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Markers of Inflammation and Coagulation may be Modulated by Enteral Feeding Strategy

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Abstract

Background—Despite the fact that enteral nutrition is provided to the majority of mechanically ventilated patients, the effect of specific feeding strategies on circulating markers of coagulation and inflammation are unknown.

Methods—We measured markers of inflammation (TNF- α , IL-1 β , IFN- γ , IL-6, IL-8, IL-10, IL-12) and coagulation (TF, PAI-1) at baseline (N=185) and 6 days (N=103) in mechanically ventilated ICU patients enrolled in a randomized, controlled study of trophic versus full-energy feeds. We hypothesized that trophic enteral feeds would be associated with decreases in markers of inflammation and coagulation compared to full-energy feeds.

Results—There were no differences in any of the biomarkers measured at day 6 between patients who were randomized to receive trophic feeds compared to full-energy feeds. However, TF levels decreased modestly in patients from baseline to day 6 in the trophic feeding group (343.3 vs 247.8 pg/ml, $p=0.061$) while TF levels increased slightly in the full-calorie group (314.3 vs 331.8 pg/ml). Lower levels of TF at day 6 were associated with a lower mortality and patients that died had increasing TF levels between day 0 and day 6 (median increase of 39.7) compared to decreasing TF levels in patients that lived (median decrease of 95.0, $p = 0.033$). Baseline markers of IL-6, IL-8, TNF- α and TF were also associated with mortality.

Conclusions—Enteral nutrition strategy in critically ill patients with acute respiratory failure does not significantly modify inflammation and coagulation by day 6 however trophic feeds may have some modest effects in attenuating inflammation and coagulation.

Keywords

acute respiratory failure; acute lung injury; acute respiratory distress syndrome; enteral nutrition; trophic; cytokines; coagulation; tissue factor

BACKGROUND

Acute respiratory failure (ARF) requiring intubation and mechanical ventilation is common in critically ill patients. A recent, large prospective multi-center study found that 39% of patients admitted to the intensive care unit (ICU) required ventilatory support for more than 6 hours with an overall incidence of acute respiratory failure of 149.5 per 100,000 population.¹ The overall mortality of these patients was high at 31%. Critically ill patients

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with ARF, many of whom have acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS), are often systemically ill with disordered coagulation and inflammation. Several single and multi-center trials have shown an association with markers of inflammation and coagulation with outcomes in critically ill patients with ALI and ARDS. Elevated plasma levels of IL-6^{2,3}, IL-8^{2,4} and TNF- α ³ are associated with worse outcomes in these patients. Likewise, disordered coagulation and fibrinolysis as measured by decreased levels of protein C and elevated levels of plasminogen activator inhibitor-1 (PAI-1) are associated with worse outcomes in patients with ALI and ARDS.⁵⁻⁷ Patients with ARDS have higher circulating and lung levels of Tissue Factor (TF) compared to critically ill patients with hydrostatic edema⁸ suggesting that ARDS is associated with a more intense procoagulant response. Taken together, these data show that critically ill patients with ALI/ARDS have enhanced inflammation and coagulation, both of which are associated with poor outcomes. In light of the high mortality rate in ARF, novel methods for modulating these pathways in this critically ill patient population are sorely needed.

Enteral nutrition represents one novel approach to modulating inflammation and coagulation in critically ill patients. Enteral feeding early in a patient's ICU course has been associated with beneficial outcomes including decreased infectious complications,⁹ fewer organ failures¹⁰ and reduced mortality.¹¹ Despite the widespread acceptance of early enteral nutrition (EN), few studies have addressed the specific timing and volume of tube feeds in this patient population and fewer still have studied the effects on inflammation and coagulation. One small study of enteral versus parenteral nutrition in patients with severe pancreatitis showed that EN was associated with a higher early complication rate but not with changes in IL-6 or IL-8.¹² A single center study of mechanically ventilated pediatric head injury patients showed that an immune enhancing enteral diet decreased plasma IL-8 levels.¹³ The same group studied children with septic shock and found that immune enhancing tube feeds decreased IL-6 levels but increased IL-8 levels compared to non-immune enhancing feeds.¹³ Similar studies have not been done in a population with acute respiratory failure so the effects of nutrition on inflammatory markers in this patient population are unknown.

