ventilation in 2013. Eleven patients had ICU stays of less than 2 hours and were excluded from the population. Because of missing data, some visits were excluded from the analysis, resulting in an analytical dataset of 811 hospitalizations for 777 patients. The reasons for exclusion are shown in Figure 1.

As shown in Table 1, 45.3% of our cohort was female and 74.9% was white. Most of the patients (61.5%) had an order for enteral feeding (Table 1). Our chart review of 50 admissions revealed that 90% of patients with an order for tube feeding received enteral nutrition. The median length of stay in the ICU was 3.6 days overall. For 29.3% of the cohort, the Pao_2 was less than 150 mm Hg. The median age was 64 years and median BMI was 28.0. Patients with an order for enteral feeding had a longer duration of mechanical ventilation (median, 113.0 hours) than did patients who did not have such an order (median, 22.9 hours).

Overall, 182 patients (23.4% of the study population) died in the hospital. Of the 478 patients with an enteral feeding order, 102 (21.3%) died in the hospital, as compared with 80 (26.8%) of the 299 patients without an order. As shown in Table 2, most deaths (56.3%) among patients without a tube feeding order occurred within 48 hours of ICU admission, whereas most deaths among those with a tube feeding order occurred much later.

In a Cox regression model excluding BMI but controlling for other variables associated with mortality, having an order for enteral feeding was associated with reduced mortality (hazard ratio [HR], 0.43; 95% CI, 0.30-0.61; $P < .001$). Adding BMI categories in the model (Table 3) did not change this association (HR, 0.41; 95% CI, 0.29-0.59; $P < .001$). Sex, race, and BMI were not associated with mortality, although as expected, older age was associated with increased risk of mortality. Diagnosis of septicemia and a Pao_2 to fraction of inspired oxygen ratio of less than 150 were also associated with mortality. The interaction between BMI and tube feeding was not significant. As shown in Figure 2, patients with an order for enteral feeding had a longer survival throughout the hospital stay than did patients without an enteral feeding order.

Results of the sensitivity analysis included the following: (1) Excluding patients who received TPN (n = 7) did not modify the results of the association between tube feeding order and mortality (HR, 0.44; 95% CI, 0.30-0.63) in a model including all the covariates and BMI. (2) Using the minimum BMI for each patient did not modify the results (HR, 0.64; 95% CI, 0.42-0.99). (3) As shown in Figure 3, excluding patients who stayed in the ICU less than 24 hours, whether they died or not, did not modify the association between an order for tube feeding and survival (HR, 0.52; 95% CI, 0.34-0.80.). (4) Excluding patients who died in the ICU within 24 hours did not modify the association (HR, 0.52; 95% CI, 0.35-0.80).

Discussion

We sought to determine the association between an order for enteral feeding and mortality. Although our methods did not allow us to assess the timing of initiation of enteral feeding, the fact that the median length of ICU stay for patients who received enteral feeding in our cohort was 5.6 days suggests that most patients who received enteral feeding did so during the first week of their ICU stay. Therefore, our primary finding that an order for enteral feeding is associated with lower mortality is consistent with prior observational studies that showed a benefit of early enteral nutrition.[14] Additionally, we found that BMI status did not mediate this association.

The optimal nutritional management of critically ill patients has been increasingly controversial in light of trials that failed to show a benefit from feeding to goal during the first week of critical illness.[15] It is noteworthy that recent trials, which showed no difference in outcomes between higher- or lower-energy feeding, did not address the question of feeding versus no feeding.[12,16] Therefore, these trials should be interpreted not as showing that enteral nutrition is not important for critically ill patients but rather as adding to the debate over timing and dose of nutrition.

The reason for the association between an order for enteral feeding and reduced mortality requires further investigation. Note that association is not the same as causation, and therefore we cannot determine if enteral feeding results in reduced mortality. In our model, we controlled for other factors associated with mortality, such as age and severity of hypoxemia. However, other unmeasured factors could explain the association. For example, perhaps patients subjectively judged unlikely to survive or planning withdrawal of life support are less likely to receive enteral feeding (indication bias), or ICU teams that are more attentive to nutritional guidelines could also be more attentive to other guidelines, such as those for prophylaxis of deep venous thromboembolism. Future work will also need to determine if patients benefit from the provision of calories and nutrients or if the benefit in the early period is limited to other effects such as preservation of gut mucosal integrity.

