

Early Achievement of Enteral Nutrition Protein Goals by Intensive Care Unit Day 4 is Associated With Fewer Complications in Critically Injured Adults

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Objective: We hypothesized that failure to achieve protein goals early in the critical care course via enteral nutrition is associated with increased complications.

Background: Although robust randomized controlled trials are lacking, present data suggest that early, adequate nutrition is associated with improved outcomes in critically ill patients. Injured patients are at risk of accumulating significant protein debt due to interrupted feedings and intolerance.

Methods: Critically injured adults who were unable to be volitionally fed were included in this retrospective review. Data collected included demographics, injury characteristics, number and types of operations, total prescribed and delivered protein and calories during the first 7 days of critical care admission, complications, and outcomes. Group-based trajectory modeling was applied to identify subgroups with similar feeding trajectories in the cohort.

Results: There were 274 patients included (71.2% male). Mean age was 50.56 ± 19.76 years. Group-based trajectory modeling revealed 5 Groups with varying trajectories of protein goal achievement. Group 5 fails to achieve protein goals, includes more patients with digestive tract injuries (33%, $P = 0.0002$), and the highest mean number of complications (1.52, $P = 0.0086$). Group 2, who achieves protein goals within 4 days, has the lowest mean number of complications (0.62, $P = 0.0086$) and operations (0.74, $P = 0.001$).

Conclusions: There is heterogeneity in the trajectory of protein goal achievement among various injury pattern Groups. There is a sharp decline in complication rates when protein goals are reached within 4 days of critical care admission, calling into question the application of current guidelines to healthy trauma patients to tolerate up to 7 days of nil per os status and further reinforcing recommendations for early enteral nutrition when feasible.

Keywords: critical care, nutrition, protein delivery, trauma

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Critically injured patients are often kept nil per os (NPO) due to ongoing massive resuscitation, deference to life-threatening concerns, lack of enteral access, or the historical practices of the

providers. As such, the patient who cannot participate in volitional oral intake will rapidly accumulate a significant protein and calorie debt. Although there is widespread agreement that delayed initiation of, or prolonged hypocaloric feeding should be avoided, 30%-50% of intensive care unit (ICU) patients do not receive their prescribed protein and energy requirements,^{1,2} despite evidence that early, adequate nutrition decreases infectious complications and hospital length of stay.^{3–10} Although the benefits of early nutrition, specifically protein delivery, have been extensively studied, definitive randomized controlled trials are lacking. Current guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN) recommend early initiation of enteral nutrition (EN) and delaying, for up to 7 days, the initiation of parenteral nutrition (PN) in otherwise healthy patients due to the lack of evidence supporting the benefit of early PN, or worse, the potential for harm from early or short-course PN.¹¹ This leaves the clinician with the practical problem of trying to predict the number of days the patient will remain NPO when weighing the risks versus benefits of the timing (early vs late) and duration (early vs short-course) of PN when EN cannot be started.

Though limited in scope and of varying quality, early nutrition delivery has been studied in the brain-injured patient^{12–14} and shown to improve functional outcomes. Less is known about complications and outcomes in multiply injured trauma patients in relationship to the adequacy of early EN therapy, specifically the impact of protein debt. By retrospectively examining all critically injured patients admitted to our trauma ICU, we sought to analyze patterns in injury and nutrition delivery and their association with overall complications. We hypothesized that tolerance of 7 days of failure to achieve protein goals in the critically injured trauma patient would be associated with more complications than earlier achievement of protein goals.

METHODS

This study was approved by the Institutional Review Board at Indiana University School of Medicine with waiver of consent. A retrospective chart review was conducted on all 987 patients admitted to the Trauma ICU during a 1-year period. Patients were included if they were age >16 and unable to eat of their own volition during the first 7 days of admission. Patients were excluded if they were pregnant, receiving EN/PN before admission, died within 48 hours or transferred from ICU within 24 hours of admission, or never received EN before transfer from ICU. Patients who never received EN before transfer from ICU were excluded due to: volitional intake; contraindication to EN (eg, intestinal discontinuity); too critically ill to receive EN (eg, high dose vasopressors); or whose surrogate decision-makers elected to transition to comfort care measures and withhold EN. Data extracted included: demographics, injury characteristics, co-morbid conditions, ICU, and hospital length of stay, acute physiology and chronic health evaluation (APACHE II) score, mortality, complications suffered any day before hospital discharge, number and type of operations, discharge disposition,