Despite the beneficial effects of EN in the critically ill, there is little consensus as to the volume of EN necessary to confer these benefits. Furthermore, studies have shown that markers of inflammation and coagulation are associated with outcomes in critically ill patients. We designed this study as an ancillary study to a randomized, single center clinical trial of two EN strategies (initial trophic versus full-calorie EN) in a heterogeneous group of intubated patients with acute respiratory failure.¹⁴ Although there were no differences in ventilator free days or mortality between the treatment groups, more patients in the trophic group were discharged to home versus a rehabilitation facility. To test whether EN strategy had effects on systemic coagulation or inflammation we measured markers of coagulation (tissue factor, plasminogen activator inhibitor-1 (PAI-1)) and inflammation (interleukin (IL) -10, -12, -6, -8, -1 β , interferon- γ and tumor necrosis factor- α) at enrollment and at day 6. We hypothesized that a low calorie, low volume (trophic) EN strategy would be associated with improvements in markers of inflammation and coagulation. We found that in our heterogeneous critically ill patient population, markers of inflammation and coagulation correlate with mortality. This is consistent with prior studies in patients with ALI/ARDS. We also found that although the differences were not statistically significant, trophic EN was associated with a modest decrease in markers of inflammation and coagulation.

METHODS

Patients

Two hundred critically ill, mechanically ventilated patients with acute respiratory failure were recruited in one academic medical center from August 20, 2003 through July 8, 2009. Details of the trial protocol and main study outcomes have been published previously.¹⁴ Briefly, patients were included in the study if they were within 48 hours of initiating mechanical ventilation, if mechanical ventilation was anticipated to be needed for at least 72 hours and if their primary team planned to start or continue enteral nutrition (EN). The most common exclusions were severe chronic lung disease, exceeding the time window for enrollment, patient unexpected to survive 24 hours, presence of severe liver disease and failure to obtain consent. The study protocol was approved by the Vanderbilt Institutional Review Board (Clinicaltrials.gov registration: NCT00252616) and informed consent was obtained from all participants or duly authorized surrogates. Clinical outcomes were collected including 28 day mortality, specific organ failure-free days and ventilator-free days.

Enteral Nutrition Strategies

Patients were randomized in a 1:1 ratio to receive trophic EN at 10cc/hr or full-energy EN started at 25cc/hr and increased per protocol to a patient-specific target of 25–30 kcal/kg/predicted body weight/day. The median time to start EN from the time of intubation was 1.0 ± 1.0 days in the trophic group and 1.1 ± 1.2 in the full-energy group. The full energy group reached goal feeding rates in an average of 13.3 ± 12.6 hours. Feeding was continued until the earlier of day 6, death, or extubation. Immune modulating enteral products were not used. The type of tube feed was not specified in this study. The protocol for managing feeding intolerance episodes has been published previously.¹⁴

Sample collection and processing

Blood samples (EDTA plasma) were collected at enrollment prior to randomization and day 6. There were 15 patients who did not have a baseline sample and 97 patients who did not have a day 6 sample. In total, 10 patient in the trophic group and 7 patients in the full calorie group died by day 6 while 25 patients in the trophic group and 40 patients in the full calorie group were discharged from the ICU ($p=0.170$ by Chi Square). The remaining 15 patients did not have samples available due to collection or processing issues. Plasma obtained from two, 10 ml EDTA anti-coagulated blood samples was divided immediately after centrifugation at $4,000 \times g$ for 12 minutes into equal 1 ml aliquots in specified tubes and frozen at -70°C .

Biomarker measurements

All biomarkers were measured in a blinded fashion in duplicate using commercially available immunoassays. Cytokines (tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , (interferon) IFN- γ , IL-6, IL-8, IL-10, IL-12) were measured using a cytokine multiplex immunoassay from Meso Scale Discovery (MSD, Gaithersburg, MD). Tissue factor (American Diagnostica, Stamford, CT) and plasminogen activator inhibitor (PAI)-1 (American Diagnostica, Stamford, CT) were measured by enzyme linked immunosorbent assay (ELISA) according to manufacturers instructions.

Statistical Analysis

All analyses were completed using SPSS for Mac version 18.0 (IBM, Armonk, NY). Biomarker measurements and clinical parameters are non-normally distributed. Median values were compared between groups using the Mann-Whitney U test for non-paired values

and the Wilcoxon signed rank test for paired values and values are expressed as median with confidence intervals (CI) for the 25th-75th percentile. Chi square was used to compare discrete variables. A multivariable analysis was done to determine odds ratios for quartiles of each biomarker comparing the highest to lowest quartile in both unadjusted and adjusted (age, APACHE II, presence of shock at admission) binary logistic regression for an association with mortality. All analyses were two-sided with $p < 0.05$ considered statistically significant.

