ORIGINAL ARTICLE

Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*

ABSTRACT

BACKGROUND

The effect of delivering nutrition at different calorie levels during critical illness is uncertain, and patients typically receive less than the recommended amount.

METHODS

We conducted a multicenter, double-blind, randomized trial, involving adults undergoing mechanical ventilation in 46 Australian and New Zealand intensive care units (ICUs), to evaluate energy-dense (1.5 kcal per milliliter) as compared with routine (1.0 kcal per milliliter) enteral nutrition at a dose of 1 ml per kilogram of ideal body weight per hour, commencing at or within 12 hours of the initiation of nutrition support and continuing for up to 28 days while the patient was in the ICU. The primary outcome was all-cause mortality within 90 days.

RESULTS

There were 3957 patients included in the modified intention-to-treat analysis (1971 in the 1.5-kcal group and 1986 in the 1.0-kcal group). The volume of enteral nutrition delivered during the trial was similar in the two groups; however, patients in the 1.5-kcal group received a mean (±SD) of 1863±478 kcal per day as compared with 1262±313 kcal per day in the 1.0-kcal group (mean difference, 601 kcal per day; 95% confidence interval [CI], 576 to 626). By day 90, a total of 523 of 1948 patients (26.8%) in the 1.5-kcal group and 505 of 1966 patients (25.7%) in the 1.0-kcal group had died (relative risk, 1.05; 95% CI, 0.94 to 1.16; P=0.41). The results were similar in seven predefined subgroups. Higher calorie delivery did not affect survival time, receipt of organ support, number of days alive and out of the ICU and hospital or free of organ support, or the incidence of infective complications or adverse events.

CONCLUSIONS

In patients undergoing mechanical ventilation, the rate of survival at 90 days associated with the use of an energy-dense formulation for enteral delivery of nutrition was not higher than that with routine enteral nutrition. (Funded by National Health and Medical Research Institute of Australia and the Health Research Council of New Zealand; TARGET ClinicalTrials.gov number, NCT02306746.)

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Drs. Chapman and Peake contributed equally to this article.

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For critically ill patients, guidelines recommend that energy intake match energy expenditure[1,2] in order to prevent cumulative energy deficits, which have been associated with adverse outcomes.[3-5] Accordingly, enteral nutrition is commonly commenced early after admission to the intensive care unit (ICU) with the use of a formulation that has an energy content of approximately 1 kcal per milliliter, prescribed at a rate of approximately 1 ml per kilogram of body weight per hour.[6,7] Because of factors such as gastrointestinal intolerance (defined as large gastric residual volumes, regurgitation, and vomiting)[8] and fasting for procedures,[9] less than 60% of recommended energy intake is usually delivered to patients.[10,11]

The literature addressing the relationship between energy delivery and outcomes after critical illness is conflicting. Some studies report that increasing delivery improves outcomes,[3-5,12-14] whereas others suggest that short-term energy delivery below recommended goals — either "permissive underfeeding" (approximately 1000 kcal per day) or "trophic feeding" (approximately 400 kcal per day) — is not associated with adverse effects.[15,16] Increased delivery has also been reported to be harmful, albeit when nutrition has been supplemented intravenously rather than exclusively delivered enterally.[17,18] Many studies examining energy delivery have been limited by insufficient power, lack of blinding, and a failure to deliver the full recommended energy intake. Accordingly, a definitive effect of energy delivery on outcomes has not been clear. After a pilot study,[19] we designed a binational, multicenter trial, the Augmented versus Routine Approach to Giving Energy Trial (TARGET), to test the hypothesis that delivering a larger number of calories with the use of energy-dense enteral nutrition in patients receiving mechanical ventilation would result in higher rates of survival within 90 days than routine care.

Methods

Trial Design

We conducted an investigator-initiated, randomized, double-blind, pragmatic trial in 46 ICUs in Australia and New Zealand (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) between June 21, 2016, and November 14, 2017. The trial, which was endorsed by the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, was designed by the management committee and conducted and analyzed by the investigators (see the Supplementary Appendix). The trial was funded by national peer-reviewed organizations. The funders had no role in the design or conduct of the trial; in the collection, analysis, or interpretation of the data; or in the approval of the manuscript for submission. In-kind support was provided by Fresenius Kabi Deutschland, which supplied both of the enteral nutrition formulations. Representatives from Fresenius Kabi Deutschland reviewed and provided feedback on the manuscript before submission; however, the authors on the writing committee wrote the manuscript, made the decision to submit it for publication, and vouch for the accuracy and completeness of the data, held by Monash University, and for the fidelity of the trial to the protocol, which has been published elsewhere[20] and is available at NEJM.org. Ethics approval was provided by all relevant local institutional review boards (Fig. S1 in the Supplementary Appendix). An independent data and safety monitoring board provided trial oversight.

Patient Population

Patients 18 years of age or older in the ICU were eligible for inclusion if they were receiving invasive mechanical ventilation, were about to commence enteral nutrition, or had commenced enteral nutrition within the previous 12 hours and were expected to be receiving enteral nutrition in the ICU beyond the calendar day after randomization. Patients for whom the treating clinician considered the trial enteral nutrition formula or the rate of delivery to be clinically contraindicated or in whom death was deemed inevitable were excluded. A full list of the exclusion criteria is provided in the Supplementary Appendix.