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nutrition data including the diagnosis of malnutrition on admission (per 2012 Consensus Statement,¹⁵ documented by the dietitian who used criteria of body mass index $<18\text{ kg/m}^2$, weight loss, poor oral intake, muscle wasting, validated scoring scales), prescribed and delivered protein and calories from the time of admission via the emergency department to initiation of oral diet (including calories from propofol, dextrose containing fluids), and periods of feeding intolerance [defined by professional judgment, documentation of elevated gastric residual volumes ($>400\text{ mL}$), abdominal distention, emesis]. Patients were started on EN within 24–48 hours of admission per institutional guidelines, with exceptions made as noted above. The dietitian was automatically consulted for all ICU patients, who calculated protein and calorie goals assuming baseline needs of 25 kcal/kg/d (Penn State 2003 equation; Modified Penn State Equation for patients with body mass index $>30\text{ kg/m}^2$)¹⁶ and $1.5\text{ g protein/kg ideal body weight}$. All patients received Impact Peptide 1.5 (Nestle), for the initial 5 days then were switched to Promote (Nestle, Florham Park, NJ, USA). Our standard practice was to initiate small bowel EN at 20 mL/h and advance by 20 mL every 4 hours until the goal rate was reached. In the event small bowel feeding access was not obtainable or there would be a delay to establish it, gastric access was used. Patients were prescribed Prostat (30 mL/dose ; 100 kcal , 15 g protein) as needed to achieve protein goals without overprescribing calories. Time latency from admission to initiation of EN was calculated. The protein and calorie debts were calculated by subtracting the amount of protein and calories delivered from those prescribed: the deficit, was tabulated for each day, and a cumulative debt was calculated for the first 7 days. The deficit was considered closed when daily goals were met. Once an oral diet was prescribed, we ceased calculation of protein and calorie deficits as the ability to precisely measure accurate values dropped precipitously when the patient was eating of their own volition.

The main outcome of interest was the number and type of complications suffered during the hospital course, but at least 48 hours after admission. Infections or “complications” present on admission were excluded. A complete description of all complications and definitions are summarized in Supplementary Table 1, <http://links.lww.com/SLA/B836>.

Statistical Analysis

The 7-day trends in protein and calorie deficiencies were analyzed using the repeated measures of generalized estimating equation with first-order autoregressive-1 correlation structure. This accounted for the correlation due to clustering of the protein deficiencies that were assessed within the same individual over time and for longitudinal deficit data that were assessed at the same intervals (days); these measurements were strongly correlated closer in time than further apart.¹⁷ Trajectories of deficiency in protein and calorie intake were modeled using each of the 7 consecutive deficit scores.¹⁸ PROC TRAJ in SAS version 9.4 was used to apply group-based trajectory modeling (GBTM), a semi-parametric approach. GBTM allows for the discovery of subgroups that follow distinct progression patterns and tests whether the patients who follow those trajectories respond differently to different interventions over time.¹⁹ Bayesian information criterion with the highest (least negative) values was used to select an optimal number of groups and type of model. Final models for protein debt revealed 5 groups with quadratic trajectory models: fewer groups would cluster dissimilar patients together, but more groups would so specifically separate out insignificant differences with too few patients in each group for meaningful analysis, leaving 5 as the optimal number based on the model.¹⁹ A multivariable regression analysis was performed controlling for age, race, sex, injury severity score (ISS), mechanism of injury, malnutrition status at admission, and feeding intolerant days to examine the association of the identified trajectory

groups with the outcome of complications. Chi-square, Fisher exact tests, and analysis of variance with Tukey adjustment for multiple comparisons were used to compare the groups in terms of injury pattern, ISS, APACHE II, and outcomes of operations, complications, time to first nutrition, and feeding intolerant days.