RESULTS

As previously reported,¹⁴ patients randomized to the trophic feeding arm received an average of $15 \pm 11\%$ of target goal calories compared to $75 \pm 39\%$ for the full calorie group. There were no differences in survival, ventilator free or organ failure free days between arms.

Baseline biomarkers were lower in patients who survived versus those who died

Clinical characteristics differed between survivors and non-survivors. Patients who died were older (median age 67 (CI 43–75) in non-survivors versus 53 (CI 39–63) in survivors, $p = 0.005$), more severely ill (APACHE II¹⁵ 29.5 (CI 24.3–33.8) in non-survivors versus 26.0 (CI 22.0–31.0) in survivors, $p = 0.017$), had more shock at baseline (55% of non-survivors versus 34% of survivors, $p = 0.019$) and had a higher minute ventilation at baseline (10.2 L/min (CI 8.2–11.0) in non-survivors versus 8.2 L/min (CI 6.9–11.1) in survivors, $p = 0.043$). There were no differences in body mass index, or baseline bilirubin, platelets or creatinine. To determine the clinical relevance of the biomarkers measured, we first examined the association between biomarkers and clinical outcomes. Overall, median baseline coagulation and inflammation biomarkers were lower in patients who survived compared to those who died by 28 days. IL-6 (106.8 (CI 29.4–391.2) versus 34.6 (CI 13.9–90.7), $p = 0.001$), IL-8 (43.3 (CI 21.6–167.4) versus 14.6 (CI 8.7–30.3), $p < 0.001$) and TNF- α (12.1 (CI 9.3–23.9) versus 8.9 (CI 6.2–14.1), $p = 0.005$) were statistically significantly higher in non-survivors compared to survivors while there were no statistically significant differences in IFN- γ , IL-10, IL-12, IL-1 β , TF or PAI-1. Patients in the lowest quartile of plasma IL-6, IL-8 and TNF- α levels had mortality rates of 8.7%, 2.1% and 12.8% respectively compared to patients in the highest quartiles with mortality rates of 37.0%, 45.7% and 30.4% (Figure 1). Baseline levels of the coagulation and fibrinolysis markers TF and PAI-1 were also associated with mortality in a dose-dependent fashion. (Figure 2) Patients in the lowest quartile of plasma TF and PAI-1 levels had mortality rates of 10.9% and 13.0% respectively compared to patients in the highest quartiles with mortality rates of 23.9 and 28.3% respectively ($p = 0.049$ for TF; $p = 0.147$ for PAI-1). In both treatment groups, non-survivors had higher levels of both TF and PAI-1 at day 6 compared to survivors (Table 1) although this difference was only statistically significant in TF levels in the trophic EN group. In models adjusted for age, APACHE II, and presence of shock at admission, IL-6, IL-8 and TF were independently associated with mortality. (Table 2) In addition to mortality, lower baseline levels of IL-6, IL-8 and TNF- α were also associated with more ventilator-free days, ICU free days (except for TNF- α), hospital-free days, shock-free days, hepatic failure-free days, renal failure-free days, and hematologic failure-free days. (data not shown) Day 6 levels of IL-6 were lower in patients that survived compared to those that died ($p = 0.003$). TF levels at day 6 were also associated with mortality (Figure 3) and patients that died had increasing TF levels between day 0 and day 6 (median increase of 39.7) compared to decreasing TF levels in patients that lived (median decrease of 95.0, $p = 0.033$).