The percentage of patients with an order for enteral feedings in our study (61.5%) is consistent with an earlier study in which up to 40% of patients were not fed within 48 hours of ICU admission.[17] Several factors could explain our finding that so many patients were not fed. First, many patients had a relatively short duration of mechanical ventilation, which lessens the time during which they were eligible to receive enteral feeding. Given that patients without an order for enteral feeding had a shorter duration of mechanical ventilation than those with an order for enteral feeding, this is certainly part of the explanation. However, the authors of a recent review article commented, “Unfortunately, intensivists are getting the message that nutrition therapy in the first week of hospitalization in the ICU does not matter and, in fact, that it may be better to do nothing.”[15] If this last possibility is responsible for even a portion of the low rate of enteral nutrition, then it suggests a potential area for performance improvement.

Our study has several limitations related to the use of EHR data. First and foremost, our study is observational and not a randomized clinical trial, and therefore the results are subject to an unavoidable indication bias. For example, as mentioned before, patients subjectively judged unlikely to survive or planning withdrawal of life support may be less likely to receive enteral feeding. We tried to minimize the indication bias in sensitivity analyses by excluding patients with short length of stay in the ICU or who died in the ICU within 24 hours and still found the same association between tube feeding and survival. Second, our database allows identification only of patients who received an order for enteral feeding. However, because of procedures at our institution we do know that no patient without an order could have received feeding. In addition, our chart review confirmed that an order for feeding was a good proxy for actual administration of enteral feeding.

Third, we were not able to distinguish between patients who were fed early and those fed later in their medical ICU stay. Fourth, we do not know the clinical reasons why patients were fed or not fed (such as contraindications to enteral nutrition or decisions to limit life support). However, we do know that excluding patients who received TPN did not change the results, so adverse effects from this intervention are unlikely to be driving the increased mortality in patients who did not receive enteral feeding. Fifth, we do not know if patients received enteral feeding to goal or received only trophic feeding or how well the feedings were tolerated. During our study period, these data were recorded in a separate electronic record that is not part of the data warehouse. We also do not know which patients received vasopressors. Finally, the small number of underweight patients in the population may have limited our ability to detect a difference in benefit of enteral feeding in this group. BMI may be a poor surrogate for nutritional status. Although the World Health Organization and the European Society for Clinical Nutrition and Metabolism use BMI to help identify malnutrition, BMI is not included in the American Society for Parenteral and Enteral Nutrition consensus statement on this topic.[18] Additionally, malnutrition is known to occur in obese patients.[19,20]

Although we report a signal of overall benefit in a general medical ICU population, clinicians at the bedside must work to optimize care for individual patients. Future studies focusing on more narrowly defined populations and/or using biomarkers may help determine which aspects of enteral nutrition are most beneficial to which patients. Ultimately, the application of precision medicine to identify the therapy most likely to benefit an individual patient holds great promise for the field of nutritional support of the critically ill.

The finding that enteral feeding was associated with survival at any BMI level suggests that the benefit of enteral nutrition is not limited to patients with preexisting caloric deficits. This supports the recommendation that both nutritional status and disease severity should be considered when evaluating nutritional risk.[21,22] However, 2 studies published after the most recent nutrition guidelines offer conflicting evidence on the effectiveness of evaluating nutritional risk. In the first study, use of a scoring system that accounts for both nutritional status and illness severity did not enable identification of patients who benefit from full enteral feeding.[23] In the other study, among patients with high nutritional risk and longer ICU stays, early enteral nutrition was associated with improved mortality.[24] Our finding of an association of enteral feeding and survival in critical illness supports guidelines that encourage initiation of enteral feeding when possible; however, further research is needed to determine the reasons for this association. From a clinician's perspective, the association of reduced mortality with enteral nutrition is at least reassuring that enteral feeding may cause no harm. This finding should be encouraging to clinicians considering performance improvement initiatives to increase adherence to guidelines for nutritional therapy.

