The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 30, 2014 VOL. 371 NO. 18

Trial of the Route of Early Nutritional Support in Critically Ill Adults

Sheila E. Harvey, Ph.D., Francesca Parrott, M.Sci., David A. Harrison, Ph.D., Danielle E. Bear, M.Res., Ella Segaran, M.Sc., Richard Beale, M.B., B.S., Geoff Bellingan, M.D., Richard Leonard, M.B., B.Chir., Michael G. Mythen, M.D., and Kathryn M. Rowan, Ph.D., for the CALORIES Trial Investigators*

ABSTRACT

BACKGROUND

Uncertainty exists about the most effective route for delivery of early nutritional support in critically ill adults. We hypothesized that delivery through the parenteral route is superior to that through the enteral route.

METHODS

We conducted a pragmatic, randomized trial involving adults with an unplanned admission to one of 33 English intensive care units. We randomly assigned patients who could be fed through either the parenteral or the enteral route to a delivery route, with nutritional support initiated within 36 hours after admission and continued for up to 5 days. The primary outcome was all-cause mortality at 30 days.

RESULTS

We enrolled 2400 patients; 2388 (99.5%) were included in the analysis (1191 in the parenteral group and 1197 in the enteral group). By 30 days, 393 of 1188 patients (33.1%) in the parenteral group and 409 of 1195 patients (34.2%) in the enteral group had died (relative risk in parenteral group, 0.97; 95% confidence interval, 0.86 to 1.08; P=0.57). There were significant reductions in the parenteral group, as compared with the enteral group, in rates of hypoglycemia (44 patients [3.7%] vs. 74 patients [6.2%]; P=0.006) and vomiting (100 patients [8.4%] vs. 194 patients [16.2%]; P<0.001). There were no significant differences between the parenteral group and the enteral group in the mean number of treated infectious complications (0.22 vs. 0.21; P=0.72), 90-day mortality (442 of 1184 patients [37.3%] vs. 464 of 1188 patients [39.1%], P=0.40), in rates of 14 other secondary outcomes, or in rates of adverse events. Caloric intake was similar in the two groups, with the target intake not achieved in most patients.

CONCLUSIONS

We found no significant difference in 30-day mortality associated with the route of delivery of early nutritional support in critically ill adults. (Funded by the United Kingdom National Institute for Health Research; CALORIES Current Controlled Trials number, ISRCTN17386141.)

From the Clinical Trials Unit, Intensive Care National Audit and Research Centre (S.E.H., F.P., D.A.H., K.M.R.), the Departments of Nutrition and Dietetics (D.E.B.) and Adult Critical Care (D.E.B., R.B.), Guy's and St. Thomas' NHS Foundation Trust, the Department of Intensive Care, Imperial College Healthcare NHS Trust (E.S., R.L.), the Division of Asthma, Allergy and Lung Biology, King's College London (R.B.), National Institute for Health Research Biomedical Research Centre, University College London Hospitals NHS Foundation Trust and University College London (G.B., M.G.M.), and the Department of Surgery and Cancer, Imperial College London (R.L.) — all in London. Address reprint requests to Dr. Rowan at the Intensive Care National Audit and Research Centre, Napier House, 24 High Holborn, London WC1V 6AZ, United Kingdom, or at kathy.rowan@icnarc.org.

*A complete list of the investigators and committee members in the CALORIES trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 1, 2014, at NEJM.org.

N Engl J Med 2014;371:1673-84.
DOI: 10.1056/NEJMoa1409860

Nutritional support is standard for critically ill patients and requires a complex calculus of timing, route of delivery, and the amount and type of nutrients that are administered — all of which may affect patient outcomes. The interpretation of published meta-analyses of trials comparing nutritional support through the parenteral route versus the enteral route in critically ill patients[1-3] is complicated by small sample sizes, variable quality, selection bias, lack of standardized definitions, and interventions that combine multiple elements of nutritional support (e.g., timing and route). Currently, the enteral route is the mainstay, largely on the grounds of physiological rationale and modest evidence suggesting an association with fewer infections,[2,4,5] yet it can also be associated with gastrointestinal intolerance and underfeeding.[6,7] The parenteral route, though more invasive, more often secures delivery of the intended nutrition[6] but has been associated with greater risks and rates of complications.[1-3] However, these studies have not considered improvements in delivery, formulation, and monitoring of parenteral nutrition.[8,9]

Although recent studies have evaluated supplemental parenteral nutrition,[10,11] the most effective route for early nutritional support in critically ill patients is unknown. In the CALORIES trial, we tested the hypothesis that the parenteral route is superior to the enteral route for the delivery of early nutritional support in adults who had an unplanned admission to an intensive care unit (ICU) and who could be fed through either route.