RESULTS

All 987 patients admitted to our Level 1 Trauma Center ICU from January 1, 2013, to December 31, 2013, were screened. Ultimately, 274 patients were included after 616 patients were excluded for no EN delivery, 76 for ICU stay <24 hours, and 21 for death <48 hours (Fig. 1).

The mean age was 50.6 years [standard deviation (SD) 19.8, range 16–94], 71% male, 93.4% blunt mechanism, with the most common injury being falls (29.6%) and 59.9% having a traumatic brain injury (TBI) of any severity. Patient demographics are summarized in Table 1 and all operations in Table 2, including the number of severely injured patients requiring subsequent tracheostomy and gastrostomy to facilitate long-term rehabilitation. The total number and type of complications are in Table 3, most notably, pneumonia (38.7%), urinary tract infection (22.3%), and superficial skin/soft tissue infection (14.6%). Overall, co-morbid conditions were rare, with coronary artery disease being the most common (15.3%), followed by diabetes (14.2%), and chronic obstructive

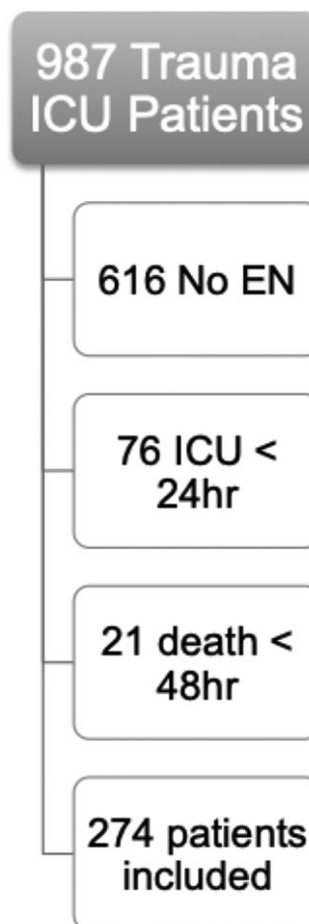


FIGURE 1. Inclusion/exclusion flow chart. EN indicates enteral nutrition; Hr, hours; ICU, intensive care unit.

TABLE 1. Demographics-entire Study Population (n = 274)

Age (mean, yr)	50.6 (range: 16–94, SD ± 19.8)
Sex (n, % male)	195 (71%)
Malnutrition on admission (n, %)	66 (24%)
BMI (mean, kg/m ²)	28.8 (range: 16–63.5, SD ± 6.9)
ISS	26.4 (range: 1–75, SD ± 14.3)
APACHE II	16.91 (range: 2–37, SD ± 7.5)
GCS	6 (SD ± 5.3)
ICU LOS (mean, d)	11.6 (SD ± 7.4)
ICU LOS (median, d)	10 (IQR: 9)
Hosp LOS (mean, d)	17.9 (SD ± 15.2)
Hosp LOS (median, d)	14.5 (SD ± 12)
Total caloric debt (median, kcal)	5472.5 (IQR: 2990)
Total protein debt (median, g)	356.5 (IQR: 192)
Time to first nutrition (mean, h)	39.6 (SD ± 24.3)
Mechanism	
Blunt (n, %)	256 (93.4%)
Fall (n, %)	81 (29.6%)
Traumatic brain injury (TBI) (n, %)	164 (59.9%)
Spinal cord injury (SCI) (n, %)	22 (8.0%)
Mortality (n, %)	40 (14.6%)
Discharge disposition (n, %)	
Home	52 (19%)
Skilled nursing facility	25 (9.1%)
Long term acute care hospital	47 (17.2%)
Rehabilitation center	103 (37.6%)
Death	40 (14.6%)
Other	7 (2.5%)

APACHE II indicates acute physiologic assessment and chronic health evaluation scoring system; GCS, Glasgow coma scale; ICU, intensive care unit; IQR, interquartile range; ISS, injury severity score; LOS, length of stay; SD, standard deviation.

pulmonary disease/emphysema (9.9%). A summary of co-morbid conditions can be found in Supplementary Figure 1, <http://links.lww.com/SLA/B836>.