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1. Describe the relationship between an order for enteral nutrition and mortality.
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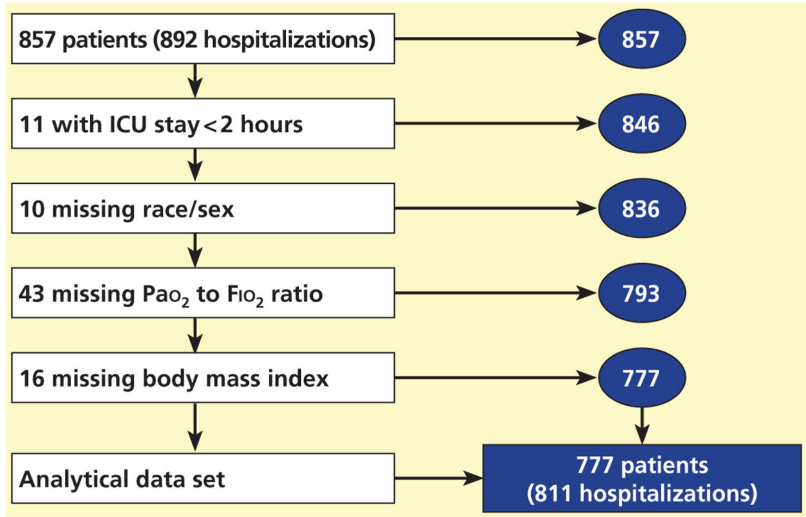

Figure 1.
Flow diagram shows reasons for exclusion from analytical data set.
Abbreviations: FIO_2, fraction of inspired oxygen; ICU, intensive care unit.

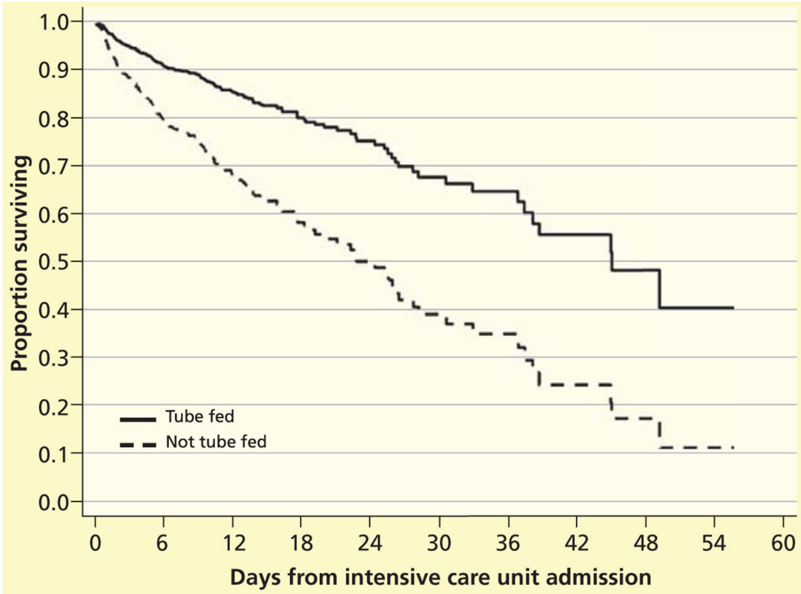

Figure 2.

Survival curves for patients with an order for enteral nutrition versus no order for enteral nutrition.

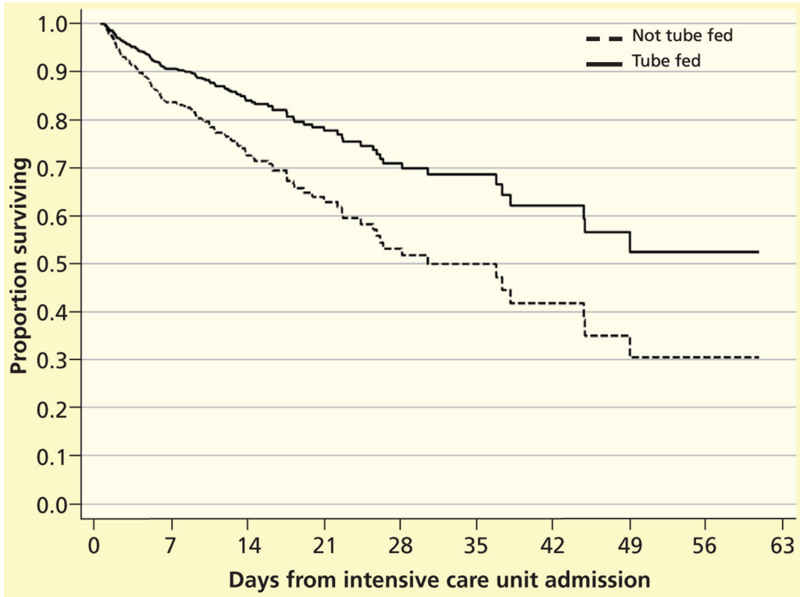

Figure 3.