Methods

Study Design and Oversight

Our study was a pragmatic, open, multicenter, parallel-group, randomized, controlled trial. The North West London Research Ethics Committee approved the study protocol, which is available with the full text of this article at NEJM.org. The United Kingdom National Institute for Health Research funded the study and convened a trial steering committee and independent data and safety monitoring committee. The Clinical Trials Unit at the U.K. Intensive Care National Audit and Research Centre (ICNARC) managed the study (for details, see the Supplementary Appendix, available at NEJM.org).

Sites and Patients

The study was conducted in 33 adult general ICUs in England participating in the national clinical audit for adult critical care coordinated by ICNARC.[12] Patients who were at least 18 years of age were eligible if they were expected to require nutritional support for at least 2 days, as determined by a clinician within 36 hours after an unplanned ICU admission that was expected to last at least 3 days. Patients were excluded if they could not be fed through either the parenteral or the enteral route, had received nutritional support in the past 7 days, had a gastrostomy or jejunostomy in situ, were pregnant, or were not expected to be in the United Kingdom for the next 6 months. (A detailed list of inclusion and exclusion criteria is provided in the Supplementary Appendix.) All patients or their consultees provided written informed consent or agreement according to the provisions of the United Kingdom Mental Capacity Act of 2005.

Using a 24-hour telephone randomization system, we assigned patients in a 1:1 ratio to receive early nutritional support through the parenteral route or the enteral route. We used a computerized minimization algorithm with a random component to balance patients according to ICU, age (<65 years or ≥65 years), surgical status (surgery <24 hours before ICU admission or no surgery <24 hours before ICU admission), and the presence or absence of severe malnutrition.

Study Interventions

Nutritional support was initiated as soon as possible after randomization (within 36 hours after admission) and used exclusively for 5 days (120 hours) or until transition to exclusive oral feeding, discharge from the ICU, or death (termed the intervention period). Oral feeding could be initiated if clinically indicated during the intervention period. Patients in the parenteral group received nutrition through a central venous catheter with a dedicated lumen positioned in accordance with National Health Service guidelines.[13] Patients in the enteral group received nutrition through a nasogastric or nasojejunal tube positioned in accordance with U.K. guidelines.[14,15]

Energy targets were set at 25 kcal per kilogram of actual body weight per day, with a goal of reaching the target within 48 to 72 hours. Protein or amino acid targets were set according to local practice. Glycemic control was main-

tained in accordance with international guidelines (with a target level for serum glucose of <180 mg per deciliter [10 mmol per liter]).[16] Calories from non-nutritional sources (e.g., propofol) were included in the calculations of total calories. All other treatments and nutritional support were provided according to local practice guidelines and at the clinicians' discretion. (Details about the study interventions are provided in the Supplementary Appendix.)

OUTCOME MEASURES

We report the evaluation of clinical effectiveness, including the primary outcome at 30 days and all secondary outcomes within 90 days after randomization. The primary outcome was all-cause mortality at 30 days. Secondary outcomes were the duration of organ support, treated infectious and noninfectious complications, length of stay in the ICU and hospital, the duration of survival, and mortality at the time of discharge from the ICU and from the hospital, at 90 days, and at 1 year. Adverse events were monitored for 30 days. (Definitions for all outcomes are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

We assumed a baseline 30-day mortality of 32% for patients receiving nutrition through the enteral route. On the basis of our updated meta-analysis, we estimated that the patients in the parenteral group, as compared with those in the enteral group, would have a potential relative risk reduction of approximately 20% in the primary outcome (Fig. S1 in the Supplementary Appendix). On the basis of these estimates, we determined that an enrollment of 2400 patients would have a power of 90% to detect a 20% relative risk reduction (absolute risk reduction, 6.4 percentage points) in the parenteral group with a two-sided alpha level of 0.05, assuming that 2% of patients would cross over to the other group or have a protocol violation and that 2% of patients would be lost to follow-up or withdraw from the study.[17]

A single, planned interim analysis was performed and was reviewed by the data and safety monitoring committee at the point when 30-day outcomes for the first 1200 patients were available. A Haybittle–Peto stopping rule ($P<0.001$) was used to guide recommendations for early termination.[18]

We performed all statistical analyses using the intention-to-treat principle on the basis of a prespecified statistical analysis plan.[19] A P value of 0.05 was considered to indicate statistical significance. All tests were two-sided, and there was no adjustment for multiple variables. Continuous variables are reported as means and standard deviations or as medians and interquartile ranges. Categorical variables are reported as proportions. The time to the initiation of exclusive oral feeding was analyzed as the time to event, with censoring of data for all patients who died while receiving nutritional support.