The patients were under sedation and were not able to provide informed consent before randomization; however, both types of nutrition used in the trial are considered acceptable as current management. The consent process is described in detail in Fig. S1 in the Supplementary Appendix.

Randomization and Treatment

Using permuted block randomization and variable block sizes with stratification according to site, we randomly assigned eligible patients in a 1:1 ratio to

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receive energy-dense or routine enteral nutrition. Concealment of the treatment assignments was maintained with a secure, Web-based randomization system, which was accessible 24 hours a day. Both the energy-dense enteral nutrition (1.5 kcal per milliliter, Fresubin Energy Fiber Tube Feed) and the routine enteral nutrition (1.0 kcal per milliliter, Fresubin 1000 Complete Tube Feed) were administered in identical 1000-ml bags (Fig. S2 in the Supplementary Appendix). The formulations were indistinguishable in color and packaging.[19] The difference in calorie content between the energy-dense and routine formulations was shared between fat (58 g per liter in the energy-dense formulation vs. 27 g per liter in the routine formulation) and carbohydrates (180 g per liter vs. 125 g per liter); the protein content of the two formulations was similar (56 g per liter and 55 g per liter). Full product information is provided in Figure S3 in the Supplementary Appendix.

Administration of the trial enteral nutrition was commenced as soon as possible after randomization. The target rate for both groups was 1 ml per kilogram per hour and was based on the calculated ideal body weight (see the Supplementary Appendix).[15,17,21] We recommended that the target rate be achieved within 48 hours after commencement of the trial nutrition. A clinician estimation of baseline energy requirements was not used to determine the target rate for the trial; however, when such an estimation was performed, we collected the information. To minimize the risk of overfeeding, the maximum target rate was 100 ml per hour; catch-up feeds were not permitted. Blood glucose concentrations of 180 mg per deciliter (10 mmol per liter) or less were recommended. All other aspects of management were handled according to local practice, including the rate at which trial nutrition was commenced and incremented, the method and frequency of measurement of gastric residual volumes, and strategies to increase delivery. If the treating clinician deemed supplemental parenteral nutrition necessary, the trial enteral nutrition was continued unless contraindicated.

The trial enteral nutrition was administered for up to 28 days or until the patient discontinued enteral nutrition, died, or was discharged from the ICU, whichever occurred first. In addition, the trial enteral nutrition was ceased if specific nutritional requirements developed, including the need for protein supplements; if the patient commenced oral nutrition; or if the trial enteral nutrition was no longer deemed to be in the patient's best interest. Patients who were readmitted to the ICU within 28 days and still required enteral nutrition had feeding with their previously assigned formulation restarted.

TRIAL OUTCOMES

The primary outcome was all-cause mortality within 90 days after randomization. Secondary outcomes included survival time (evaluated until day 90), 90-day cause-specific mortality, day 28 and in-hospital all-cause mortality, ICU-free and hospital-free days between randomization and day 28, the number of days free of organ support between randomization and day 28, and the percentages of patients receiving invasive ventilation, vasopressors, or new renal replacement therapy. Other secondary outcomes were the percentage of patients with positive blood cultures and the percentage receiving intravenous antimicrobial agents between randomization and day 28. On the basis of prerandomization variables, seven subgroups were predefined for the evaluation of the primary outcome: age (≥65 or <65 years), diagnostic subgroups (trauma, sepsis,[22] a neurologic diagnosis, and treatment type [medical vs. surgical]), quintiles for the absolute risk of death based on the Australian and New Zealand Risk of Death Score after linkage to the ANZICS Center for Outcome Resource Evaluation (CORE),[23,24] and body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) according to the World Health Organization categories (<18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥30.0).[25]

STATISTICAL ANALYSIS

All analyses were conducted in accordance with our prepublished statistical analysis plan.[26] On the basis of data from the TARGET feasibility study and the ANZICS CORE Adult Patient Database, we calculated that a sample of 3774 patients would provide 80% power to detect a difference of 3.8 to 4.3 percentage points in 90-day mortality, assuming a baseline mortality of 20 to 30%.[19,23] A 6% sample size inflation to 4000 patients who could be evaluated allowed for anticipated losses during follow-up and for one interim analysis. The interim analysis was performed after completion of the day 90 follow-up of the first 1500 pa-

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	1.5-kcal Group (N=1971)	1.0-kcal Group (N=1986)
Age — yr	57.2±16.6	57.5±16.5
Male sex — no. (%)	1221 (61.9)	1272 (64.0)
Actual body weight — kg	84.6±23.3	84.9±23.6
Ideal body weight — kg	64.4±11.1	64.7±10.9
Body-mass index†	29.2±7.7	29.3±7.9
ICU admission category — no. (%)		
Nonoperative	1443 (73.2)	1435 (72.3)
Emergency operative	331 (16.8)	352 (17.7)
Elective operative	197 (10.0)	199 (10.0)
Insulin-treated diabetes mellitus — no. (%)	146 (7.4)	133 (6.7)
APACHE II score at ICU admission‡	22.0±8.3	22.1±8.5
Median time from ICU admission to randomization (IQR) — hr	14.1 (6.0–24.4)	14.3 (6.3–25.4)
Organ support at randomization — no. (%)		
Invasive ventilation§	1970 (100)	1980 (99.8)
Vasopressor infusion	1235 (62.7)	1253 (63.1)
New renal replacement therapy	172 (8.7)	177 (8.9)