Feeding formulas and glucose control

The EN formulation was chosen at the discretion of the treating physicians and was not specified in the study protocol. The majority of patients, 147 of the 200 patients (73.5%) received a formula that had 1.2kcal/cc while 48 of the remaining 53 received a formula that had 2 kcal/cc, 3 received a formula that contained 1.0kcal/cc, one received an unknown formula and one did not receive EN. The main reason for use of the higher calorie formula was to minimize fluid intake in patients with renal failure. Overall, 38% of the patients received Osmolite, 17% received Isosource, 16% received Diabeta source, 14% received Novasource renal and the remainder of the patients received other EN. The types of EN did not differ between the treatment groups and the EN formulations by calories per ml were similar between groups ($p=0.66$). A tight glucose control strategy was used for all patients who had two glucose readings above 200 mg/dL. There were no differences in baseline glucose levels between trophic and full calorie groups [median (95% CI) 134 (107–168) mg/dL versus 131 (101–182) respectively, $p=0.772$]. Day 6 glucose levels were also similar between the two treatment groups [109 (85–144) versus 116 (90–179) respectively, $p=0.514$]. Day 6 glucose levels were associated with mortality with patients who lived having lower blood glucose levels compared to those who died (108 mg/dl (85–132 versus 145 (105–170), $p=0.004$). There was no association between either baseline or day 6 blood glucose level and biomarker levels (data not shown).

Comparison of biomarkers between enteral feeding treatment groups

There were no differences in median biomarker levels measured at baseline or day 6 when comparing the trophic group to the full-energy EN group. (Table 3) However, trophic EN was associated with modest changes over time in coagulation and inflammation biomarkers. Among the cytokines, circulating levels of IL-12, IL-1 β , and IL-6 dropped significantly by day 6 compared to day 0 in patients receiving trophic EN (Table 4) while only IL-6 decreased in the full-energy group. (Figure 4) The trophic EN strategy was associated with a reduction in plasma TF levels between day 0 to 6 while TF levels rose slightly in the full-energy group. (Figure 5) A similar pattern was observed for PAI-1 levels and overall, PAI-1 levels fell in 58.8% of patients in the trophic EN group compared to 39.6% of patients in the full feeding group although this difference did not reach statistical significance ($p = 0.056$).

DISCUSSION

Despite expert recommendations advocating *early* initiation of enteral feeding because of its association with improved clinical outcomes the optimal amount of feeding for intubated ICU patients with acute respiratory failure is unknown. Furthermore, the mechanism(s) by which a particular feeding strategy might improve clinical outcomes remains uncertain. Therefore we measured the effects of the amount of enteral nutrition on markers of inflammation and coagulation in a randomized, controlled single center study of early trophic versus early full-energy enteral feeds in critically ill mechanically ventilated ICU patients with acute respiratory failure. The two enteral feeding strategies resulted in similar clinical outcomes including ventilator free-days, hospital-free days, organ failure-free days, and hospital survival.¹⁴ Our current study defines the effects of these two different feeding strategies on systemic markers of inflammation and coagulation. Our patient population was critically ill with a median APACHE II score of 26.5 and a mortality rate of 20%, slightly lower than what has been reported in a large prospective cohort study of patients with acute respiratory failure.¹ Furthermore, the cytokine profiles in patients who lived versus those who died are consistent with published data showing higher levels of IL-6, IL-8 and TNF- α in patients who died versus those who survived.^{3, 4, 16} Elevated levels of inflammatory cytokines are not only markers of disease, but they are also thought to be pathogenic. In fact, the ARDS Network lower tidal volume ventilation study¹⁷ showed that lower tidal volume

ventilation not only improves mortality in patients with ALI it also attenuates markers of inflammation by day 3.² Given the lack of current therapies and the unacceptably high mortality rate for patient with acute respiratory failure, interventions in the ICU that modulate inflammation might be beneficial.

In our study, tissue factor was an important predictor of mortality. Elevated levels of both baseline and day 6 TF levels were associated with increased mortality, as was the change in TF levels between day 0 and day 6. TF is the most potent initiator of the extrinsic coagulation cascade and is elevated in cancer associated thrombosis,¹⁸ cardiovascular disease,¹⁹ obesity,²⁰ and sepsis.²¹ In addition, TF levels are elevated in patients with ARDS compared to those at risk for ARDS who did not develop disease^{22, 23}. However, no previous studies have shown a relationship between TF levels and outcome in patients with acute respiratory failure. TF upregulation and activation of coagulation is central to the pathogenesis of sepsis and ARDS and multiple animal models have shown beneficial effects of TF blockade in sepsis and multiorgan failure.^{24, 25} Therefore, modulation of coagulation is an appealing therapeutic target in critically ill patients.