We used Fisher's exact test to compare between-group differences in the primary outcome. Absolute and relative risks are reported with 95% confidence intervals without adjustment. Reported as a secondary analysis is the adjusted odds ratio from multilevel logistic regression after adjustment for age, ICNARC Physiology Score,[20] surgical status, degree of malnutrition, and a site-level random effect. A sensitivity approach was taken for missing data with respect to the primary outcome by assuming that all patients with missing outcomes survived in the enteral group and died in the parenteral group, with the analyses then repeated with the opposite assumptions. Missing baseline data were imputed in adjusted analyses with the use of multivariate imputation by means of chained equations.[21]

For secondary outcomes, we used Fisher's exact test to analyze binary outcomes, t-tests to analyze the number of infectious complications and duration of organ support (with bootstrapping for anticipated non-normality in the latter[22]), and Wilcoxon rank-sum tests to analyze the length of stay, stratified according to survival. Unadjusted relative risks and adjusted odds ratios are reported for all mortality outcomes. We used the log-rank test to compare Kaplan–Meier curves for 90 days with no adjustment and a Cox proportional-hazards model to compare survival with adjustment.

The likelihood-ratio test was used to assess interactions between groups and prespecified subgroups in adjusted multilevel logistic-regression models. Subgroups were defined according to age quartiles, the presence or absence of malnutrition, quartiles of predicted risk of death,[20,23] the presence or absence of mechanical ventilation, the presence or absence of cancer, and the