* Plus–minus values are means ±SD. P>0.05 for the comparison between the groups for all characteristics. ICU denotes intensive care unit, and IQR interquartile range.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death. The score was calculated with the values recorded for each variable during the 24 hours before randomization that would result in the highest score.
§ Three patients who were randomly assigned to the 1.0-kcal group were not receiving invasive ventilation before randomization. Data were not available for one patient in the 1.5-kcal group and for three patients in the 1.0-kcal group.

tients with the use of a twin-sided O'Brien–Fleming design and a two-sided P value of 0.005 and was reviewed by the data and safety monitoring committee.

All analyses were conducted with the use of a modified intention-to-treat principle.[27] Per-protocol and as-treated sensitivity analyses in the modified intention-to-treat population were performed for the analysis of the primary and secondary outcomes (see the Supplementary Appendix). No imputation was used to estimate missing data, and analyses were based on all available data with numbers of available observations reported. The methods for calculating daily delivery of nutrition and gastrointestinal tolerance of enteral nutrition are described in the Supplementary Appendix. Continuous variables are reported as means and standard deviations or as medians and interquartile ranges. Categorical variables are reported as percentages. Between-group differences were analyzed with Student's t-test or Wilcoxon rank-sum tests for continuous variables and a chi-square test for categorical variables and are reported as estimated mean difference, median difference (Hodges–Lehman estimate), or relative risk with 95% confidence intervals.

We report the relative risk and 95% confidence interval for death from any cause by day 90 using log-binomial regression with adjustment for site (random effect) and for predefined baseline covariates (age, Acute Physiology and Chronic Health Evaluation [APACHE] II score at ICU admission, BMI, country [Australia or New Zealand], sex, and ICU admission type [medical, elective surgical, or emergency surgical]) (fixed effects). The same unadjusted and adjusted analyses were performed for 28-day and in-hospital mortality. Modified Poisson regression with robust standard errors was used to estimate the relative risk when log-binomial models did not converge. Survival time, evaluated from randomization to day 90, is shown as a Kaplan–Meier curve and compared with the use of a log-rank test. Hazard ratios with 95% confidence intervals were obtained with the use

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Table 2. Daily Nutrition Delivery up to Day 28.*

Measure	1.5-kcal Group (N=1971)	1.0-kcal Group (N=1985)†	Difference or Relative Risk (95% CI)‡
Median time from ICU admission to commencing trial nutrition (IQR) — hr	15.8 (7.7 to 26.3)	15.9 (7.9 to 28.3)	–0.4 (–1.1 to 0.4)
Median duration of trial nutrition (IQR) — days§	6.0 (3.0 to 11.0)	6.0 (3.0 to 11.0)	0
Volume of trial nutrition delivered — ml/day¶	1242±318	1262±313	–20 (–40 to 0)
Percentage of trial target rate delivered	81±17	82±16	–1 (–2 to 0)
Calories delivered — kcal/day¶			
Trial nutrition	1863±478	1262±313	601 (576 to 626)
Trial nutrition plus other sources‖	1930±547	1407±397	523 (493 to 553)
Calories delivered — kcal/kg of ideal body weight per day¶			
Trial nutrition	29.1±6.2	19.6±4.0	9.5 (9.2 to 9.9)
Trial nutrition plus other sources‖	30.2±7.5	21.9±5.6	8.3 (7.9 to 8.7)
Calories delivered — kcal/kg of actual body weight per day¶**			
Trial nutrition	23.1±7.1	15.6±4.8	7.5 (7.1 to 7.9)
Trial nutrition plus other sources‖	23.9±7.8	17.4±5.5	6.6 (6.2 to 7.0)
Protein delivered¶			
Trial nutrition — g/day	69.6±17.8	69.4±17.2	0.1 (–1.0 to 1.2)
Trial nutrition — g/kg of ideal body weight per day	1.09±0.22	1.08±0.23	0.01 (–0.01 to 0.02)
Gastrointestinal tolerance			
Median largest gastric residual volume (IQR) — ml††	250 (100 to 441)	180 (65 to 360)	40 (30 to 50)
Regurgitation or vomiting — no./total no. (%)‡‡	370/1959 (18.9)	309/1966 (15.7)	1.20 (1.05 to 1.38)
Receipt of promotility agents — no./total no. (%)‡‡	929/1959 (47.4)	779/1966 (39.6)	1.20 (1.11 to 1.29)
Median bowel movements per day (IQR)‡‡§§	0.5 (0 to 1.3)	0.6 (0 to 1.3)	0
Median insulin administration (IQR) — IU/day¶¶	3.0 (0 to 41.8)	0 (0 to 30.6)	0
Median highest daily blood glucose concentration (IQR) — mg/dl¶¶	225.2 (185.6 to 277.4)	212.6 (174.7 to 261.2)	12.6 (9.0 to 18.0)