With regards to enteral feeding strategy, our data suggest that in a population of patients with acute respiratory failure, trophic enteral feeds may modulate inflammation and coagulation to a greater degree than do full-energy feeds. Although there were no statistically significant differences in markers of coagulation and inflammation between the two treatment groups at day 6; IL-10, IL-12, IL-8 and TF were non-significantly lower at day 6 in the trophic EN group compared to the full-energy EN group. Furthermore, in patients with paired day 0 and day 6 samples, all of the markers of coagulation and inflammation were non-significantly lower at day 6 compared to day 0 in the trophic group while many of the markers of inflammation and both coagulation markers were higher at day 6 in the full-energy group. Finally, a larger percentage of patients in the trophic group had falling PAI-1 levels. Why might enteral feeding modulate inflammation? Pre-clinical and clinical studies suggest links between nutrition and inflammation. It is well established that caloric restriction modulates both the innate and adaptive immune system by warding off immune senescence, maintaining naïve T cells and modifying the host response to infection or autoimmunity.²⁶ Interestingly, chronic caloric restriction also prolongs life in organisms from fruit flies to humans.²⁷ How these effects relate to critical illness are unknown. Although the data on enteral feeds in critically ill patients is limited, several studies have shown that inflammatory markers can be modulated by diet in ambulatory populations. Hermsdorff *et al* placed obese subjects who were otherwise healthy on a hypocaloric diet and found that markers of inflammation, C-reactive protein, complement C3 and TNF- α , were reduced compared to baseline after 8 weeks.²⁸

Other studies have not shown any effect of diet or nutrition on markers of inflammation.^{29, 30} In addition, there are genetic links between metabolism and inflammation. A polymorphism of the IL-6 gene promoter is associated with higher levels of C-reactive protein, a marker of inflammation, as body fat increases³¹ suggesting an interplay between metabolism and response to inflammation. Our study shows that TF levels increased slightly on average in the full-energy group while levels decreased in patients on trophic tube feeds. It is worth noting that only half of the patients had a day 6 sample and thus were included in the day 6 analysis so the study was underpowered to detect a difference in day 6 TF levels. The current findings suggest that volume of enteral nutrition may have some modest effects on circulating TF levels in critically ill patients. Although several studies have demonstrated the effects of nutrition and antioxidants on circulating markers of coagulation and fibrinolysis, none have examined these in an ICU population or where patients receive continuous enteral feedings. In healthy adults who consume a 40% fat meal there is a 56.2% increase in circulating TF levels 3.5 hours after the meal and levels

are still 34% above baseline at 6 hours without a change in TFPI levels³². One study in diabetic patients showed a transient increase in post-prandial tissue factor pathway inhibitor (TFPI) at 4 hours that decreased to baseline by 8 hours³³. This study did not measure TF levels so the effect of this transient increase of TFPI on TF procoagulant activity in this population is unknown. Plasma levels of PAI-1 are increased after starch and fat meals³⁴ and after an oral fat load in patients with coronary artery disease³⁵.

There are several potential mechanisms by which EN may modulate inflammation and coagulation. Changes in gut flora are associated with septic complications and death in critically ill patients.³⁶ Enteral feeding can modulate the microbial flora of the intestinal tract.³⁷ In addition to changes in gut flora, critical illness and sepsis are associated with changes in intestinal barrier function.³⁸ enteral nutrition has been shown in several experimental models and some human studies to promote the maintenance of intestinal barrier function.^{39–42} Furthermore, changes in intestinal immune function are deranged in critical illness⁴³ and enteral nutrition can restore gut immunity.^{44,45} Although there are several potential mechanisms by which EN may modulate inflammation, less is known about the effects of volume of tube feeds on these pathways. Overfeeding in critical illness can cause hyperglycemia and alter oxygen consumption and carbon dioxide production and underfeeding has been linked with an increased risk of ICU complications.⁴⁶ Our study attempts to address some unanswered questions by studying the effects of different feeding strategies on inflammation and coagulation in critically ill patients.

Our study has some limitations. First, it is a single center study of a deliberately heterogeneous patient population who may have very different inflammation and coagulation profiles depending on their reason for developing acute respiratory failure. This could have biased us toward the null hypothesis and caused us to overlook an important effect of enteral nutrition on systemic inflammation and coagulation in important subgroups of patients. Second, we only collected plasma samples from patients who were still receiving enteral feeds or were still in the ICU on day 6. By day 6, half of the patients had either died or been extubated and not available to provide specimens, although these numbers were similar between the two groups. Without blood samples from these patients it is impossible to know what effects the enteral feeding strategy had on inflammation and coagulation on patients who were extubated or died prior to day 6. Future studies should either look at earlier time points or measure biomarkers even in patients who were extubated by day 6.