Analysis from t-tests revealed patients who had any surgical procedure had an additional 7.3 hours delay in time to first nutrition, compared to patients who had no operation, 41.8 hours (SD ± 25.4 hours) versus 34.5 hours (SD ± 20.7 hours) ($P = 0.0134$); an increase in caloric deficit of 1128 kcal (SD ± 2223 kcal, $P = 0.0001$); and in increase in any complication, 1.3 complications (SD ± 1.3) for those with an operation versus 0.9 (SD ± 1.1) for no operation ($P = 0.0104$).

TABLE 2. Type of Procedure or Operation, Entire Study Population (n, %)

Initial operation:	
Intramedullary nail/ORIF	62 (22.6%)
Craniectomy/craniotomy	50 (18.3%)
Skin/soft tissue	46 (16.8%)
Exploratory laparotomy	39 (14.2%)
Damage control/open abdomen	22 (8%)
VATS/thoracotomy	31 (11.3%)
Spine stabilization	27 (9.9%)
External fixator	26 (9.5%)
Oral/facial	24 (8.8%)
Subsequent elective operation:	
Tracheostomy	104 (38%)
Gastrostomy/PEG	72 (26.3%)

Total initial operation >100% as some patients had more than 1 procedure.
ORIF indicates open reduction internal fixation; PEG, percutaneous endoscopic gastrostomy; VATS, video-assisted thorascopic surgery.

TABLE 3. Total Number and Types of Complications (n, %)

Number of complications:	
0	103 (37.6%)
1	82 (29.9%)
2	48 (17.5%)
3	26 (9.5%)
4	12 (4.4%)
≥5	3 (1.1%)
Pneumonia or treatment for suspected pneumonia	106 (38.7%)
Urinary tract infection	61 (22.3%)
Superficial skin and soft tissue infection	40 (14.6%)
Deep organ space infection, abscess	19 (6.9%)
Decubitus ulcer	17 (6.2%)
Feeding intolerance	13 (4.7%)
Bacteremia, catheter related blood stream infection	13 (4.7%)
Osteomyelitis	1 (0.4%)
“Other”	52 (19.2%)
Thrush	15 (5.5%)
Sinusitis	11 (4%)
<i>Clostridium difficile</i>	9 (3.3%)
Stroke	4 (1.5%)
Ileus	4 (1.5%)
Gastrointestinal bleeding	3 (1.1%)
Deep vein thrombosis	2 (0.7%)
Gastrostomy tube displacement-wound	1 (0.4%)
Renal failure	1 (0.4%)
myocardial infarction	1 (0.4%)
Latent infection: shingles	1 (0.4%)

Patients with documented malnutrition upon admission had a decreased latency to first nutrition (38.2 hours, SD ± 22.3 hours) compared to those without malnutrition (40.0 hours, SD ± 25.0 hours) but this was not statistically significant ($P = 0.6027$). Malnourished patients had a smaller caloric debt than nonmalnourished by 604 kcal ($P = 0.0478$) but they did not have fewer overall complications: 1.2 (SD ± 1.3), versus 1.1 complications (SD ± 1.2), respectively ($P = 0.8023$).

For each additional operation, the caloric debt from the bivariate regression was increased by 791 kcal (SE ± 124 kcal, $P = 0.0001$). In the generalized estimating equation model after adjusting for the effect of age, race, and sex, the number of operations was still statistically significant [Coeff: 109.51 (SE ± 17.33 kcal, $P < 0.0001$)].

After statistical models were applied, 5 distinct groups were revealed and named according to their trajectory towards protein goal achievement during the first week of ICU admission: Group 1: regression of progress (REGRESS)-nutrition goals initially met but then ultimately fail to be met; Group 2: early achievers (EARLY)-met, maintained nutrition goals early in ICU stay; Group 3: late achievers (LATE)-ultimately met nutrition goals, not as rapidly as other groups; Group 4: almost achievers (ALMOST)-came closest to reaching nutrition goals without actually meeting them; and Group 5: never achievers (NEVER)-furthest from, never achieved nutrition goals (Fig. 2). There were no statistically significant differences between the groups in regards to ISS ($P = 0.0557$) or APACHE II ($P = 0.3383$) (Table 4). Table 5 provides post-hoc pairwise comparison between groups for the means or proportions reported in Table 4. Patients who consistently failed to achieve protein goals over the first 7 days of ICU care (NEVER) compared to EARLY were reported to have a significantly higher proportion of abdominal or digestive tract injuries ($P = 0.0002$) and a significantly higher number of complications ($P = 0.0393$) (Table 5). EARLY patients achieved their protein goals within the first 4 days and had the lowest proportion of complications, 0.62 (see Table 4). Overall,