* Plus–minus values are means (±SD). Data on the delivery of trial nutrition and administration of insulin (excluding patients who never received the trial nutrition) were available for 1959 patients in the 1.5-kcal group and 1967 patients in the 1.0 kcal-group; the exceptions were the time from ICU admission to commencement of trial nutrition and the duration of trial nutrition, for which data were available for 1968 patients in the 1.0-kcal group. Data on the largest gastric residual volume were available for 1935 patients in the 1.5-kcal group and 1941 in the 1.0-kcal group, data on bowel movements were available for 1939 and 1951 patients, respectively, and data on the highest daily blood glucose concentration were available for 1955 and 1965 patients.

† Data were not available for 1 patient who withdrew from the trial on day 1.

‡ Differences between the groups are presented as differences in means, differences in medians (Hodges–Lehman estimate), or (for percentages) relative risk. The widths of the confidence intervals have not been adjusted for multiplicity, and the intervals should not be used to infer definite differences between the groups.

§ Durations were calculated in days from the time of commencement of the trial nutrition until cessation of the last episode of trial nutrition.

¶ Values are for the total time during which trial nutrition was delivered.

‖ Other sources include parenteral nutrition, propofol, dextrose (including dextrose for drug administration), and citrate.

** Actual body weight was estimated or measured and was not used to determine trial target rate.

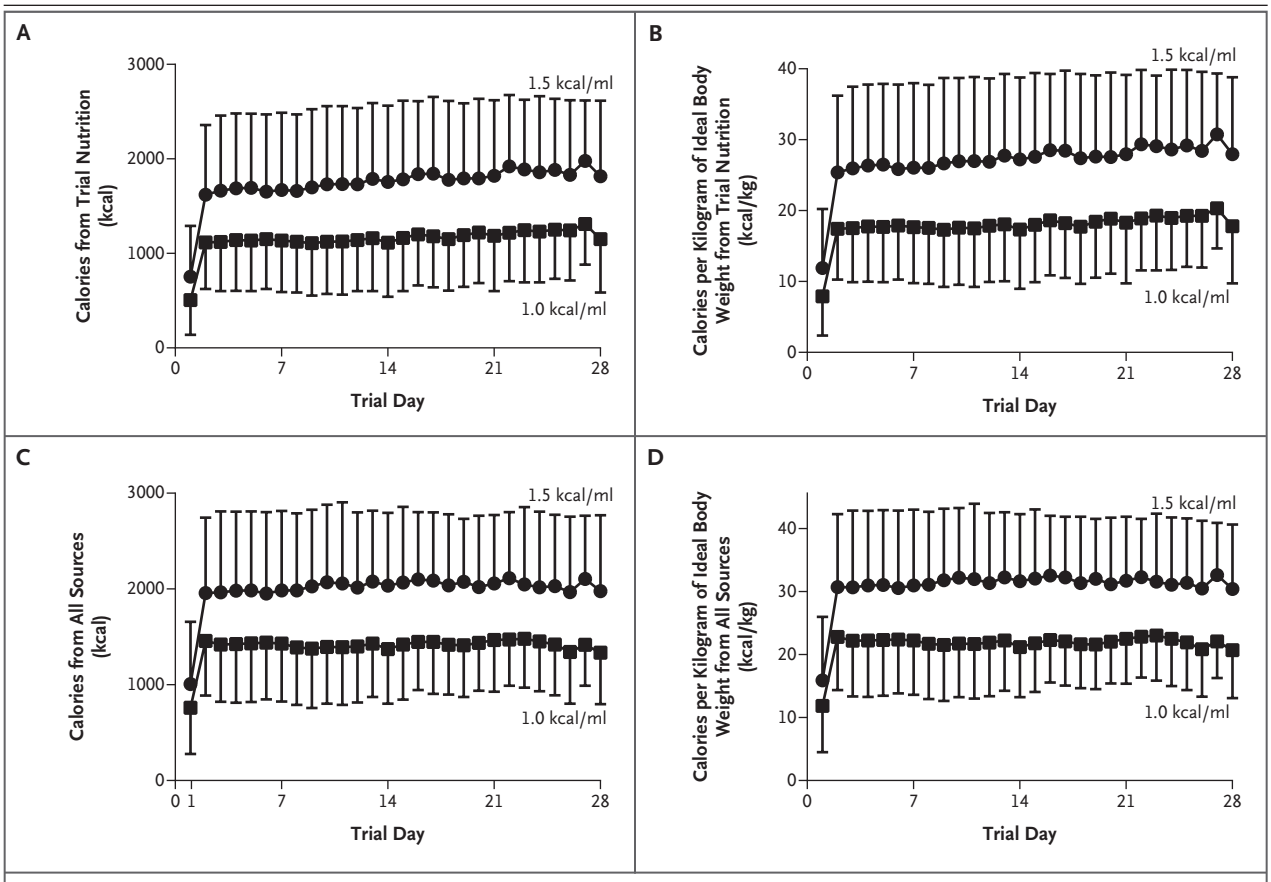
†† The largest gastric residual volume was the largest single volume of gastric fluid aspirated in a given day while the patient was receiving the trial nutrition.