In summary, we have shown that trophic EN may have some modest effects on markers of inflammation and coagulation in a more favorable way compared to full-energy EN. A number of these cytokines and markers of coagulation and fibrinolysis were associated with mortality in this and other studies in critical illness. Although the randomized clinical trial did not show a benefit to either strategy in ventilator free days, the primary endpoint, patients who received full-energy EN were more likely to be discharged home with or without help versus to a rehabilitation facility (68.3% for the full-energy group versus 51.3% for the trophic group, $p=0.04$).¹⁴ Our findings of modestly attenuated coagulation and inflammation suggest a potential protective role for trophic EN compared to full-energy EN in the acute setting that may or may not translate into long-term clinical outcomes. Thus the effects of enteral feeding strategy on systemic inflammation and coagulation may result in small changes in clinical outcomes in larger studies with more power or specific subgroups of critically ill patients. Future studies in modulation of inflammation and coagulation using enteral feeds should be conducted to identify the specific patient population, proper timing, and duration of intervention to maximally modulate systemic inflammation and coagulation.

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Figure 1. Percent mortality according to baseline cytokine quartile

Bar graph showing 28 day mortality percent for quartiles of IL-6, IL-8, and TNF-α. p values by Chi Square are * $p=0.0005$, ** $p<0.001$, and $\pi p=0.039$ respectively.

Figure 2. Percent mortality according to baseline coagulation protein quartile

Bar graph showing 28 day mortality percent for quartiles of TF or PAI-1. In a multivariable model the 4th TF quartile was associated with a 3.7 fold increased odds of death compared to the first quartile (*p=0.049) while PAI-1 quartiles were not associated with mortality (OR 2.6, p=0.147).

Figure 3. Boxplot of day 6 TF levels according to 28 day mortality

Of the patients who were alive and in the study at 6 days, TF levels were higher at 6 days in patients who died versus those who were alive at 28 days. $p=0.014$

Figure 4. Boxplot of change in IL-6 by treatment group

IL-6 levels decreased by day 6 in both the trophic and full-energy treatment groups (* $p < 0.001$ by Mann Whitney U).

Figure 5. TF levels are decreased in the trophic group at day 6

Boxplot of TF levels at baseline and day 6 in patients randomized to trophic versus full-energy feeds. Only patients with paired day 0 and day 6 samples were included in analysis. Horizontal lines represent median values, boxes represent 25th-75th confidence interval (CI) and whiskers represent 10th-90th CI. *p=0.061 by Wilcoxon signed rank test.

Table 1

TF and PAI-1 levels in trophic and full-energy feeding groups

	Trophic feeds		P value	Full-energy feeds		P value
	Survivors (N=46)	Non-survivors (N=8)		Survivors (N=41)	Non-survivors (N=8)	
TF pg/ml	233.4 (161.2–111.5)	502.4 (252.3–754.6)	0.041	283.9 (138.9–758.4)	438.7 (239.4–746.5)	0.099
PAI-1 ng/ml	169.1 (101.4–10.1)	208.4 (119.3–349.8)	0.592	171.4 (82.6–301.8)	178.7 (34.1–772.7)	0.914

Data expressed as median (CI)

Table 2

Multivariable analysis of mortality and biomarker levels

	Unadjusted Analysis Odds Ratio for Mortality ^a	P value	Adjusted Analysis Odds Ratio for Mortality ^a	P value
IFN- γ (pg/ml)	1.97 (0.70–5.56)	0.160	2.08 (0.69–6.27)	0.194
IL-10 (pg/ml)	2.63 (0.90–7.67)	0.077	1.84 (0.58–5.83)	0.302
IL-12 (pg/ml)	1.66 (0.61–4.59)	0.315	1.90 (0.66–5.46)	0.236
IL-1 β (pg/ml)	2.42 (0.84–6.00)	0.108	2.07 (0.73–5.83)	0.170
IL-6 (pg/ml)	6.16 (1.88–20.18)	0.003	8.50 (1.91–37.84)	0.005
IL-8 (pg/ml)	38.6(4.9–304.5)	0.001	43.8 (4.57–420.6)	0.001
TNF- α (pg/ml)	2.99 (1.03–8.65)	0.043	2.67 (0.72–9.87)	0.142
TF (pg/ml)	2.58 (0.82–8.13)	0.106	3.73 (1.01–13.81)	0.049
PAI-1 (ng/ml)	2.63 (0.90–7.67)	0.770	2.56 (0.72–9.17)	0.147

^aOdds ratio for mortality comparing the highest versus lowest quartile of each biomarker. Adjusted odds ratios were adjusted for age, APACHE II, presence of shock at admission.