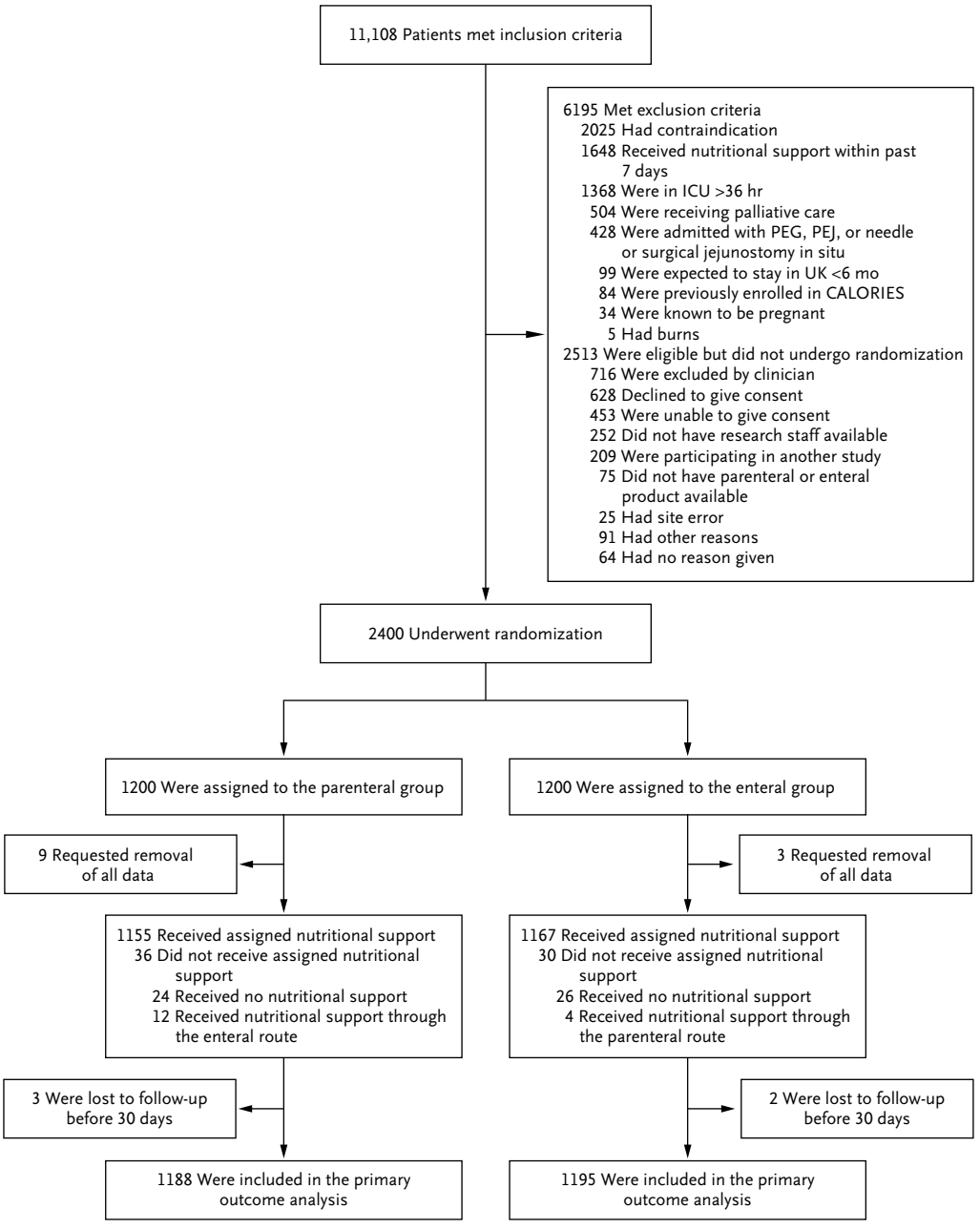

Figure 1. Screening, Randomization, and Follow-up.

Patients who requested removal of all data or were lost to follow-up (12 in the parenteral group and 5 in the enteral group) were not included in the primary outcome analysis. ICU denotes intensive care unit, PEG percutaneous endoscopic gastrostomy, and PEJ percutaneous endoscopic jejunostomy.

time from ICU admission to the initiation of nutritional support (<24 hours or ≥24 hours).

We repeated the primary analysis after adjustment for adherence using a structural-mean model[24] with an instrumental variable for the study group, assuming a linear relationship between the degree of adherence (proportion of the intervention period that the assigned route

was used) and treatment effect to estimate the efficacy of early nutritional support delivered through the parenteral route, as compared with the enteral route.[25] All analyses were performed with the use of Stata/SE software, version 13.0.

RESULTS

PATIENTS

From June 22, 2011, to March 2, 2014, we screened 11,108 patients at 33 sites in England (Table S1 in the Supplementary Appendix). Of these patients, 2400 were enrolled, including 12 patients who subsequently withdrew from the study (Table S2 in the Supplementary Appendix), which resulted in an intention-to-treat population of 2388 patients (1191 in the parenteral group and 1197 in the enteral group) (Fig. 1). Baseline characteristics of the patients were similar in the two study groups (Table 1, and Table S3 in the Supplementary Appendix).

ADHERENCE AND NUTRITIONAL SUPPORT

Overall, 97% of the patients received early nutritional support through the assigned route, and rates of nonadherence to the protocol were similar in the two groups (Table 2). Initiation was delayed for 37 patients (3.1%) in the parenteral group and 41 (3.4%) in the enteral group. Crossover occurred in 81 patients (6.8%) in the parenteral group and 18 patients (1.5%) in the enteral group during the intervention period; most of the crossover occurred toward the end of the 120 hours. Patients in the enteral group were more likely than those in the parenteral group to have complete days without nutrition (Table S4 and Fig. S2 in the Supplementary Appendix).

Nutritional support was initiated early and is summarized in Table 2 and in Tables S5 and S6 in the Supplementary Appendix. In the enteral group, the mean gastric residual volume (253 ml per 24 hours, with cutoff volumes of 200 to 500 ml in local protocols) was higher and more patients received prokinetic agents than in the parenteral group. Scores on the Sequential Organ Failure Assessment (SOFA)[26] and amounts of calories and proteins or amino acids are provided in Figure 2. The target nutritional value of 25 kcal per kilogram per day was not achieved for the majority of patients in the two study groups, although caloric intake was similar in the two groups.

ADVERSE EVENTS

One or more serious adverse events were reported in 58 patients (4.9%) in the parenteral group and 58 patients (4.8%) in the enteral group (P=1.00) (Table 2, and Table S7 in the Supplementary Appendix). There were five serious, unexpected adverse events that were deemed by the site investigator to be potentially related to the study treatment in 4 patients (1 with ischemic bowel and hypoglycemia and 1 each with upper gastrointestinal hemorrhage and anterolateral myocardial infarction in the parenteral group and 1 with lower gastrointestinal hemorrhage in the enteral group).