‡‡ This measure was evaluated only up to day 7, while the patient was receiving the trial nutrition.

§§ Bowel movements per day was not evaluated for 36 patients who had a fecal management system in situ.

¶¶ Insulin and glucose measures were recorded for 28 days while the patient was present in the ICU. To convert the values for blood glucose to millimoles per liter, multiply by 0.05551.

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	Trial Day				
	1	7	14	21	28
No. of Patients					
1.5 kcal/ml	1841	871	371	172	82
1.0 kcal/ml	1851	881	350	158	64

Figure 1. Daily Calorie Delivery over the 28-Day Trial Period.

Panel A shows the mean (±SD) calories delivered from the trial enteral nutrition, and Panel B shows the calories delivered per kilogram of ideal body weight.[21] Panel C shows the total calories delivered from all calorie sources and Panel D the calories delivered per kilogram of ideal body weight from all calorie sources. Calorie sources include trial and nontrial enteral nutrition, parenteral nutrition, other dextrose solutions, propofol, and citrate infusion for renal replacement therapy. Daily data were calculated from the time of commencement of the trial enteral nutrition until cessation of the last episode of trial enteral nutrition, excluding 29 patients who never received trial enteral nutrition, 1 patient who withdrew from the trial on day 1 without daily data, and 1 patient with missing trial nutrition volume on all days.

of Cox proportional-hazards models. Numbers of ICU-free, hospital-free, and organ support–free days are reported as medians and interquartile ranges. The methods used for subgroup analyses are described in the Supplementary Appendix. Analyses were performed with SPSS Statistics software, version 22 or later (IBM), and Stata software, version 15.1 (StataCorp). No correction for multiplicity when conducting tests for secondary and other outcomes was predefined; the results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the groups.

RESULTS

PATIENTS

Randomization was performed 4000 times during the 17 months of the trial (Fig. S4 in the Supplementary Appendix): 1997 assignments to receive

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Table 3. Outcomes and Adverse Events.

Outcome	1.5-kcal Group	1.0-kcal Group	Difference or Relative Risk (95% CI)*
Primary outcome: death by day 90 — no./total no. (%)	523/1948 (26.8)	505/1966 (25.7)	1.05 (0.94 to 1.16)†
Secondary outcomes			
Death by the time of hospital discharge — no./total no. (%)	468/1967 (23.8)	470/1981 (23.7)	1.00 (0.97 to 1.04)
Death by day 28 — no./total no. (%)	450/1961 (22.9)	455/1976 (23.0)	1.00 (0.89 to 1.12)
Median days alive and not in ICU (IQR)‡	17.0 (0 to 23.0)	17.4 (0 to 23.1)	0
Median days alive and not in hospital (IQR)‡	2.9 (0 to 15.7)	2.9 (0 to 15.3)	0
Use and duration of organ support§			
Received invasive mechanical ventilation — no./total no. (%)	1971/1971 (100)	1982/1984 (99.9)	
Median days alive and free of invasive ventilation (IQR)	20.0 (0 to 25.0)	20.0 (0 to 25.0)	0
Received vasopressor support — no./total no. (%)	1599/1971 (81.1)	1615/1984 (81.4)	1.00 (0.97 to 1.03)
Median days alive and free of vasopressor support (IQR)	23.0 (2.0 to 26.0)	23.0 (4.0 to 26.0)	0
Received renal replacement therapy — no./total no. (%)	367/1946 (18.9)	361/1955 (18.5)	1.02 (0.90 to 1.16)
Median days alive and free of renal replacement therapy (IQR)	28.0 (8.0 to 28.0)	28.0 (10.0 to 28.0)	0
Microbiology — no./total no. (%)¶			
Positive blood cultures	228/1971 (11.6)	221/1984 (11.1)	1.04 (0.87 to 1.24)
Administration of intravenous antimicrobial agent	1662/1971 (84.3)	1658/1985 (83.5)	1.01 (0.98 to 1.04)
Adverse events — no./total no. of adverse events‖			
Electrolyte abnormality	45/69	42/63	
Gastrointestinal event	22/69	20/63	
Other	2/69	1/63	
Serious adverse events — no./total no.‖	1/1971	1/1986	

* Differences are presented as differences in medians (Hodges–Lehman estimate) or as relative risk. The widths of the confidence intervals have not been adjusted for multiplicity, and the intervals should not be used to infer definite differences between the groups. An unadjusted relative risk of less than 1.0 indicates better results in the 1.5-kcal group.

† P=0.41 by unadjusted chi-square test.

‡ Days alive and not in the ICU or hospital were calculated from the time of randomization to day 28. Patients who died before day 28 were assigned 0 ICU-free or hospital-free days. Data were analyzed with the Mann–Whitney rank-sum test and were available for 1961 patients in the 1.5-kcal group and 1976 patients in the 1.0-kcal group up to day 28 after randomization.

