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Nutrition for Critically Ill Patients

How Much Is Enough?

Richard D. Griffiths, BSc, MBBS, MD, FRCP, FFICM

HEALTHY ADULTS HAVE A CLOSELY INTERRELATED nutritional, metabolic, and immune system that regulates food requirements and responds well to short-term nutritional deprivation but not to nutrient excess.¹ However, when critically ill, patients no longer have control over their food intake, and clinicians may administer nutritional support with little understanding of individual patient needs in the light of inflammatory demands, injury responses, and the underlying influences of genotype and age.² Because robust evidence about the nutritional requirements for critically ill patients at the various stages of their illness is lacking, particularly when they are acutely ill,³ clinicians often base nutritional support on “requirements” based on averages and guesswork.

Nutritional support in excess of actual requirements may contribute to metabolic stress.⁴ In the intensive care unit (ICU), parenteral nutrition can facilitate excessive early provision of nutrients during a period of considerable uncertainty about requirements. This was illustrated in the study by Casaer et al,⁵ in which very early targeting of full feeding requirements with parenteral nutrition in the first few days was not beneficial. The authors of that study suggested the possibility that nutrition might suppress the normal activation of acute mechanisms necessary to remove cellular damage.⁶ In patients receiving mechanical ventilation, enteral feeding rarely delivers consistently more than 80% of the target full feeding, but it is still reasonable to question whether further restriction of enteral nutrition would be preferable during the early stages of an acute illness.

In this issue of JAMA, Rice and colleagues, writing for the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network,⁷ report findings examining whether there is any advantage to restricting the amount of initial enteral intake among mechanically ventilated patients with acute lung injury (ALI). The EDEN study was a large, unblinded trial from 44 sites that recruited 1000 patients soon after starting ventilation and developing ALI (about 80% of which was attributable to primary pneumonias or sepsis). The study hypothesis was that administration of considerably reduced, trophic feeding (about 25% of the target full feeding) during the first 6 days would increase ventilator-free

days (VFDs) compared with a more actively advanced conventional full enteral nutrition regimen achieving a target target intake of 80%. This hypothesis was not supported by the study findings: there was no difference between trophic feedings vs full enteral feedings in VFDs or any important secondary end points, including ICU stay, organ failure-free days, 28-day mortality, and 60-day mortality.

Nonetheless, this study highlights several important practical points. The majority of these patients can be fed nasogastrically; the majority tolerate gastric residual volumes of 400 mL, measured at 6-hour intervals, without high rates of aspiration or increased ventilator-associated pneumonia; and using a protocolized approach for feeding allows clinicians to deliver a greater volume of the target feeding amounts than prior groups have reported. One potentially confounding factor was that the study was initially combined in a factorial design with another study, the OMEGA trial,⁸ which randomized patients to receive a supplement containing omega-3 fatty acids, γ -linolenic acid, and antioxidants until stopped for futility after 272 patients (27%) had been recruited.

The results of the trial by Rice et al⁷ cannot be used to conclude that trophic feeding is equivalent to full feeding in critically ill patients. This study was not designed or powered as an equivalence study and does not provide definitive data to inform clinicians about how much nutritional support is enough, how early it should be started, or even if there should be “no nutrition provision” in the initial phase of critical illness—a case that has been persistently argued and remains to be tested.⁹

The effect of nutrition on an end point such as VFDs does not simply depend on dose and duration but on several other factors. These may include a complex interaction of prior nutritional reserves; the effects of any initial or evolving nutritional deficiency; the extent and severity of the underlying illnesses; the processes of recovery interacting with the metabolic signaling and stress from the nutrients; and the burdens imposed by the complications of providing nutritional support. These factors suggest that not all patients may benefit equally.¹⁰ An important challenge is identifying patients at increased nutritional risk.

Author Affiliation: Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, Faculty of Health & Life Sciences, University of Liverpool, Liverpool, United Kingdom.

Corresponding Author: Richard D. Griffiths, BSc, MBBS, MD, FRCP, FFICM, Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, Faculty of Health & Life Sciences, University of Liverpool, Duncan Bldg, Daulby Street, Liverpool, L69 3GA, United Kingdom (rdg@liverpool.ac.uk).

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In the study by Rice et al,⁷ patients were relatively young (mean, 52 years), apparently well nourished, and relatively overweight (body mass index of 30), and 29% had diabetes. All patients had a reasonably functional gastrointestinal tract and may not have been nutritionally challenged. The most severely ill patients with lung injury were probably excluded because of gastrointestinal failure, and 90% of patients in the full-feeding group in the study tolerated full feedings within little more than a day. It appears that the patients in this study were relatively less critically ill, such that more than half of patients no longer required mechanical ventilation within the 6-day nutrition test period. An important question is whether the relationship between nutrition and the risk of developing a new infection was the same among noninfected patients entering the study compared with the majority of patients who had pneumonia and sepsis at the time of admission.

Although Rice et al enrolled a large number of patients, as with any large study conducted in ICU settings, there is always significant case-mix heterogeneity, such as variation in primary pathology, illness severity, age, or nutritional state. By studying only patients with ALI, the authors limited heterogeneity, although inevitably some mix of causative pathologies remains.

It is possible that some inherent limitations hampered the ability to find a difference in outcomes. First, it is possible that the difference in the interventions was too modest. The full-feeding group was based on a calculated ideal body weight, which may have underestimated the nutritional requirements in many patients with higher body mass indices. Even though the investigators on average achieved 80% of the nutritional target in the full-feeding group, the data presentation may have concealed a wider variance that includes a proportion of patients with a lesser amount of nutritional support delivered. Some patients might have only received a more trophic feeding because of some gastrointestinal dysfunction, possibly the patients who theoretically may have benefited most from the intervention. Second, the hypothesis that trophic feeding has benefit in ALI may be incorrect. There was no evidence that any patient subgroup may have benefited. Neither the primary end point of VFDs nor any secondary end point, such as 60-day mortality, was different in relation to body mass index, shock, or severity of lung injury. There appears to be no strong biological mechanism to provide a firm pathophysiological explanation for how a few days of less enteral nutrition (amount and volume) might produce a reduced need for ventilation. Third, because nutritional support is not just about the acute state, longer-term end points, including functional outcomes, were not reported but may have been informative. For instance, in an earlier study, Rice et al¹¹ had observed that significantly more patients receiving full feedings, compared with trophic feedings, were discharged directly home rather than to a rehabilitation facility. The 6 days of profoundly limited protein intake in the trophic-feeding group in the current study had no apparent short-term effects, although the effects on longer-term outcomes remain unknown.

