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Objective To determine the effect of early enteral feeding on the outcome of critically ill medical patients whose hemodynamic condition is unstable.

Methods Prospectively collected data in a multi-institutional medical intensive care unit database were analyzed retrospectively. A total of 1174 patients were identified who required mechanical ventilation for more than 2 days and were treated with vasopressor agents to support blood pressure. The patients were divided into 2 groups: those who received enteral nutrition (n = 707) within 48 hours of the start of mechanical ventilation, termed the early enteral nutrition group, and those who did not (n = 467), termed the late enteral nutrition group. The primary end points were overall intensive care unit and hospital mortality. Subgroup analyses were used to evaluate potential confounding variables. The data were also analyzed after adjustments for confounding by matching for propensity score.

Results Intensive care unit and hospital mortality were lower in the early enteral nutrition group than in the late enteral group: 22.5% vs 28.3%; \( P = 0.03 \); and 34.0% vs 44.0%; \( P < 0.001 \), respectively. The beneficial effect of early feeding was more evident in the sickest patients, that is, those treated with multiple vasopressors (odds ratio, 0.36; 95% confidence interval, 0.15-0.85) and those without early improvement (odds ratio, 0.59; 95% confidence interval, 0.39-0.90). When adjustments were made for confounding by matching for propensity score, early feeding was associated with decreased hospital mortality.

Conclusion Early enteral nutrition may be associated with reduced intensive care unit and hospital mortality in patients whose hemodynamic condition is unstable. (American Journal of Critical Care. 2010;19:261-268)
In healthy adults, enteral nutrition is associated with an increase in blood flow to the gut.\(^{20,21}\) In patients whose hemodynamic condition is unstable, enteral nutrition has been considered problematic mainly for 2 reasons. The first reason is gut ischemia, and the best data indicating an increase in ischemia with feeding were obtained in a study of rats with occlusion of the mesenteric artery.\(^{22}\) The relevance of this model to patients without occluded arteries has been questioned.\(^{23}\) The second reason is the “steal” phenomenon, an increase in splanchnic blood flow without an increase in overall cardiac output.\(^{24,25}\) The impact of this phenomenon on clinical outcomes is not clear. Nevertheless, because of these concerns, hemodynamic instability has been considered a relative or absolute contraindication to early enteral feeding.\(^{26-28}\)

Despite the guidelines, many clinicians continue to feed patients whose hemodynamic condition is unstable. Thus, we sought to examine the impact of early enteral nutrition in critically ill medical patients as indicated by treatment with vasopressors. We hypothesized that early enteral feeding would be associated with lower mortality.

### Methods

Data were obtained from a large, multi-institutional critical care patient data set (Project Impact Critical Care Data System, Society of Critical Care Medicine, Des Plaines, Illinois; see [http://www.trianalytics.com/programs_pi.html](http://www.trianalytics.com/programs_pi.html) for project details). For the Project Impact data set, coordinators at each of the participating sites collected the data prospectively from patients’ charts. Data for the study reported here were acquired in January 2003, after approval of the study protocol by the Project Impact study committee. The research design was approved by the appropriate institutional review board.

For the study reported here, data were requested on all nonsurgical patients admitted to an ICU who received mechanical ventilation during their ICU stay whose hemodynamic condition was unstable at the time mechanical ventilation was started. Patients were considered in unstable hemodynamic condition if they were given the vasopressor agents norepinephrine, epinephrine, dopamine, or phenylephrine.
during the first 2 days of ventilatory support. Study variables included age, sex, race, admitting diagnosis, medications received, Mortality Prediction Model at time zero (MPM-0) score, Simplified Acute Physiologic Score (SAPS) II, and Acute Physiologic and Chronic Health Evaluation (APACHE) II score. Ventilator-associated pneumonia (VAP) in the Project Impact database was defined as new or progressive infiltrate, consolidation, cavitation or pleural effusion, and any of the following: new onset of purulent sputum or change in character of sputum; organism isolated from blood culture; isolation of pathogen from specimen obtained by tracheal aspirate, bronchial brushing, or biopsy; and diagnosis of pneumonia based on histopathological findings. Data on expected (based on the SAPS II score) and observed mortality rate for each ICU were also collected. These data were used to calculate a standardized mortality ratio for each ICU.