§ Receipt of organ support was recorded up to day 28 after randomization. Days alive and free of organ support were calculated from the time of randomization to day 28 and were analyzed with the Mann–Whitney rank-sum test. Patients who died before day 28 were classified as having 0 organ support–free days. The number of organ support–free days was calculated from the number of whole calendar days without receiving invasive ventilation, vasopressors, or renal replacement therapy after the final episode of organ support up to day 28. Data for invasive ventilation–free days were available for 1961 patients in the 1.5-kcal group and for 1975 patients in the 1.0-kcal groups; data for vasopressor-free days were available for 1971 and 1984 patients, respectively. A total of 54 patients (25 in the 1.5-kcal group and 29 in the 1.0-kcal group) who were receiving long-term renal support were excluded from the calculation of days free of renal replacement therapy; data were therefore available for 1936 patients in the 1.5-kcal group and 1947 patients in the 1.0-kcal group.

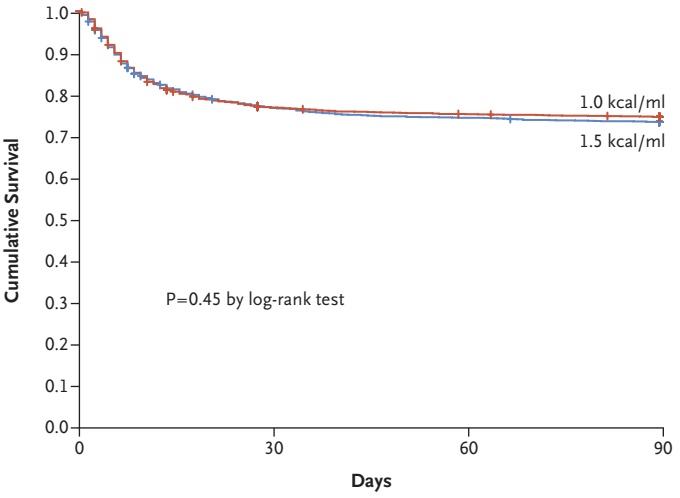
¶ Data were recorded up to day 28 after randomization.

‖ Adverse events were reported at the discretion of the treating clinician. "Other" includes aspiration (1 patient in the 1.5-kcal group), allergic reaction (1 patient in the 1.5-kcal group), and arrhythmia (1 patient in the 1.0-kcal group). The serious adverse events were bowel ischemia. All deaths up to day 90 were excluded.

the 1.5 kcal per milliliter formulation (the 1.5-kcal group) and 2003 assignments to receive the 1.0 kcal per milliliter formulation (the 1.0-kcal group) were made. In total, 3997 patients underwent randomization (3 patients inadvertently underwent randomization twice), and 3957 patients were included in the modified intention-to-treat population (1971 in the 1.5-kcal group and 1986 in the 1.0-kcal group). Data from 3914 patients (97.9%) were available for the analysis of the primary outcome in the modified intention-to-treat population (1948 patients in the 1.5-kcal group and 1966 patients in the 1.0-kcal group) (Fig. S5 in the Supplementary Appendix). Demographic and

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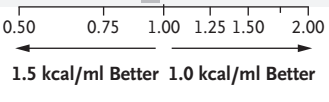
A Survival



No. at Risk				
1.5 kcal/ml	1971	1495	1445	1425
1.0 kcal/ml	1985	1512	1477	1461

B Subgroup Analysis of Death by Day 90

Subgroup	1.5-kcal Group	1.0-kcal Group	Relative Risk (95% CI)
	no. of events/total no. (%)		
Overall	523/1948 (26.8)	505/1966 (25.7)	1.05 (0.94–1.16)
Age			
<65 yr	223/1182 (18.9)	237/1200 (19.8)	0.95 (0.81–1.13)
≥65 yr	300/766 (39.2)	268/766 (35.0)	1.12 (0.98–1.28)
Trauma			
Yes	23/199 (11.6)	28/202 (13.9)	0.83 (0.50–1.40)
No	500/1749 (28.6)	477/1764 (27.0)	1.06 (0.95–1.18)
Sepsis			
Yes	236/924 (25.5)	230/923 (24.9)	1.02 (0.88–1.20)
No	287/1024 (28.0)	275/1043 (26.4)	1.06 (0.92–1.22)
Neurologic diagnosis			
Yes	104/379 (27.4)	90/351 (25.6)	1.07 (0.84–1.36)
No	419/1569 (26.7)	415/1615 (25.7)	1.04 (0.92–1.17)
Treatment			
Medical	409/1424 (28.7)	388/1424 (27.2)	1.05 (0.94–1.19)
Surgical	114/524 (21.8)	117/542 (21.6)	1.01 (0.80–1.27)
Quintile for risk of death			
1	20/386 (5.2)	31/378 (8.2)	0.63 (0.37–1.09)
2	48/380 (12.6)	48/392 (12.2)	1.03 (0.71–1.50)
3	96/382 (25.1)	95/393 (24.2)	1.04 (0.81–1.33)
4	128/389 (32.9)	115/381 (30.2)	1.09 (0.89–1.34)
5	225/385 (58.4)	210/390 (53.8)	1.09 (0.96–1.23)
BMI			
<18.5	13/40 (32.5)	15/48 (31.3)	1.04 (0.56–1.92)
18.5–24.9	190/608 (31.3)	163/588 (27.7)	1.13 (0.95–1.34)
25.0–29.9	170/595 (28.6)	164/612 (26.8)	1.07 (0.89–1.28)
≥30	150/705 (21.3)	163/718 (22.7)	0.94 (0.77–1.14)



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Figure 2 (facing page). Time-to-Death and Subgroup Analyses of the Risk of Death by Day 90.