The evidence base with respect to nutritional issues in critically ill patients is limited. Studies evaluating drugs or other interventions among patients who only require short ICU stays often assume that only 1 factor is being assessed in a predictably consistent manner and in an attempt to modify a single pathology (as a drug action). These studies also attempt to recruit a sufficient number of patients so that other important differences between intervention groups are evenly distributed. However, this has not been the case with nutrition studies in critically ill patients and has contributed to widely differing interpretations in nutrition guidelines.¹² The outcomes from nutrition interventions need to be assessed over longer time frames and with consideration of the nature and type of patient and presence of gastrointestinal tract dysfunction.¹³ For studies of critically ill patients, individual patient requirements might have to be more accurately assessed or even measured to provide optimal therapy.

Providing effective nutritional support for critically ill patients represents a difficult aspect of the overall management of complex patients. The current study by Rice et al,⁷ taken together with existing data from other recent rigorous studies, highlights the need to challenge commonly used nutritional support practices and to achieve an individualized, evidence-based approach for optimal nutritional therapy in patients with ALI.

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Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury

The EDEN Randomized Trial

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

M ECHANICALLY VENTILATED patients cannot eat normally and if not fed for long periods become malnourished. Because malnutrition is associated with poor outcomes in critically ill patients, artificial nutrition is often provided, especially in those with acute lung injury (ALI) and with expected longer duration of mechanical ventilation. When feasible, enteral nutrition targeting full caloric needs has been advocated over parenteral nutrition.^{1,2} However, feeding intolerance and common care practices (eg, gastric residual volume [GRV] limits) often serve as practical barriers to reaching recommended goals.²⁻⁷

Although confounded by indication and severity of illness, several observational studies have shown improved clinical outcomes, including fewer infections, shorter duration of mechanical ventilation, and lower mortality for patients receiving a higher percentage of calculated caloric needs.^{6,8} Nonetheless, the best timing, formulation, and amount of enteral nutrition remain unknown. In fact, some recent data suggest that hypocaloric feeding, or permissive underfeeding, may result in shorter

Context The amount of enteral nutrition patients with acute lung injury need is unknown.

Objective To determine if initial lower-volume trophic enteral feeding would increase ventilator-free days and decrease gastrointestinal intolerances compared with initial full enteral feeding.

Design, Setting, and Participants The EDEN study, a randomized, open-label, multicenter trial conducted from January 2, 2008, through April 12, 2011. Participants were 1000 adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition at 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network.

Interventions Participants were randomized to receive either trophic or full enteral feeding for the first 6 days. After day 6, the care of all patients who were still receiving mechanical ventilation was managed according to the full feeding protocol.

Main Outcome Measures Ventilator-free days to study day 28.

Results Baseline characteristics were similar between the trophic-feeding (n=508) and full-feeding (n=492) groups. The full-feeding group received more enteral calories for the first 6 days, about 1300 kcal/d compared with 400 kcal/d ($P < .001$). Initial trophic feeding did not increase the number of ventilator-free days (14.9 [95% CI, 13.9 to 15.8] vs 15.0 [95% CI, 14.1 to 15.9]; difference, -0.1 [95% CI, -1.4 to 1.2]; $P = .89$) or reduce 60-day mortality (23.2% [95% CI, 19.6% to 26.9%] vs 22.2% [95% CI, 18.5% to 25.8%]; difference, 1.0% [95% CI, -4.1% to 6.3%]; $P = .77$) compared with full feeding. There were no differences in infectious complications between the groups. Despite receiving more prokinetic agents, the full-feeding group experienced more vomiting (2.2% vs 1.7% of patient feeding days; $P = .05$), elevated gastric residual volumes (4.9% vs 2.2% of feeding days; $P < .001$), and constipation (3.1% vs 2.1% of feeding days; $P = .003$). Mean plasma glucose values and average hourly insulin administration were both higher in the full-feeding group over the first 6 days.

Conclusion In patients with acute lung injury, compared with full enteral feeding, a strategy of initial trophic enteral feeding for up to 6 days did not improve ventilator-free days, 60-day mortality, or infectious complications but was associated with less gastrointestinal intolerance.

Trial Registration clinicaltrials.gov Identifiers: NCT00609180 and NCT00883948
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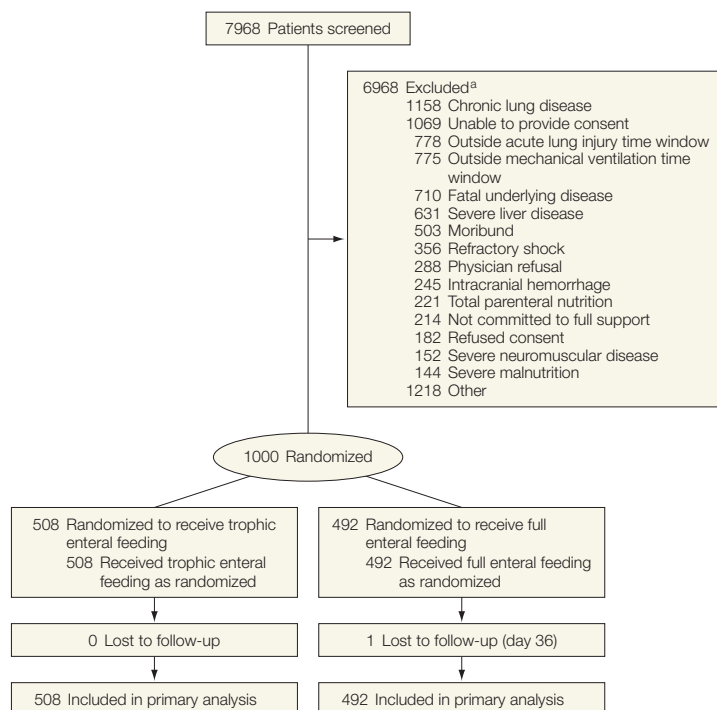
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*The authors/members of the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network Writing Committee and members of the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network are listed at the end of this article.

Corresponding Author: Todd W. Rice, MD, MSc, T-1218 MCN, Vanderbilt Medical Center, Nashville, TN 37232-2650 (todd.rice@vanderbilt.edu).

Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, *JAMA* (angusdc@upmc.edu).

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Figure 1. Enrollment, Randomization, and Follow-up

^aPatients may have had more than 1 exclusion criterion.

duration of mechanical ventilation and improved mortality.⁹⁻¹² Even minimal amounts of enteral feedings, sometimes called trophic nutrition, have beneficial effects, such as preserving intestinal epithelium, stimulating secretion of brush border enzymes, enhancing immune function, preserving epithelial tight cell junctions, and preventing bacterial translocation, despite not meeting daily caloric needs.¹³⁻¹⁵

Because of these conflicting data, we conducted a prospective randomized controlled trial comparing the effect of initial trophic enteral feeding vs initial protocolized full enteral feeding for the first 6 days of mechanical ventilation on clinical outcomes, including ventilator-free days (VFDs) and survival. We hypothesized that initial trophic feeding would increase the number of VFDs to study day 28 by reducing the number of instances of gastrointestinal intolerance compared with early, full enteral feeding.