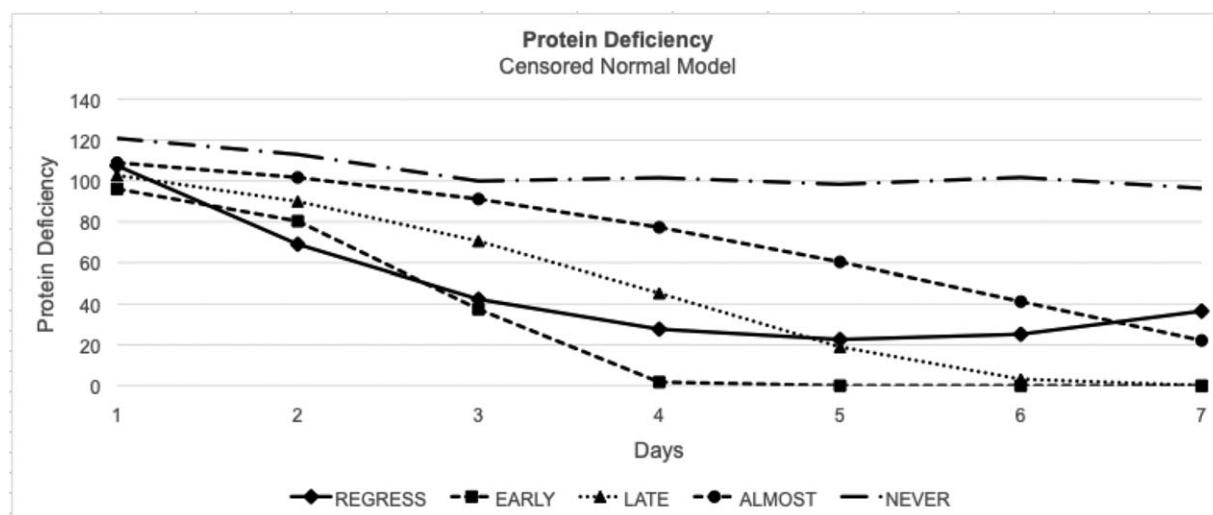


FIGURE 2. Protein deficit (grams) first week of ICU admission. ICU indicates intensive care unit.

TABLE 4. Characteristics of the Protein Debt Groups in the Trajectory Model

	Group Name (n)					P value
	REGRESS (105)	EARLY (42)	LATE (50)	ALMOST (56)	NEVER (21)	
TBI (n)	67.62	61.90	62.00	46.43	47.62	0.081 [†]
Blunt (%)	94.29	90.48	90.00	89.29	85.71	0.571 [†]
Penetrating (%)	3.81	9.52	8.00	7.14	14.29	0.571 [†]
Ortho Injury (%)	20.95	16.67	22.00	44.64	42.86	0.0026 *
Digestive Tract Injury (%)	6.67	0.00	12.00	19.64	33.33	0.0002 [†]
Malnutrition on Admission (%)	26.67	26.19	24.00	21.43	14.29	0.8047 [†]
ISS (mean)	26	21	23	26	28	0.0557 [‡]
APACHE II (mean)	17.98	15.69	15.70	16.93	16.80	0.3383 [‡]
Age (mean)	55.25	46.88	48.30	49.64	42.29	0.0177 [‡]
Complications (mean)	1.34	0.62	1.02	1.23	1.52	0.0086 [‡]
Operations (mean)	0.93	0.74	0.90	1.70	1.71	< 0.001 [‡]
Time to first Nutrition (mean, h)	32.18	23.67	42.60	54.43	61.9	< 0.001 [†]
Feeding Intolerance >1 d (%)	2.86	0.00	0.00	3.57	33.33	< 0.001 [†]
Protein Debt day 1 (mean, g)	105.62	100.82	100.90	108.09	120.86	0.0046 [‡]
Protein Debt day 4 (mean, g)	22.03	0.57	56.80	79.32	100.14	< 0.001 [‡]
Protein Debt day 7 (mean, g)	36.87	0.0	0.0	18.70	99.76	< 0.001 [‡]

Bold font indicates statistically significant.