Panel A shows the Kaplan–Meier estimates for the probability of death from randomization to day 90, excluding 1 patient for whom the date of death was unknown. Panel B shows the relative risk of death up to day 90 after randomization in the two treatment groups, among all patients and in the seven prespecified subgroups. A relative risk of less than 1.0 indicates better results for the 1.5-kcal group. The size of the square represents the relative number within each subgroup, and the horizontal bars represent the 95% confidence interval. Sepsis was categorized according to the Sepsis-3 criteria[22] with the use of the physiological and biochemical data that were recorded closest to, but before, randomization. The quintiles for the risk of death were based on the Australian and New Zealand Intensive Care Risk of Death model; quintile 1 indicates the lowest and quintile 5 the highest risk of death,[23] and the quartiles for body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) were based on the World Health Organization classification system.[25] Risk of death and BMI as continuous variables did not differ significantly between the groups: P=0.64 (base 1) and P=0.23 (base 2) for the risk of death and P=0.09 (linear interaction) and P=0.10 (quadratic interaction) for BMI.

clinical characteristics were balanced between the groups at baseline (Table 1, and Table S2 in the Supplementary Appendix). The median time from ICU admission to randomization was 14.2 hours (interquartile range, 6.2 to 24.9) and was similar in the two groups (Table 1). Most of the patients (72.7%) were admitted with a nonoperative diagnosis.

ENTERAL DELIVERY OF NUTRITION

Patients received the trial nutrition for a median of 6.0 days (interquartile range, 3.0 to 11.0) in the 1.5-kcal group and 6.0 days (interquartile range, 3.0 to 11.0) in the 1.0-kcal group (P=0.84) (Table 2). The reasons for ceasing the trial enteral nutrition were similar in the two groups (Table S4 in the Supplementary Appendix). The mean (±SD) volume of trial enteral nutrition delivered (1242±318 ml per day in the 1.5-kcal group and 1262±313 ml per day in the 1.0-kcal group; mean difference, –20 ml; 95% confidence interval [CI], –40 to 0) and the volume delivered as a percentage of the target rate (81±17% and 82±16%, respectively; mean difference, –1 percentage point; 95% CI, –2 to 0) were similar in the two groups (Table 2, and Fig. S6 in the Supplementary Appendix), as were the rates of nonadherence to the protocol (Table S5 in the Supplementary Appendix).

Patients in the 1.5-kcal group received 47.6% more calories from the trial enteral nutrition than did patients in the 1.0-kcal group: 1863±478 kcal per day as compared with 1262±313 kcal per day (mean difference, 601 kcal per day; 95% CI, 576 to 626) (Table 2 and Fig. 1). Estimations of daily calorie requirements were available for 65% of the patients in the trial; the trial enteral nutrition delivered 103±27% of the clinician-estimated requirements in the 1.5-kcal group as compared with 69±18% in the 1.0-kcal group (mean difference, 34 percentage points; 95% CI, 32 to 36) (Table S3 and Fig. S7 in the Supplementary Appendix). The number of patients who received supplemental parenteral nutrition was 109 (5.5%) in the 1.5-kcal group and 85 (4.3%) in the 1.0-kcal group (relative risk, 1.29; 95% CI, 0.98 to 1.70). The mean number of calories delivered from all sources combined was higher in the 1.5-kcal group than in the 1.0-kcal group (1930±547 kcal per day vs. 1407±397 kcal per day; mean difference, 523; 95% CI, 493 to 553) (Table 2 and Fig. 1).

GASTROINTESTINAL TOLERANCE AND METABOLIC EFFECTS OF ENTERAL NUTRITION

The median largest gastric residual volume was larger in the 1.5-kcal group than in the 1.0-kcal group (250 ml [interquartile range, 100 to 441] vs. 180 ml [interquartile range, 65 to 360]; median difference, 40 ml; 95% CI, 30 to 50). Regurgitation or vomiting was more common in the 1.5-kcal group (18.9% vs. 15.7%; relative risk, 1.20; 95% CI, 1.05 to 1.38), and the 1.5-kcal group received more promotility drugs (47.4% vs. 39.6%; relative risk, 1.20; 95% CI, 1.11 to 1.29) and insulin (3.0 IU per day [interquartile range, 0 to 41.8] vs. 0.0 IU per day [interquartile range, 0 to 30.6]; median difference, 0.0 IU per day; 95% CI, 0.0 to 0.0) (Table 2, and Table S3 in the Supplementary Appendix). The number of patients in the 1.5-kcal group who received insulin was 1093 (55.8%), as compared with 964 (49.0%) in the 1.0-kcal group (relative risk, 1.14; 95% CI, 1.07 to 1.21), and daily blood glucose levels were higher in the 1.5-kcal group than in the 1.0-kcal group (225.2 mg per deciliter [interquartile range, 185.6 to 277.4]

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[12.5 mmol per liter; interquartile range, 10.3 to 15.4] vs. 212.6 mg per deciliter [interquartile range, 174.7 to 261.2] [11.8 mmol per liter; interquartile range, 9.7 to 14.5]; median difference, 12.6 mg per deciliter; 95% CI, 9.0 to 18.0 [0.7 mmol per liter; 95% CI, 0.5 to 1.0]). The respiratory and biochemical data are summarized in Table S3 in the Supplementary Appendix.