METHODS

Investigators from 44 hospitals of the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network enrolled patients in this randomized, open-label study from January 2, 2008, through March 15, 2011. The institutional review board at each hospital and the data and safety monitoring board approved the study. Each patient or legally authorized representative provided written informed consent prior to any study procedures.

Patients

Patients within 48 hours of ALI onset who had received mechanical ventilation for less than 72 hours and whose physicians intended to administer enteral nutrition were eligible. ALI was defined by a ratio of the partial pressure of arterial oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) of less than 300 (adjusted if altitude ex-

ceeded 1000 m) with bilateral pulmonary infiltrates consistent with edema on chest radiograph without clinical evidence of left atrial hypertension.¹⁶

FIGURE 1 lists the most common exclusion criteria; a complete list of criteria is presented in the eMethods available at <http://www.jama.com>.

Participants were randomized via a web-based randomization system, stratified by site and presence of shock at enrollment, to receive either trophic or full enteral feeding for the first 6 days of mechanical ventilation. The initial 272 patients were also simultaneously randomized to a separate trial (the OMEGA study) comparing a nutritional supplement containing omega-3 fatty acids and antioxidants with an isocaloric, isovolemic control in a 2 × 2 factorial design.¹⁷

Study Procedures

The designated feeding strategy was initiated within 6 hours of randomization and continued until death, extubation, or day 6. The care of mechanically ventilated patients still receiving enteral feedings after day 6 was managed according to the full feeding strategy in both groups. In extubated patients who then required reintubation, enteral nutrition was restarted and managed according to the study protocol.

In the full-feeding group, enteral nutrition was initiated at 25 mL/h and advanced to goal rates as quickly as possible, adhering to the protocol in FIGURE 2. Gastric residual volumes were checked every 6 hours while enteral feeding was increased. Full-feeding rates were calculated with goals of 25 to 30 kcal/kg per day of nonprotein calories and 1.2 to 1.6 g/kg per day of protein (eMethods).

Patients randomized to the initial trophic-feeding group had enteral nutrition initiated at 10 mL/h (10-20 kcal/h) for the first 272 patients who also received the omega-3 or control supplement (240 mL volume per day). After the data and safety monitoring board stopped the OMEGA portion of the factorial design, the initial trophic feed-

ing rate was changed to 20 kcal/h to approximate the calories that had been delivered in the OMEGA study. GRVs were checked every 12 hours during trophic feeding. In patients randomized to trophic feeding, enteral nutrition was advanced to full-energy feeding rates following the same protocol used for the full-feeding group (Figure 2) if they were still receiving mechanical ventilation at 144 hours.

Both feeding strategies specified when and for how long to hold enteral nutrition for GRVs greater than 400 mL and for other gastrointestinal intolerances (eMethods). Per usual intensive care unit (ICU) practice, patients were maintained in the semirecumbent position whenever possible.¹⁸

Simplified versions of previous ARDS Network lung protective ventilation¹⁹ and fluid-conservative hemodynamic management protocols²⁰ were used in all patients. Blood glucose control was accomplished using institution-specific insulin protocols targeting ranges of 80 to 150 mg/dL (to convert to mmol/L, multiply by 0.0555), with tighter control allowed.

Primary and Secondary End Points

Ventilator-free days (VFDs) through day 28 was the primary end point (eMethods). Hospitalized patients who died before day 28 were considered to have zero VFDs. Secondary end points included daily percentage of goal enteral feeding, frequency of gastrointestinal intolerances, 60-day mortality before hospital discharge with unassisted breathing, ICU- and organ failure-free days, and new infections. Patients discharged to rehabilitation or chronic ventilator facilities who died while receiving assisted breathing prior to day 60 are included in hospital mortality. Patients alive in the hospital at day 60 were considered to have survived.

Statistical Analysis

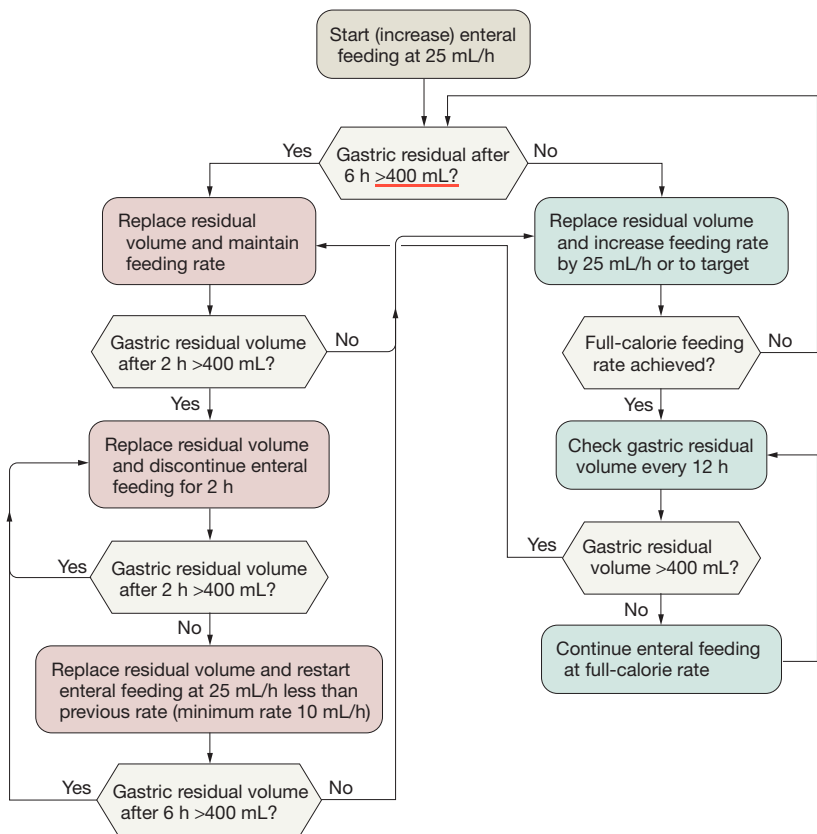
Enrollment of 1000 patients with 4 planned interim analyses had statistical power of 91% to detect a 2.25-day difference in VFDs, assuming a mean of 14 and standard deviation of 10.5

VFDs.²⁰ All analyses were by intention-to-treat and were performed using SAS version 9.2. Interim assessments followed the O'Brien-Fleming method, with a 2-sided *P* value of .0429 for determining significance of VFDs at the final analysis. For other analyses, 2-sided *P* values of .05 or less were considered significant.