*Chi-square.

[†]Fisher exact tests.

[‡]ANOVA.

APACHE II indicates acute physiologic assessment and chronic health evaluation scoring system; ISS, injury severity score; TBI, traumatic brain injury.

TABLE 5. Post-hoc Pair-wise Comparison Between Trajectory Groups

Group Pair	Ortho Injury	Digestive tract Injury	Age	Complications	Operations	Time to First Nutrition	Feeding Intolerance >1 d
Overall	0.0026	0.0002	0.0177	0.0086	<0.001	<0.001	<0.001
REGRESS versus EARLY	NS	NS	NS	0.0090	NS	NS	NS
REGRESS versus LATE	NS	NS	NS	NS	NS	0.0373	NS
REGRESS versus ALMOST	0.0016	0.0128	NS	NS	<0.001	<0.001	NS
REGRESS versus NEVER	0.0334	0.0004	0.0451	NS	0.0084	<0.001	<0.001
EARLY versus LATE	NS	0.0296	NS	NS	NS	0.0003	—
EARLY versus ALMOST	0.0035	0.0021	NS	NS	<0.001	<0.001	NS
EARLY versus NEVER	0.0244	0.0002	NS	0.0393	0.0021	< 0.001	0.0002
LATE versus ALMOST	0.0140	NS	NS	NS	0.0004	0.0365	NS
LATE versus NEVER	NS	0.0339	NS	NS	0.0132	0.0050	<0.001
ALMOST versus NEVER	NS	NS	NS	NS	NS	NS	0.0012

Listed *P*-values are statistically significant, Tukey adjusted *P*-values account for multiple testing; bold font indicates statistically significant differences in regards to complications. NS indicates not significant (ie, *P* > 0.05).

there was a statistically significant difference in the mean protein debt among all 5 groups for each of the first 7 days of admission; days 1, 4, and 7 are highlighted in Table 4 ($P = 0.0046$, $P < 0.001$, $P < 0.001$, respectively). Comparisons between each of the groups are summarized in Table 5, which reveals significant differences in the total number of complications between REGRESS and EARLY, and EARLY and NEVER.

A multivariable regression analysis of the number of complications reported as an outcome variable was performed controlling for age, race, sex, ISS, mechanism of injury, malnutrition status at admission, and feeding intolerant days to confirm that the identified trajectory groups were indeed associated with the noted complications. After multivariable analysis, compared to EARLY, the REGRESS, and ALMOST patients had 0.64 [95% confidence interval (CI) 0.22–1.06, $P = 0.0029$] and 0.49 additional complications (95% CI: 0.03–0.96, $P = 0.0386$), respectively. A similar multivariable analysis was completed for caloric debt. In comparison to EARLY, the LATE, and ALMOST groups both had an additional 0.61 complications [(95% CI: 0.14–1.10), $P = 0.0166$ and (95% CI: 0.04–1.17), $P = 0.0352$, respectively].

DISCUSSION

There is increasing evidence that early EN for critically ill patients, specifically protein delivery while tempering the administration of non-protein calories, is associated with a decrease in later complications.^{20–22} Because of the risks associated with the administration of PN,^{11,23,24} many clinicians delay its initiation. In the absence of data specific to poly-trauma patients, recommendations from other patient populations are often extrapolated to critically ill trauma patients, such as the current recommendations by ASPEN that PN be withheld during the first 7 days of admission in patients who cannot establish or maintain adequate EN,¹¹ thereby accepting periods of up to 7 days of NPO status. Our findings in the present study challenges the acceptance of that practice as we found that patients who achieved their protein goals by the fourth ICU day had fewer complications than those in whom a persistent protein debt was tolerated through day 7. Whereas traditional statistical models capture patients in a more binary fashion (ie, met protein goals by day 7 vs did not), GBTM uncovered unique trajectories otherwise unstudied, such as the REGRESS group in our study.