The primary outcome variables were ICU and hospital mortality. Secondary outcome variables included occurrence of VAP and ICU length of stay, ventilator-free days, and vasopressor-free days. Ventilator-free days were defined as the number of days within the first 28 days after initial intubation that a patient was breathing independently of the ventilator. Vasopressor-free days were defined as the number of days within the first 28 days after initial intubation that a patient was alive and not receiving vasopressor agents. No information allowing identification of individual patients, hospitals, or physicians was supplied.

The cohort was divided into 2 groups according to when enteral nutrition was first started. The early enteral nutrition group included patients who were started on enteral feeding within 48 hours of the start of mechanical ventilation. The remainder of the patients were the late enteral nutrition group. Patients who died or were extubated within 2 days of the start of mechanical ventilation were excluded. Attempts were made to exclude patients who most likely had an absolute or relative contraindication to enteral feeding at the time of admission. Thus, patients admitted because of gastrointestinal obstruction or bleeding, intestinal ileus, gastroparesis, acute pancreatitis, peritonitis, ischemic colitis, or esophageal rupture were excluded. Patients who received total parenteral nutrition before treatment with mechanical ventilation also were excluded.

In order to ensure that the impact of feeding was not valid solely in the patients given minimal vasopressor treatment, analyses were done on 2 subgroups: patients who were given 2 or more vasopressor agents and patients who were treated with vasopressors for more than 2 days after the start of intubation. Also, because the main analysis was based on vital status at discharge regardless of time, further analyses were done by using only 28-day outcomes. Finally, the subgroup of patients for whom a decision may have been made to forgo aggressive therapy in the ICU who did not die in the ICU were defined as patients whose ICU discharge condition was “moribund.”

Statistical Analysis

SAS software (SAS Institute Inc, Cary, North Carolina) was used for all statistical analysis. Baseline characteristics of the early and late enteral nutrition groups were compared by using unpaired t tests for normally continuous variables and the Kruskal-Wallis test for nonnormally distributed data. The $\chi^2$ test was used for dichotomous variables. Kaplan-Meier survival analysis was used to evaluate the impact of early feeding on mortality; the time from mechanical ventilation to death was compared in the 2 groups by using a log-rank test.

Logistic regression was used to evaluate the effect of early enteral nutrition on ICU and hospital mortality after adjustments were made for important confounders. In order to control for severity of illness, 3 separate models were developed: 1 model used APACHE II scores, 1 used SAPS II values, and 1 used MPM-0 scores. In each model, adjustments were made for age, sex, race, source of admission, standardized mortality ratio for the ICU, and admitting diagnosis, because these variables were considered important confounders. Thus, the variables were included in all models regardless of the $P$ values associated with the variables. Odds ratio were computed from the coefficients in the logistic model, and 95% confidence intervals were calculated for all variables. Findings were considered significant at $\alpha<.05$. In order to determine the effect of feeding on the risk of death, Cox proportional hazard analyses were used. Again, 3 different models were constructed, each with a different severity-of-illness score and controls for all of the variables included in the logistic regression.

Logistic regressions were also used to evaluate the effect of early enteral nutrition on VAP. In these analyses, the models also included the use of drugs that might have confounded the analysis, specifically, histamine2-blockers, proton pump inhibitors, narcotics, and paralytic agents.
Matching by Propensity Score

As in any nonrandomized protocol, the 2 groups might have had inherent differences. Therefore, analyses were done to specifically control for potential confounding variables (see preceding). However, even with these methods, residual bias may exist. Propensity score methods have been proposed to control for such biases.29-31 Use of propensity scores enables better control for the likelihood of being assigned to a group.

In this study, the likelihood of being fed early was modeled by using logistic regression. SAPS II value, age, sex, site of origin, standardized mortality ratio for the ICU, and APACHE II score at admission were used in the regression. This analysis allowed calculation of the probability of being fed for each patient. Matching was done according to the procedure described by Connors et al2 by using an SAS software macro described by Parsons.32 Basically, a randomly selected patient who was fed early was selected from the population. Then, data on all of the patients who were not fed early were searched to find a match on the propensity score (within 0.01 on a scale from 0 to 1). This procedure was continued until all possible pairs were identified. The success of the matching was determined by evaluating differences in individual demographic data.