Per National Institutes of Health protocol, race/ethnicity information was collected from administrative data using census definitions. All baseline assessments used prerandomization values. Baseline continuous variables are reported as means and standard deviations, while categorical variables are reported as percentages, with differences assessed using *t* tests and χ^2 analyses, respectively. Gastrointestinal intolerances are reported as percent-

age of patients receiving enteral feeding who experience any intolerance each day through day 12 and compared using logistic regression. Specific gastrointestinal intolerances are reported as the percentage of days patients were fed through day 12 on which they experienced the intolerance and analyzed using a Poisson regression model. Daily percentage of goal calories received was calculated as total volume received through enteral feeding each day divided by 24 times the hourly goal feeding rate times 100. Overall incidence of gastrointestinal intolerances, percentage of goal calories received, VFDs, ICU-free days, and organ failure-free days are reported as means and standard deviations, with differences assessed using analysis of variance controlling for

Figure 2. Full-Feeding Protocol



Left side indicates actions to be taken for gastric residual volumes greater than 400 mL; right side advances enteral feeding every 6 hours to goal rates as long as gastrointestinal intolerances are not present.

baseline shock and OMEGA group assignment.

A secondary analysis tested for significance of 2-way interactions between OMEGA assignment and tro-

phic vs full feeding on VFDs. Cochran-Mantel-Haenszel test stratified by baseline shock and OMEGA assignment was used to analyze mortality. Proportion curves were plotted sepa-

rately for time to death and hospital discharge. One patient in the full-feeding group, lost to follow-up at day 36, was assumed alive in the mortality analysis and censored in the curves.

RESULTS

Approximately 8000 patients were screened to accrue 1000 study participants; exclusions are shown in Figure 1. The groups were comparable at baseline (TABLE 1). There was no difference between groups with regard to the primary end point, VFDs to day 28, with the trophic-feeding group having an average of 14.9 (95% CI, 13.9 to 15.8) VFDs compared with 15.0 (95% CI, 14.1 to 15.9) VFDs in the full-feeding group (difference, -0.1 [95% CI, -1.4 to 1.2]; $P = .89$). There was no interaction between OMEGA assignment and feeding group on VFDs ($P = .47$). There also were no differences in 60-day mortality (23.2% [95% CI, 19.6% to 26.9%] vs 22.2% [95% CI, 18.5% to 25.8%]; difference, 1.0% [95% CI, -4.1% to 6.3%]; $P = .77$) (FIGURE 3), organ failure-free days, ICU-free days, or the incidence of infection between groups (TABLE 2). Similarly, there were no differences between groups in VFDs or survival when analyzed by body mass index category or when subsets of patients with shock or more severe lung injury (acute respiratory distress syndrome) were examined (eTable).

There was prompt treatment separation between groups that persisted for the first 6 days, with the trophic-feeding group receiving approximately 400 kcal per day, representing 25% of their calculated caloric goal, compared with approximately 1300 kcal per day, or 80% of the calculated caloric goal, in the full-feeding group (FIGURE 4A and B) ($P < .001$). Postpyloric tubes were used in less than 20% of patients. In the full-feeding group, 444 patients (90%) reached goal feeding rates in a mean time of 1.3 (SD, 1.2) days. In the trophic-feeding group, 217 of the 242 patients still receiving ventilation on day 6 (90%) reached goal feeding rates in 6.7 (SD, 1.8) days ($P < .001$).

Table 1. Baseline Characteristics

Characteristic	Mean (SD)	
	Trophic Feeding (n = 508)	Full Feeding (n = 492)
Age, y	52 (17)	52 (16)
Women, No. (%)	241 (47)	249 (51)
White, No. (%)	387 (81)	375 (79)
Medical ICU, No. (%)	309 (61)	309 (63)
Primary lung injury category, No. (%)		
Pneumonia	341 (67)	309 (63)
Sepsis	82 (16)	63 (13)
Aspiration	42 (8)	54 (11)
Trauma	17 (3)	19 (4)
Transfusion	4 (1)	12 (2)
Other	21 (4)	34 (7)
Hours from intubation to randomization, No. (%)		
<24	202 (40)	180 (37)
24-<48	252 (50)	256 (52)
48-72	50 (10)	53 (11)
Weight, kg	85.9 (23.5)	87.0 (25.8)
BMI ^a	29.9 (7.8)	30.4 (8.2)
APACHE III score	92 (28)	90 (27)
Diabetes, No. (%)	136 (27)	142 (29)
Baseline vasopressor use, No. (%)	188 (37)	190 (39)
Prestudy fluid intake, L/24 h	4.4 (2.8)	4.3 (3.2)
Mean arterial pressure, mm Hg	75 (13)	77 (15)
Central venous pressure, mm Hg	11.8 (5.0)	11.6 (4.9)
Tidal volume, mL/kg patient body weight	6.8 (1.4)	6.7 (1.3)
Minute ventilation, L/min	11.1 (3.4)	10.8 (3.3)
Plateau pressure, cm H ₂ O	23.6 (5.9)	23.8 (5.9)
PEEP, cm H ₂ O	9.2 (3.9)	9.8 (4.4)
Paco ₂ , mm Hg	39.4 (9.9)	40.2 (9.3)
PaO ₂ :Fio ₂ ratio	168 (79)	164 (82)
PaO ₂ :Fio ₂ ratio ≤ 200 , No. (%)	356 (70)	351 (71)
Oxygenation index	11.7 (8.7)	12.6 (8.9)
Hemoglobin, mg/dL	10.4 (2.0)	10.3 (1.9)
Creatinine, mg/dL	1.6 (1.4)	1.8 (1.6)
BUN, mg/dL	28 (22)	29 (24)
Glucose, mg/dL	133 (54)	136 (51)
Albumin, mg/dL	2.3 (0.7)	2.3 (0.7)
Total protein, g/dL	5.0 (1.1)	5.1 (1.1)
Gastric tube position, No. (%)	422 (85)	404 (86)
Feeding in 12 h before randomization		
Any intake, No. (%)	153 (30)	146 (30)
Volume delivered, mL	316 (299)	321 (289)

Abbreviations: APACHE III, Acute Physiology and Chronic Health Evaluation III; BMI, body mass index; BUN, blood urea nitrogen; Fio₂, fraction of inspired oxygen; ICU, intensive care unit; PEEP, positive end-expiratory pressure. SI conversion factors: To convert creatinine values to $\mu\text{mol/L}$, multiply by 88.4; BUN values to mmol/L , multiply by 0.357; glucose values to mmol/L , multiply by 0.0555.

^aCalculated as weight in kilograms divided by height in meters squared.