Survival curves for patients with an order for enteral nutrition versus no order for enteral nutrition excluding patients who stayed in the intensive care unit for less than 24 hours.

Table 1

Characteristics of patients[a]

Variable	All patients (N = 777)	Order for enteral nutrition (n = 478)	No order for enteral nutrition (n = 299)
Age, y			
Mean (SD)	63.1 (16.6)	63.6 (16.6)	62.3 (16.6)
Median (IQR)	64 (53-76)	65 (53-76)	63 (52-76)
Male, %	54.7	55.4	53.5
Race, %			
White	74.9	74.1	76.3
Black	20.9	22.4	18.4
Other	4.3	3.6	5.4
No. of comorbid conditions, median (IQR)	9 (6-11)	9 (7-11)	8 (6-11)
Septicemia, %	21.8	26.4	14.4
Respiratory failure, %	12.7	14.6	9.7
Pneumonia, %	3.7	4.0	3.3
Days in ICU, median (IQR)	3.6 (1.9-7.2)	5.6 (3.4-9.4)	1.8 (1.2-2.8)
ICU ventilator hours, median (IQR)	58.7 (26.4-150.0)	113.0 (58.9-226.8)	22.9 (13.4-38.0)
$Pao_2/FIO_2 < 150$, %	29.3	30.8	27.1
BMI, median (IQR)	28.0 (23.7-34.2)	27.9 (23.4-34.2)	28.1 (24.1-34.2)
Normal BMI, %	27.3	28.5	25.4
Underweight, %	4.5	5.0	3.7
Overweight, %	26.4	24.1	30.1
Obese, %	41.8	42.5	40.8

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FIO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range.

[a]Data are based on first hospitalization only.

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Table 2

Time from intensive care unit admission to death among patients who died

Time, h	No. (%) of patients		
	Total (n = 182, 100%)	With an order for enteral nutrition (n = 102, 56%)	Without an order for enteral nutrition (n = 80, 44%)
1-24	19 (10.4)	2 (2.0)	17 (21.3)
25-48	32 (17.6)	4 (3.9)	28 (35.0)
49-72	16 (8.8)	4 (3.9)	12 (15.0)
73-96	14 (7.7)	10 (9.8)	4 (5.0)
97-120	11 (6.0)	8 (7.8)	3 (3.8)
121-144	15 (8.2)	13 (12.8)	2 (2.5)
145-168	8 (4.4)	5 (4.9)	3 (3.8)
> 168	67 (36.8)	56 (54.9)	11 (13.8)

Table 3

Adjusted association of enteral feeding and in-hospital death

Variable	Hazard ratio	95% CI	*P*
Age (10-year increments)	1.17	1.06-1.29	.002
Male	1.07	0.80-1.45	.64
Race			
White	1.00		
Black	1.32	0.91-1.91	.14
Other	2.18	1.19-4.00	.01
Order for enteral feeding	0.41	0.29-0.59	< .001
Comorbid conditions	0.95	0.91-1.00	.04
Septicemia	2.05	1.45-2.89	< .001
Respiratory failure	1.12	0.67-1.88	.66
Pneumonia	0.64	0.26-1.60	.34
Days in ICU	1.01	1.00-1.01	< .001
ICU ventilator hours	1.00	1.00-1.00	.004
$Pao_2/FIO_2 < 150$	1.59	1.17-2.16	.003
Normal weight	1.00		
Underweight	1.25	0.62-2.50	.53
Overweight	0.72	0.49-1.07	.11
Obese	0.85	0.59-1.23	.39

Abbreviations: Fio_2, fraction of inspired oxygen; ; ICU, intensive care unit.