Table 3

Baseline and day 6 coagulation and cytokine biomarkers by treatment group.

	Day 0			Day 6		
	Trophic (N=89)	Full-Energy (N=96)	P value	Trophic (N=54)	Full-Energy (N=49)	P value
IFN- γ (pg/ml)	1.6 (0.9–3.4)	1.3 (0.7–2.8)	0.129	2.0 (0.8–4.0)	1.6 (0.9–3.5)	0.446
IL-10 (pg/ml)	8.3 (3.8–24.4)	6.8 (3.8–14.5)	0.155	6.9 (4.4–22.4)	5.9 (3.2–19.3)	0.169
IL-12 (pg/ml)	1.9 (0.9–4.5)	1.8 (0.9–3.8)	0.436	1.7 (0.9–3.9)	2.2 (0.9–4.6)	0.456
IL-1 β (pg/ml)	0.6 (0.3–1.3)	0.6 (0.3–1.0)	0.884	0.6 (0.3–1.2)	0.6 (0.3–0.9)	0.825
IL-6 (pg/ml)	42.5 (19.6–112.5)	40.6 (15.2–106.7)	0.606	14.6 (9.3–40.8)	12.0 (5.9–33.8)	0.330
IL-8 (pg/ml)	18.4 (9.3–59.9)	19.0 (9.4–124.2)	0.420	20.3 (13.6–35.7)	23.0 (12.8–34.9)	0.825
TNF- α (pg/ml)	9.4 (6.2–18.9)	10.2 (6.7–14.0)	0.839	10.8 (7.9–14.8)	9.9 (7.0–15.8)	0.436
TF (pg/ml)	415.0 (225.6–692.1)	346.0 (230.9–585.6)	0.300	247.4 (171.4–532.8)	322.4 (143.5–620.1)	0.864
PAI-1 (ng/ml)	131.7 (57.2–318–8)	117.0 (59.5–222.7)	0.204	172.7 (106.1–310.1)	169.8 (68.1–257.3)	0.620

Biomarkers at days 0 and 6 in patients randomized to trophic versus full energy feeds. Biomarker levels were compared in all patients who had paired samples at day 0 and day 6.

Table 4

	Trophic Feeds (N=51)		P Value	Full-Energy Feeds (N=47)		P value
	Day 0	Day 6		Day 0	Day 6	
IFN- γ (pg/ml)	2.4 (1.1–4.0)	2.0 (0.7–4.0)	0.521	1.2 (0.6–2.9)	1.6 (0.9–2.7)	0.615
IL-10 (pg/ml)	8.6 (3.8–24.2)	6.8 (4.2–22.0)	0.230	8.6 (3.2–21.2)	5.7 (3.2–16.7)	0.068
IL-12 (pg/ml)	2.3 (0.9–3.9)	1.7 (0.9–4.0)	0.041	2.0 (0.9–4.7)	2.2 (0.9–4.7)	0.562
IL-1 β (pg/ml)	0.6 (0.3–1.5)	0.5 (0.3–1.3)	0.024	0.6 (0.4–1.1)	0.6 (0.3–0.9)	0.334
IL-6 (pg/ml)	55.6 (24.8–144.1)	14.6 (9.1–46.1)	<0.001	32.8 (16.5–110.4)	12.0 (5.8–32.5)	<0.001
IL-8 (pg/ml)	19.0 (11.3–47.0)	20.1 (12.9–34.8)	0.168	19.7 (10.1–41.2)	22.6 (12.7–34.2)	0.816
TNF- α (pg/ml)	10.9 (6.4–20.2)	10.8 (7.7–14.3)	0.985	9.9 (6.3–14.0)	9.5 (7.0–15.5)	0.910
TF (pg/ml)	334.3 (223.8–631.5)	247.8 (171.8–529.5)	0.061	314.3 (192.2–519.5)	331.8 (143.0–652.7)	0.427
PAL-1 (ng/ml)	202.6 (93.0–626.0)	176.5 (107.2–352.4)	0.639	135.9 (68.5–305.1)	171.4 (75.1–257.7)	0.179