Gastrointestinal intolerances occurred less often in the trophic-feeding group, with significantly fewer intolerances on study days 2 and 3 (FIGURE 5). Specifically, there were fewer days on which patients in the trophic-feeding group experienced regurgitation (0.4% vs 0.7%; $P=.003$), vomiting (1.7% vs 2.2%; $P=.05$), elevated GRVs (2.2% vs 4.9%; $P<.001$), and constipation (2.1% vs 3.1%; $P=.003$) compared with the full-feeding group. There was no difference between groups in the percentage of feeding days on which diarrhea (16.5% vs 18.7%; $P=.16$), aspiration (0.2% vs 0.3%; $P=.08$), or abdominal distention or cramping (6.1% vs 6.8%; $P=.35$) occurred in the trophic- vs full-feeding groups, respectively (eFigure 1). Patients in the full-feeding group also had more feeding days on which they were given antidiarrheal (1.5% vs 0.8%; $P<.001$) and prokinetic agents (11.7% vs 7.9%; $P=.001$).

Mean plasma glucose values and average hourly insulin administration were higher in the full-feeding group during the first 6 days (FIGURE 6A and B). However, when the trophic-feeding group was increased to full feeding, glucose values and insulin doses were not different.

Fluid intake as well as output was greater on every study day in the full-feeding group (eFigure 2A and B). However, the higher output did not offset the substantially higher intake, resulting in a greater cumulative net fluid balance. By study day 7, the full-feeding group had gained 2.1 (95% CI, 1.2 to 2.9) liters of fluid, whereas the trophic-feeding group had gained 0.4 (95% CI, -0.5 to 1.3) liters ($P=.01$) (FIGURE 7). Despite differences in fluid balance, measures of circulatory physiology and support (eg, pulse, blood pressure, central venous pressure, vasopressor use) (eFigure 3A-D) and pulmonary physiology and support (eg, tidal volume, minute ventilation, $\text{PaO}_2\text{:FiO}_2$ ratio, oxygenation index, PaCO_2 , plateau pressure, positive end-expiratory pressure) did not differ between groups over time (eFigure 4A-G).

Mild hypokalemia, hypomagnesemia, and hypophosphatemia were common in both groups; however, there were no differences between groups in plasma concentrations of sodium, bicarbonate, magnesium, or phosphate (eFigure 5A-E). Small but statistically higher potassium levels were seen on days 4 through 7 in the full-feeding group (eFigure 5B). Mean total protein levels increased slightly over time in both groups, whereas mean plasma albumin levels changed little in both groups (eFigure 5F-G).

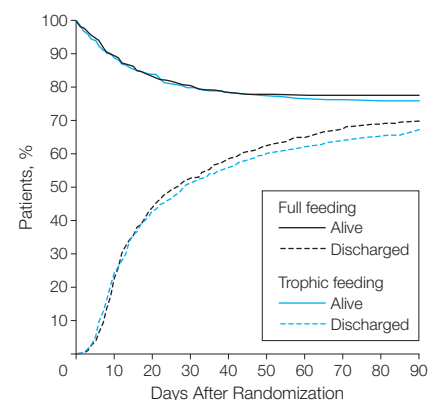
COMMENT

This study demonstrated no statistically significant difference in clinical outcomes, including VFDs, among patients with ALI initially provided trophic vs full enteral feeding for the first 6 days of mechanical ventilation. Contrary to previous reports in critically ill adults, hypocaloric nutrition did not significantly reduce mortality,^{11,12} decrease infectious complications,¹⁰⁻¹² or reduce lengths of stay.¹² Similarly, these results failed to demonstrate improved outcomes with permissive underfeeding in any body mass index subgroup, including obese, critically ill patients.⁹ Likewise, these results also differ from previously reported benefits of providing higher caloric intake in critically ill adults.^{4,6,8} However, since our study was not an equivalence design, small but potentially clinically relevant differences in either VFDs or mortality

may still exist. Patients receiving trophic enteral feedings experienced fewer episodes of feeding intolerance despite receiving fewer medications to treat intolerance.

This study does not address the safety or efficacy of foregoing all enteral intake, of trophic feeding for more than 6 days, or of trophic feeding in patients with preexisting malnutrition. Because the study design excluded pa-

Figure 3. Survival and Hospital Discharge

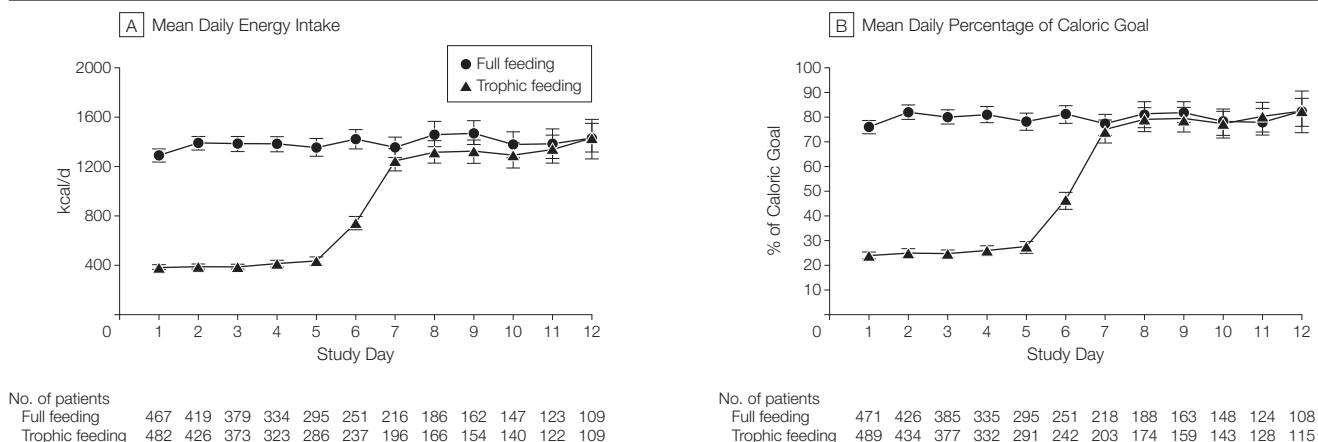


Percentages were calculated daily; the denominator at all times represents all patients in each group with the exception of 1 patient in the full-feeding group who was lost to follow-up and censored in these plots at day 36. The solid lines represent the proportion of patients surviving at each time; dashed lines represent the proportion of patients discharged from the hospital at each time. The areas above the solid lines represent the proportion of patients who have died in each group at each time; the areas below the dashed lines represent the proportion of patients alive and discharged from the hospital at each time. Areas between the solid and dashed lines represent the proportion of patients alive but still hospitalized in each group at each time.