OUTCOMES

By day 90, a total of 523 of 1948 patients (26.8%) in the 1.5-kcal group and 505 of 1966 patients (25.7%) in the 1.0-kcal group had died (relative risk, 1.05; 95% CI, 0.94 to 1.16; P=0.41) (Table 3, and Table S6 in the Supplementary Appendix). There were no significant differences in mortality between the groups after adjustment for trial site and baseline covariates (Table S7 in the Supplementary Appendix). The results were unchanged in the per-protocol and as-treated sensitivity analyses (Tables S8 and S9 in the Supplementary Appendix).

There was no significant difference in survival time up to day 90 between the treatment groups (Fig. 2A), and mortality at day 90 did not differ significantly in any of the predefined subgroups (Fig. 2B). The secondary outcomes according to treatment group are shown in Table 3, and in Table S6 in the Supplementary Appendix. The reported findings did not differ in subsidiary analyses of secondary mortality outcomes with adjustment for trial site and predefined baseline covariates (Table S7 in the Supplementary Appendix). One or more adverse events occurred in 54 patients (2.7%) in the 1.5-kcal group and 51 patients (2.6%) in the 1.0-kcal group (Table 3, and Table S10 in the Supplementary Appendix).

DISCUSSION

In this multicenter, double-blind, randomized trial, we compared energy-dense enteral nutrition with standard enteral nutrition in critically ill adults. The use of energy-dense nutrition increased energy intake to approximate full recommended goals but did not affect mortality or key secondary outcomes, including organ support and duration of hospital stay. Several open-label, randomized trials have evaluated energy delivery during critical illness.[15-17] These and subsequent meta-analyses have not reported improved outcomes in association with increased intake.[28,29] Nonetheless, guidelines recommend an energy intake of 25 to 30 kcal per kilogram per day to match expenditure.[1] Our findings do not support that recommendation.

The effect on outcome did not differ across clinically important subgroups. Of particular interest are patients who are poorly nourished at baseline. Because there is no agreed-on approach for the accurate quantification of baseline nutritional status in large nutrition trials, we used BMI as a surrogate marker. Only 89 patients (2%) had a BMI of less than 18.5, which precluded inferences about the effect of energy delivery in such patients. In contrast, one third of the patients were obese (BMI >30). Guidance documents based on expert opinion recommend hypocaloric (11 to 14 kcal per kilogram per day), high-protein feeding for obese patients.[1] Our results suggest that hypocaloric and eucaloric feeding have similar effects on survival when the protein dose is kept constant.

Previous studies have reported upper gastrointestinal intolerance and hyperglycemia with increased energy delivery, as was observed in our trial.[15,16] Intolerance may also relate to the higher osmolality and lipid content in the 1.5-kcal formulation.[30,31] In our trial, we studied two formulations with an approximate 50% difference in energy delivery. The target rate was calculated with the use of ideal, rather than actual, body weight to ensure consistency and avoid the risk of overfeeding in the 1.5-kcal group (calorie delivery, 29.1 kcal per kilogram of ideal body weight per day and 23.1 kcal per kilogram of actual body weight per day). It is important to note that no clinical evidence of overfeeding was observed, since mortality was similar in the two groups and carbon dioxide levels were not higher, weaning from mechanical ventilation did not take longer,[32] and infectious complications were not more common[17,33] in the 1.5-kcal group than in the 1.0-kcal group.

It was not feasible to measure energy expenditure in our large, pragmatic trial, with its blinded design; thus, it remains uncertain whether matching delivery to measured expenditure is beneficial. It is possible that the relationship between energy delivery and survival is nonlinear or is related to the timing of delivery or to protein administration. Of note, the amount of protein delivered exceeded that delivered in usual practice and was similar to the guideline-recommended amount of protein delivery.[1] Further, by keeping protein delivery

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constant in the two groups, we isolated any potential effect of energy delivery. Enteral nutrition was initiated at clinician discretion but occurred within 24 hours of ICU admission in both groups. Nonetheless, early delivery of full recommended energy through the enteral route was not associated with worse outcomes. Phosphate concentrations were slightly lower in patients who were assigned to the 1.5-kcal group. Although there is some evidence that caloric restriction may be appropriate for patients in whom hypophosphatemia develops,[34] we did not use a systematic approach to calorie restriction in our study. Finally, it should be noted that the majority of the patients in our trial were medical patients; thus, a different response may be possible in surgical or trauma patients who receive increased calorie delivery.

In conclusion, in the present trial, increasing energy intake with the administration of energy-dense enteral nutrition did not affect survival among critically ill adults.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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