Group Descriptions, Comparisons

The groups were not statistically different in terms of baseline malnutrition status on admission, ISS, or APACHE II (Table 4), making the groups appropriate for comparison, that is, the sickest patients were not clustered in 1 group. Our model revealed that, not surprisingly, patients without digestive tract injuries (EARLY, Table 4) had the shortest latency to first nutrition and the fewest overall complications. However, LATE and ALMOST, had 12% and 19% incidence of digestive tract injuries, respectively, yet they met or nearly met their protein goals by the end of the first week and had fewer overall complications compared to NEVER (Table 4).

Post-hoc pair-wise analysis of the groups revealed statistically significant differences in complications in EARLY versus REGRESS and EARLY versus NEVER, $P = 0.0090$ and $P = 0.0393$, respectively (Table 5). Comparing patients in the 2 extremes of trajectories, EARLY versus NEVER, we found fewer complications in EARLY, but this is not surprising as the patients were also statistically different from NEVER in terms of injuries, operations and feeding delivery characteristics. Of more interest was the comparison between EARLY and REGRESS. EARLY followed a trajectory towards protein goal achievement by day 4 and were similar to REGRESS in terms of injury pattern, age, number and

type of operations, time to nutrition, and feeding tolerance ($P =$ not significant, Table 5). REGRESS appeared to be on track, but then reversed course and increased the protein debt by the end of the week (Fig. 2) and went on to have more overall complications ($P = 0.0090$, Table 5). That the EARLY and REGRESS patients were otherwise similar suggested to us that there may be an association between early protein goal achievement and fewer overall complications.

Because we saw that REGRESS seemed to be on track, but then fell off, we sought to find hallmark characteristics of this group. Table 4 demonstrates that REGRESS had a small percentage of digestive tract injuries (6.7%) and patients did not undergo multiple operations (mean = 0.93) but they were the oldest (mean = 55.3 years), had the highest percentage of malnutrition (26.7%), had the highest percentage of TBI (67.6%) and were the most severely injured (mean ISS = 26). Although not all of these differences were statistically significant, when taken as a whole, we believe that this constellation of age, nutritional risk, and severe injury should raise awareness for the clinician to be vigilant about adequate early EN delivery. Our finding of poorer outcomes in REGRESS is consistent with the finding as stated conversely in previous studies: that greater protein delivery to the most nutritionally at-risk patients portends lower mortality and shorter time to discharge alive.^{20,25}

Malnutrition, PN

As expected for a trauma population, the majority of our patients were not classified as malnourished on admission (14.29%–26.67%, $P = 0.8047$). Our analysis revealed that NEVER had the fewest percentage of malnourished patients (14.29%), the highest mean number of complications (1.52, $P = 0.0086$), and the longest latency to first nutrition (61.9 hours, $P < 0.001$) (Table 4). As per ASPEN guidelines, our patients were not started on PN during the first 7 days of admission if they were not classified as malnourished.¹¹ As such, patients in this group, despite a large burden of digestive tract injuries (33.33%, $P = 0.0002$) did not receive supplemental PN. Based on our results that this group went on to have the most complications, we pose the question if tolerance of this extended period without adequate protein should remain the standard of care. Here, we have demonstrated evidence that crossing the threshold of day 4 without adequate enteral protein delivery may be where the complication risk rises, not day 7 as has been previously described.¹¹ Our present study echoes the findings of Heidegger et al that consideration of supplemental PN by day 4 of ICU admission may confer benefit.²⁶ We recognize that other large studies, such as EPaNIC, seem to provide evidence to the contrary in that early protein delivery as accomplished by supplemental PN does not confer benefit, and may cause harm.²⁴ It is important to note, however, that the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study included many patients in medical ICUs and nearly 20% had a diagnosis of cancer, which makes comparisons between the EPaNIC patients and our trauma population problematic.²⁴ In our present retrospective study, we did not study the effects of PN administration so we cannot comment on how its use may have affected outcomes.