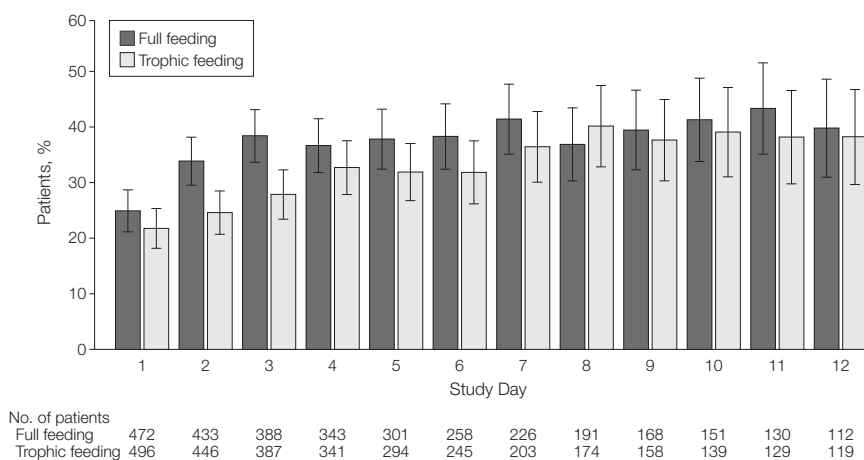
Table 2. Clinical Outcomes

Outcome	Trophic Feeding (n = 508)	Full Feeding (n = 492)	P Value
Ventilator-free days, No. (95% CI)	14.9 (13.9-15.8)	15.0 (14.1-15.9)	.89
Failure-free days, No. (95% CI)			
Cardiovascular	19.1 (18.2-20.0)	18.9 (18.1-19.8)	.75
Renal	20.0 (19.0-20.9)	19.4 (18.4-20.5)	.43
Hepatic	22.0 (21.2-22.9)	22.6 (21.8-23.5)	.37
Coagulation	22.3 (21.4-23.1)	23.1 (22.3-23.9)	.16
ICU-free days, No. (95% CI)	14.4 (13.5-15.3)	14.7 (13.8-15.6)	.67
60-d mortality, No. (%) [95% CI]	118 (23.2) [19.6-26.9]	109 (22.2) [18.5-25.8]	.77
Development of infections, No. (%) [95% CI]			
VAP	37 (7.3) [5.0-9.5]	33 (6.7) [4.5-8.9]	.72
Clostridium difficile colitis	15 (3.0) [1.5-4.4]	13 (2.6) [1.2-4.1]	.77
Bacteremia, No. (%)	59 (11.6) [8.8-14.4]	46 (9.3) [6.8-11.9]	.24

Abbreviations: ICU, intensive care unit; VAP, ventilator-associated pneumonia.

Figure 4. Daily Energy Intake and Daily Percentage of Goal Enteral Feedings

Sample sizes reflect numbers of patients with available data still receiving mechanical ventilation and enteral feeding on each day. A, Randomization occurred on day 0. Error bars represent 95% CIs. $P < .001$ at days 1, 2, 3, 4, 5, and 6; $P = .03$ at day 9. B, Randomization occurs on day 0. Error bars represent 95% CIs. $P < .001$ at days 1, 2, 3, 4, 5, and 6.

Figure 5. Daily Gastrointestinal Intolerances

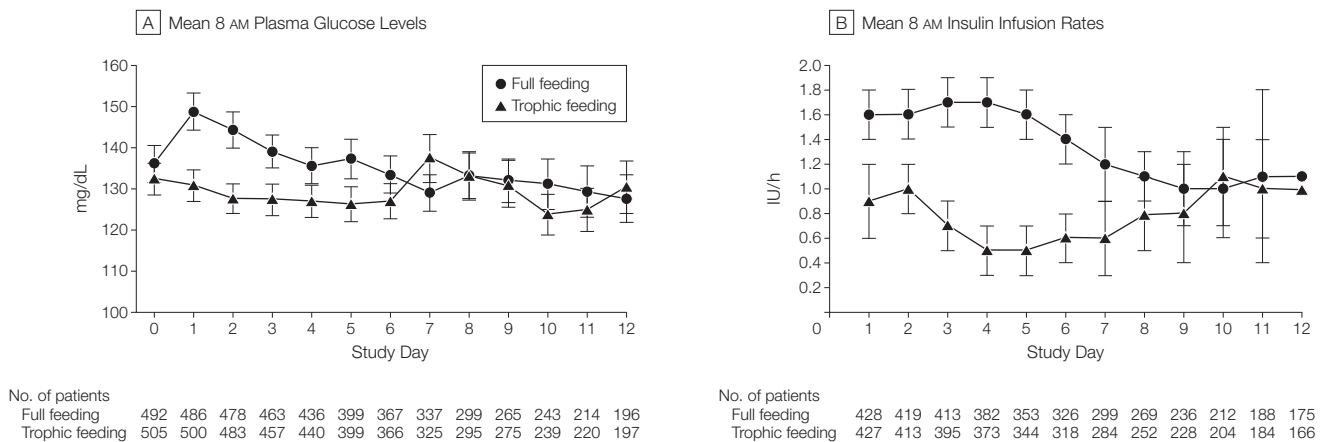
Percentage of patients on each study day meeting at least 1 gastrointestinal intolerance criterion. Sample sizes reflect numbers of patients with at least 1 intolerance and still receiving mechanical ventilation and enteral feeding. Error bars represent 95% CIs. $P < .001$ at days 2 and 3.

tients receiving ventilation for more than 72 hours and required initiation of enteral nutrition within 48 hours of developing ALI in both groups, it cannot inform regarding the safety of longer periods of withholding feeding or if outcomes of patients who received no feeding for up to 6 days would be similar to outcomes of those receiving trophic feeding. These results also neither support nor refute suggested benefits of initiating at least some enteral nutrition early in the ICU.^{21,22} Ar-

tinian et al²¹ showed better outcomes with early feeding compared with delayed feeding. However, in our study, enteral nutrition was initiated in both groups within 48 hours in 90% of patients, which is similar to the definition of early feeding used by Artinian et al. Likewise, the meta-analysis by Doig et al²² suggests benefit of starting enteral feeding within 24 hours. In our study, about 40% of patients in both groups had enteral feeding started within this period.