After matching was completed, the new matched data set was evaluated to assess the effect of feeding on ICU mortality, hospital mortality, ICU length of stay, duration of mechanical ventilation, and occurrence of VAP. All the analyses were done by using methods that accounted for the matched design. Continuous variables were compared by using a matched t test (Proc Mixed in SAS), and dichotomous outcomes were compared by using conditional logistic regression (Proc Phreg in SAS). Kaplan-Meier survival analyses were conducted without accounting for matching; however, survival was also analyzed by using Cox proportional hazard methods with adjustments for matching.

Results

Patients

At the time of the query, 1174 patients in the Project Impact database met our inclusion criteria. Among these, 707 (60%) received early enteral nutrition and 467 (40%) did not. At least 1 severity-of-illness score was available in each patient’s record: APACHE II in 924 records (78.7%), SAPS II in 1045 (89.0%), and MPM-0 in 1008 (85.9%). The means of the APACHE II, SAPS II, and MPM-0 values were 23.6 (SD, 7.4), 53.3 (SD, 15.4), and 0.60 (SD, 0.15), respectively. We found no difference (P = .06) in the lowest mean arterial pressure in the first 24 hours between the early feeding group (mean, 54.6; SD, 12.4) and late feeding group (mean, 53.2; SD, 12.4).

Patients in the early enteral nutrition group were older than those in the late enteral nutrition group and were more likely to be admitted to the ICU with a respiratory diagnosis (Table 1). Additionally, the early feeding group had a small but statistically significant lower severity of illness as indicated by the SAPS II and APACHE II values, but not by the MPM-0 score.

Mortality Analysis

In an unadjusted analysis (Table 2), patients in the early enteral nutrition group had a lower ICU mortality than did those in the late enteral nutrition group (22.5% vs 28.3%; P = .03) and lower hospital
mortality (34% vs 44%; \(P < .001\)). To evaluate the independent effect of feeding on ICU and hospital mortality, we constructed 3 different multivariate logistic models (see “Methods” section). This analysis revealed that regardless of the severity-of-illness score used, early enteral nutrition was consistently associated with a lower risk of hospital mortality (Table 3). Age, severity of illness, the ICU’s standardized mortality ratio, and source of admission were all significant factors in these analyses. Kaplan-Meier analysis of survival indicated a significant improvement in survival for the patients fed early (\(P < .001\); Figure 1). The absolute difference in survival between the 2 groups was evident within the first week of mechanical ventilation and remained constant throughout the first 28 days of follow-up after intubation. Cox proportional hazard analyses indicated that after corrections for confounders, early feeding was associated with a 30% to 35% decreased risk of death.

**Matched Analysis**
Matching for propensity score yielded 1264 pairs of patients who were within 0.01 points on this score. This matching allowed us to find 2 well-matched groups (Table 4). We found no significant differences in any of the baseline values tested.

Using this well-matched subgroup of patients, we again found significant differences in outcome (Table 5). Patients in the early enteral nutrition group had significantly (\(P = .01\)) lower hospital mortality (34.1%) than did the late enteral nutrition group (42.7%). The difference in survival is also apparent in the Kaplan-Meier survival curve (Figure 2). Because this analysis could not be done while accounting for the matched design, we did a Cox proportional hazard analysis after accounting for matching. The results indicate that being fed early was associated with a 34% decreased risk of death (odds ratio, 0.66; 95% confidence interval, 0.49-0.89; \(P = .006\)).