Latency to First Nutrition, Prolonged NPO Status

It is not surprising that NEVER had the highest percentage of digestive tract injuries (33.33%) and subsequently the longest latency to first EN (mean = 61.9 hours). However, we noticed that ALMOST also had a long latency to first EN (mean = 54.43 hours) despite having fewer digestive tract injuries (19.64%) and subsequently suffered an increase in overall complications (1.23, $P = 0.0086$). ALMOST included a large burden of TBI and orthopedic injuries, theoretically not precluding early EN. We surmised that repeated

trips to the operating room for injuries that required serial debridements and hardware adjustments contributed to prolonged periods of NPO. This realization has prompted a change in our practice to allow for the administration of small bowel EN in patients with a protected airway (eg, intubated) until 30 minutes before the operation.²⁷ We have also adopted volume-based feeding protocols to mitigate the time lost for NPO periods.^{25,28} Finally, we noted an opportunity for education for clinicians who may, by training or by habit, be slow to initiate EN in patients who have had emergency gastrointestinal (GI) surgery, despite evidence it is safe and preferable.²⁹

Limitations

This study was born out of concern that we observed repeated and prolonged orders for NPO status in our critically injured patients. The results of our inquiry revealed to us an alarming trend and from this study, we have developed the hypothesis that earlier closure (4 days vs 7 days) of protein debt may be associated with fewer overall complications. This exploratory study should prompt testing the hypothesis in future larger, randomized studies that can compare the application of varying early protein delivery rates to matched cohorts of patients with similar risk factors, injury patterns, and operations as our present study cannot definitively answer this question with its several limitations.

The study was not adequately powered to isolate each complication or to conclude that only certain complications are mitigated by early EN. Instead, we looked at overall complications. We recognize that some complications are more severe than others, thus although we made the generalization that complications may be reduced with early adequate EN, we cannot comment on the degree of morbidity avoided. Our study was not powered to determine if nutrition alone can reduce the major complications we noted in our study, such as stroke, renal failure, and myocardial infarction, which were rare events (Table 3). This retrospective study was not designed or powered to determine which complications were specifically related to perioperative risk. We did not pair each complication with the hospital day or protein delivery for the day the complication was noted, as the study was not powered to accurately interpret data from a small number of patients that would fall into each of these subgroups, so we cannot comment on the relationship between these individual patient factors, protein delivery, and complications. We recognize that the timing of complications is not predictable and is determined by many factors in addition to nutrition delivery (eg, temperature, blood loss, surgical technique). We appreciate that it is unlikely a protein debt within the first 48 hours is directly responsible for complications such as pneumonia at 72 hours and note our study design risks overstating the number of early infections that may not be directly attributable to lack of EN.

Our patient population included almost exclusively patients with a blunt mechanism of injury, who are known to undergo a tremendous inflammatory response after injury³⁰ and suffer all of the attendant consequences on the body's ability to tolerate and absorb EN early during recovery. Thus, although our results are theoretically applicable to patients with penetrating injury, caution must be used in extrapolating our findings to a population with a potentially different inflammatory response to trauma.

As with all retrospective studies, caution must be taken to differentiate between causation and correlation. It is not able to be determined from our study if patients who suffered complications such as feeding intolerance or GI bleeding failed to achieve their protein goals because of the complication or if the complication was caused by a failure to achieve protein goals. Outcomes centered retrospective studies in critically ill patients also suffer from the confounding issue of accounting for death before the outcome of interest. We attempted to correct for this by excluding patients who

suffered an early death (<48 hours) or who's surrogates elected palliative care, but we note this as a known limitation of this study type.

CONCLUSIONS

Despite the limitations, our current work using a novel GBTM approach provides additional support to the growing body of evidence that early, adequate EN may reduce complications in critically ill patients and that more aggressive achievement of protein goals by ICU day 4 may confer benefit.^{2–6,8,9,11,12,14,20–22,25,31}

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