Although there is no agreement on a standard definition of “trophic feeding” or permissive underfeeding, we chose to provide approximately one-quarter of estimated total caloric needs based on studies in animals and low-birth-weight infants,^{15,23-25} expert review by an independent protocol review committee, and our assessment of the feasibility of conducting hypocaloric feeding in a clinical context. Providing approximately 25% of goal feeding clearly resulted in less group separation than would have occurred with a “no feeding” comparator. We did not believe it feasible to have a group receiving no feeding at all, even though previous studies of usual practice indicate that many critically ill patients receive no enteral nutrition for many days.^{3,4,6,8,11}

This study has several strengths, including its large size, multicenter randomized design, intention-to-treat analysis, and significant separation of feeding groups for the first 6 days. Despite excluding patients in severe refractory shock, about 40% of our patients were enrolled while in shock and enterally fed. Furthermore, the mortality in both feeding groups was comparable to mortality reported in previous ARDS Network trials with similar inclusion and exclusion criteria.^{17,20,26}

Figure 6. Mean 8 AM Plasma Glucose and Insulin Infusion Rates

A, Day 0 glucose values are baseline. To convert values to mmol/L, multiply by 0.0555. Three patients in the trophic-feeding group did not have recorded baseline glucose measurements. Error bars represent 95% CIs. $P < .001$ at days 1, 2, 3, 4, and 5; $P = .04$ at day 6; $P = .02$ at day 7. B, Sample sizes reflect numbers of patients receiving insulin infusion. Error bars represent 95% CIs. $P < .001$ at days 1, 2, 3, 4, 5, 6, and 7.

Our feeding protocol, previously tested in a phase 2 trial,²⁷ promptly achieved higher enteral caloric delivery in the full-feeding group than reported to date.^{3,6,7,28} Comparable levels of caloric delivery were seen in the trophic-feeding group after day 6, when feeding rates were increased to match those of the full-feeding group. Additional strengths were standardized definitions and actions for gastrointestinal intolerances. Use of standardized practices including low tidal volume ventilation, conservative fluid management, and glucose control guidelines were also helpful in making sure both groups were treated comparably—an important consideration for unblinded trials.

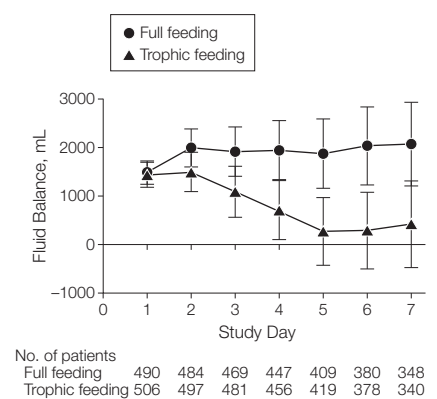
We chose not to control several study parameters, including the location of enteral tube position and use of prokinetic agents, because of lack of consensus for either. We also did not control selection of enteral feeding formula, in recognition of many diverse patient conditions (eg, diabetes, renal failure, liver disease) and local practice variation.

Our study has several limitations. The open-label design may have led to bias in reporting of gastrointestinal intolerances. Because bedside nurses and clinicians knew patients were receiving full enteral feeding, they

may have been more concerned with gastrointestinal intolerances such as vomiting, regurgitation, or constipation. In addition, GRVs were checked twice as frequently in the full enteral feeding group, although rates are reported as days with an elevated GRV and not number of elevated GRVs.

Patients in the full-feeding group received more total fluid intake during the first 6 study days; hence, net fluid balance was more positive than in the trophic-feeding group. Previously we have shown that a conservative fluid management strategy results in more VFDs than a liberal strategy.²⁰ Therefore, the higher net fluid balance could have reduced the number of VFDs in the full-feeding group compared with the trophic-feeding group. We believe this influence to be small, given the 1.5-L difference in fluid balance between groups compared with the approximately 7-L difference between fluid-liberal and fluid-conservative groups in our previous study, in which the fluid-conservative group had fewer VFDs.²⁰ In addition, central venous pressures were similar and decreased over the course of the study in both groups.

Because most patients in this study came from adult medical ICUs, we cannot be certain if similar outcomes would be observed in a surgical population or

Figure 7. Cumulative Net Fluid Balance

Sample sizes reflect numbers of patients with cumulative fluid balance data collected for the shorter of 7 days or until they were no longer receiving mechanical ventilation. The trophic-feeding group had significantly lower net cumulative fluid balance on study days 2 through 7 compared with the full-feeding group. Error bars represent 95% CIs. $P = .02$ at day 3; $P < .001$ at days 4, 5, and 6; $P = .01$ at day 7.

in children. In addition, underweight patients were also excluded. Similarly, this study enrolled patients with ALI and not all causes of acute respiratory failure. However, our results are consistent with those of a smaller phase 2 study demonstrating similar clinical outcomes between trophic and full feeding in all patients with acute respiratory failure.²⁷ Because muscle and immune function were not directly

measured, it is possible that there were undetected differences between groups. Patients receiving full-energy enteral feedings in the phase 2 study demonstrated a trend toward being discharged home over rehabilitation facilities, albeit in a post hoc analysis.²⁷ Although we did not systematically collect information on discharge location, we believe it unlikely that any differences in muscle strength were clinically significant, given the similarity between groups in ventilatory parameters and VFDs. The assumption that patients discharged home without breathing assistance prior to day 60 were still alive at 60 days may slightly underestimate 60-day mortality. Although these patients do have continued morbidity and mortality for at least a year after discharge, the additional mortality through 60 days is small.²⁹

We prohibited concomitant parenteral nutrition to restrict caloric intake to the enteral route; hence, we cannot make any conclusions with regard to the role of parenteral nutrition. However, a recent study demonstrated worse outcomes when parenteral nutrition was added to enteral nutrition to meet calculated caloric goals early in the course of critical illness.²⁸

This study adds information regarding several common nutrition support practices. For example, more than 85% of patients were initially fed using a gastric rather than a postpyloric tube, despite near-universal use of sedatives and narcotics and a substantial proportion in shock. Initial feeding in the stomach has the potential to avoid significant delays in enteral access and reduce insertion and imaging costs. In addition, we found that regurgitation, constipation, vomiting, and aspiration were uncommon in both groups, despite a significantly higher than commonly accepted GRV limit. These findings raise questions about routine use of postpyloric tubes and more conservative GRV limits when gastric tubes are used.

Because of concerns of refeeding syndrome, blood levels of potassium, phosphorus, and magnesium and

clinical adverse events were monitored. We observed no clinical or laboratory evidence of refeeding in the full-feeding group or when patients in the trophic-feeding group were advanced to full feeding. However, patients at highest risk for refeeding syndrome—malnourished patients or those with significant recent weight loss—were excluded from this study. Baseline plasma glucose values were similar in both groups but over the first 6 days, average glucose values in the full-feeding group were higher, as was insulin use. However, the values did not exceed the commonly recommended limits of 150 mg/dL.

CONCLUSION

In patients with ALI, initial trophic enteral feeding for up to 6 days did not increase the number of VFDs or reduce mortality compared with full enteral feeding.