**Subgroup Analyses**
Analyses of subgroups (Table 6) indicated that the beneficial effect of early feeding is more evident in the sickest patients, that is, patients receiving multiple vasopressors (odds ratio, 0.36; 95% confidence interval, 0.15-0.85), and in patients without early improvement, that is, patients who required vasopressors for more than 2 days (odds ratio, 0.59; 95% confidence interval, 0.39-0.90). Also, the effect was present when data on patients who were likely to die after ICU discharge (as evidenced by ICU discharge condition of "moribund") were excluded. Finally, the results did not change significantly when the outcomes were assessed at 28 days.
Severity scores, mean (SD)  
Reason for ICU admission, No. (%) of patients  
Admission source, No. (%) of patients  
Race, No. (%) of patients  
Sex, No. (%) of patients  
Characteristic  
Enteral nutrition group  
Early (n = 357)  
Late (n = 357)  
P  
Age, mean (SD), y  
63.2 (15.8)  
62.0 (17.8)  
.32  
Sex, No. (%) of patients  
Male  
189 (52.9)  
190 (53.2)  
.94  
Female  
168 (47.1)  
167 (46.8)  
Race, No. (%) of patients  
White  
280 (78.4)  
269 (75.4)  
African American  
56 (15.7)  
66 (18.5)  
Hispanic  
11 (3.1)  
11 (3.1)  
Other  
7 (2.0)  
6 (1.7)  
Unknown  
3 (0.8)  
5 (1.4)  
Outpatient  
186 (52.1)  
198 (55.5)  
General care floor  
128 (35.9)  
125 (35.0)  
Another hospital’s ICU  
31 (8.7)  
21 (5.9)  
Extended care facility  
10 (2.8)  
8 (2.2)  
Unknown  
2 (0.6)  
5 (1.4)  
Respiratory problem  
156 (43.7)  
158 (44.3)  
Sepsis  
76 (21.3)  
61 (17.1)  
Cardiac problem  
50 (14.0)  
57 (16.0)  
Central nervous system disorder  
28 (7.8)  
30 (8.4)  
Others  
47 (13.2)  
51 (14.3)  
Severity scores, mean (SD)  
APACHE II  
24.0 (6.9)  
24.2 (7.9)  
.72  
MPS-0  
0.59 (0.24)  
0.59 (0.26)  
.85  
SAPS II  
54.8 (15.4)  
54.1 (15.0)  
.50  
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; MPM-0, Mortality Prediction Model at time zero.  
* Because of rounding, not all percentages total 100.
increase in demand theoretically could exceed the supply, leading to further complications. However, contrary to this belief, enteral nutrients increase blood flow to the gastrointestinal tract, a phenomenon referred to as “postprandial hyperemic response.” Studies have been done in animals to determine the effect of postprandial hyperemia during splanchnic ischemia, as may occur in critically ill patients, especially patients treated with vasopressors. Many investigators have reported that enteral nutrition improves splanchnic blood flow. In fact, although feeding increased gastrointestinal oxygen consumption, the concomitant increase in oxygen delivery led to better delivery to consumption ratio in the fed vs the unfed state. Furthermore, this physiological process can decrease bacterial translocation and improve survival in multiple experimental sepsis models. Thus, on the basis of studies in animals, what might happen to patients in unstable hemodynamic condition who are given enteral nutrition is unclear.

Our study has some limitations. First, it is a retrospective analysis, and we base our results on intent-to-treat analysis, that is, whether a patient was started on any enteral nutrition within 48 hours of mechanical ventilation. The study does not take into account patients’ total caloric intake, rate of advancement, and whether disruptions in the feeding occurred. However, our results imply a favorable outcome with intent to provide early enteral nutrition.

The second limitation is confounding by indication, that is, the decision to feed was not made randomly. Possibly, sicker patients were not fed because of their condition, and feeding may simply be a marker of a less ill patient. Also, if a physician is more likely to initiate enteral nutrition early, he or she would also be more likely to follow other measures to improve outcome or initiatives to decrease rates of health care–associated infection. We attempted to control for this possibility by using multivariate analysis that included severity of illness and standardized mortality ratios for the individual ICUs. We also excluded patients with absolute or relative contraindications to feeding. In addition, we used propensity-score matching as has been used in other studies. Even with these methods, we could not control for the unmeasured variables, and they may have provided some residual confounding. However, we think that the differences in outcomes were too large to be explained exclusively by confounding by indication. We recommend a prospective randomized trial to evaluate the effect of early enteral nutrition on the mortality of patients receiving mechanical ventilation who are in an unstable hemodynamic condition. In such a trial, care should be taken to minimize complications from enteral feeding (eg, bowel necrosis associated with early jejunal feeding).

**Conclusion**

This comparison of early vs late enteral nutrition suggests that early enteral feeding is associated with reduction in the mortality of critically ill patients receiving mechanical ventilation who are in an unstable hemodynamic condition as indicated by use of vasopressors. The beneficial effect of early feeding is more evident in the sickest patients, that is, those treated with multiple vasopressors. In addition, we found no evidence of harm due to the early enteral nutrition. These results provide justification for further well-controlled prospective trials to evaluate the effect of enteral feeding in patients in unstable hemodynamic condition.
for a randomized controlled trial to further address this controversial issue.

ACKNOWLEDGMENTS

The research was done at Henry Ford Hospital.

FINANCIAL DISCLOSURES

None reported.

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REFERENCES


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Imran Khalid, Pratik Doshi and Bruno DiGiovine

Am J Crit Care 2010;19 261-268 10.4037/ajcc2010197
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