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network Writing Committee: The following individuals take authorship responsibility for the EDEN study results: Todd W. Rice, MD, MSc, Vanderbilt University School of Medicine, Nashville, Tennessee; Arthur P. Wheeler, MD, Vanderbilt University School of Medicine; B. Taylor Thompson, MD, Massachusetts General Hospital, Boston; Jay Steingrub, MD, Baystate Medical Center, Springfield, Massachusetts; R. Duncan Hite, MD, Wake Forest School of Medicine, Winston-Salem, North Carolina; Marc Moss, MD, University of Colorado School of Medicine, Denver; Alan Morris, MD, University of Utah School of Medicine, Salt Lake City; Ning Dong, MS, Massachusetts General Hospital; Peter Rock, MD, MBA, University of Maryland School of Medicine, Baltimore.

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Study concept and design: Rice, Wheeler, Thompson, Steingrub, Hite, Morris, Rock.

Acquisition of data: Wheeler, Thompson, Hite, Moss, Morris, Rock.

Analysis and interpretation of data: Rice, Wheeler, Thompson, Steingrub, Hite, Dong, Rock.

Drafting of the manuscript: Rice, Wheeler, Thompson, Steingrub, Morris, Rock.

Critical revision of the manuscript for important intellectual content: Rice, Wheeler, Steingrub, Hite, Moss, Morris, Dong, Rock.

Statistical analysis: Rice, Dong, Rock.

Obtained funding: Wheeler, Steingrub, Morris.

Administrative, technical, or material support: Wheeler, Thompson, Steingrub, Hite, Moss, Morris, Rock.

Study supervision: Wheeler, Thompson, Moss, Morris.

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The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: University of Washington, Harborview (*L. Hudson, S. Gundel, C. Hough, M. Neff, K. Sims, A. Ungar, T. Watkins); Baystate Medical Center (*J. Steingrub, M. Tidswell, E. Braden, L. DeSouza, J. Germain, C. Kardos, D. Kelley, L. Kozikowski, S. Ouellette); Baylor College of Medicine (K. Guntupalli, V. Bandi, C. Pope, C. Ross); Johns Hopkins University (*R. Brower, H. Fessler, D. Hager, P. Mendez-Tellez, D. Needham, K. Oakjones); Johns Hopkins Bayview Medical Center (J. Sevransky, A. Workneh); University of Maryland (C. Shanholtz, D. Herr, H. Howes, G. Netzer, P. Rock, A. Sampaio, J. Titus); Union Memorial Hospital (P. Sloane, T. Beck, D. Highfield, S. King); Washington Hospital Center (B. Lee, N. Bolouri); Cleveland Clinic Foundation (*H.P. Wiedemann, R.W. Ashton, D.A. Culver, T. Frederick, J.A. Guzman, J.J. Komara Jr, A.J. Reddy); University Hospitals of Cleveland (R. Hejal, M. Andrews, D. Haney); MetroHealth Medical Center (A.F. Connors, S. Lasalvia, J.D. Thornton, E.L. Warren); University of Colorado Hospital, Aurora (*M. Moss, E.L. Burnham, L. Gray, J. Maloney, M. Mealer); Denver Health Medical Center (I. Douglas, K. Overdier, K. Thompson, R. Wolken); Rose Medical Center (S. Frankel, J. McKeenan); Swedish Medical Center (M.L. Warner); Saint Anthony's Hospital (T. Bost, C. Higgins, K. Hodgins); Duke University (*N. MacIntyre, L. Brown, C. Cox, M. Gentile, J. Govert, N. Knudsen); University of North Carolina (S. Carson, L. Chang, S. Choudhury, W. Hall, J. Lanier); Vanderbilt University (*A.P. Wheeler, G.R. Bernard, M. Hays, S. Mogan, T.W. Rice); Wake Forest University (*R.D. Hite, K. Bender, A. Harvey, P.E. Morris, Mary Ragusky); Moses Cone Memorial Hospital (P. Wright, S. Groce, J. McLean, A. Overton); University of Virginia (J. Truwit, K. Enfield, M. Marshall); LDS Hospital and Intermountain Medical Center (*A. Morris, A. Austin, S. Barney, S. Brown, J. Fergeson, H. Gallo, T. Graydon, C. Grissom, E. Hirschberg, A. Jephson, N. Kumar, R. Miller, D. Murphy, J. Orme, A. Stow, L. Struck, F. Thomas, D. Ward, L. Weaver); LDS Hospital (P. Bailey, W. Beninati, L. Bezdiyan, T. Clemmer, S. Rimkus, R. Tanaka McKay); Dee Hospital (C. Lawton, D. Hanselman); Utah Valley Regional Medical Center (K. Sundar, W. Alward, C. Bishop, D. Eckley, T. Hill, B. Jensen, K. Ludwig, D. Nielsen, M. Pearce); University of California, San Francisco (*M.A. Matthay, C. Calfee, B. Daniel, M. Eisner, O. Garcia, K. Kordes, K. Liu, N. Shum, H. Zhou); University of California, San Francisco, Fresno (M.W. Peterson, J. Blaauw, K. Van Gundy); University of California, Davis (T. Albertson, B. Morrissey, E. Vlastelin); Mayo Foundation (*R. Hubmayr, D. Brown, M. Dubin, E. Festic, O. Gajic, R. Hinds, S. Holets, D. Kor, A. Lee, M. Passe, G. Simpson, J. Wright); Louisiana State University Health Sciences Center-New Orleans (*B. deBoisblanc, A. Antoine, D. Charbonnet, J. Hunt, P. Lauto, A. Marr, G. Meyaski, C. Romaine, R. Tejedor); Earl K. Long Medical Center, Baton Rouge General Medical Center Mid-City and Baton Rouge General Medical Center Bluebonnet (S. Brierre, J. Byrne, T. Jagneaux, C. LeBlanc, K. Moreau, C. Thomas); Ochsner Clinic Foundation (S. Jain, D. Taylor, L. Seoane); Our Lady of the Lake Medical Center (C. Hebert, J. Thompson); Tulane Medical Center (F. Simeone, J. Fearon). **Clinical Coordinating Center:** Massachusetts General Hospital and Harvard Medical School (*D. Schoenfeld, M. Guha, E. Hammond, N. Lavery, P. Lazar, R. Morse, C. Oldmixon, N. Ring-

wood, E. Smoot, B.T. Thompson, R. Wilson). **National Heart, Lung and Blood Institute:** A. Harabin, S. Bredow, M. Wacławski, G. Weinmann. **Data and Safety Monitoring Board:** R. G. Spragg (chair), A. Slutsky, M. Levy, B. Markovitz, E. Petkova, C. Wei-
Protocol Review Committee: J. Sznajder (chair), M. Begg, E. Israel, J. Lewis, S. McClave, P. Parsons.
 *Principal investigator.

Online-Only Material: The eMethods, eTable, and eFigures 1-5 are available at <http://www.jama.com>.

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