PRIMARY OUTCOME

By 30 days, 393 of 1188 patients (33.1%) in the parenteral group and 409 of 1195 patients (34.2%) in the enteral group had died, with no significant between-group difference, even after adjustment for baseline variables (relative risk in the parenteral group, 0.97; 95% confidence interval [CI], 0.86 to 1.08; absolute risk reduction, 1.15; 95% CI, −2.65 to 4.94; P=0.57) (Table 3). The results were similar after the inclusion of 5 patients with missing data for the 30-day outcome (relative risks, 0.96 and 0.97 after the application of extreme assumptions).

SECONDARY OUTCOMES

There were significant reductions in the parenteral group, as compared with the enteral group, in rates of hypoglycemia (44 patients [3.7%] vs. 74 patients [6.2%]; absolute risk reduction, 2.5 percentage points; 95% CI, 0.8 to 4.2; P=0.006) and vomiting (100 patients [8.4%] vs. 194 patients [16.2%]; absolute risk reduction, 7.8 percentage points; 95% CI, 5.2 to 10.4; P<0.001). However, there were no significant differences between the parenteral group and the enteral group for the 16 other secondary outcomes, including the mean number of infectious complications (0.22 vs. 0.21; difference, 0.01; 95% CI, −0.04 to 0.06; P=0.72) and 90-day mortality (442 of 1184 patients [37.3%] vs. 464 of 1188 patients [39.1%]; relative risk, 0.96; 95% CI, 0.86 to 1.06; P=0.40) (Table 3, and Table S8 in the Supplementary Appendix). There was no significant difference in the duration of survival up to 90 days (P=0.98 by the log-rank test; adjusted hazard ratio, 0.94; 95% CI, 0.82 to 1.07, P=0.33) (Fig. S3 in the Supplementary Appendix).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Parenteral Group (N=1191)	Enteral Group (N=1197)
Age — yr	63.3±15.1	62.9±15.4
Male sex — no. (%)	689 (57.9)	725 (60.6)
Severe coexisting illness — no./total no. (%)		
Liver	29/1181 (2.5)	34/1193 (2.8)
Renal	20/1181 (1.7)	15/1193 (1.3)
Respiratory	34/1181 (2.9)	23/1193 (1.9)
Cardiovascular	11/1181 (0.9)	14/1193 (1.2)
Immunodeficiency	78/1181 (6.6)	95/1193 (8.0)
Surgery <24 hr before ICU admission — no. (%)†	162 (13.6)	167 (14.0)
APACHE II‡		
Acute Physiology Score	15.1±6.2	15.2±6.2
Total score	19.6±6.9	19.6±7.0
Median predicted risk of death (IQR)§	0.34 (0.18–0.52)	0.34 (0.18–0.52)
ICNARC		
Physiology Score¶	25.6±8.0	25.8±7.8
Median predicted risk of death (IQR)‖	0.42 (0.22–0.65)	0.43 (0.23–0.65)
Mechanical ventilation — no./total no. (%)	979/1178 (83.1)	993/1185 (83.8)
SOFA score**	9.5±3.4	9.6±3.3
Subjective assessment of severe malnutrition — no. (%)†	151 (12.7)	152 (12.7)
Actual or estimated body-mass index††	27.7±7.4	28.2±7.5
Degree of malnutrition — no./total no. (%)‡‡		
High	74/1152 (6.4)	81/1161 (7.0)
Moderate	8/1152 (0.7)	10/1161 (0.9)
None	1070/1152 (92.9)	1070/1161 (92.2)

* Plus–minus values are means ±SD. There were no significant differences between the two groups. ICU denotes intensive care unit, and IQR interquartile range.

† This characteristic was included in the minimization algorithm.

‡ On the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Acute Physiology Score, which is based on data regarding physiological function that were obtained during the first 24 hours after admission to the ICU, ranges from 0 to 60, with higher scores indicating greater severity of illness. The total score, which is based on acute physiology, age, and severe coexisting illnesses, ranges from 0 to 71, with higher scores indicating greater severity of illness.

§ This value is the predicted risk of death before discharge from an acute care hospital in the United Kingdom on the basis of a 2013 recalibration. There were insufficient data to calculate the predicted risk of death for 29 patients in the parenteral group and 24 in the enteral group.

¶ Scores for physiological function on the Intensive Care National Audit and Research Centre (ICNARC) model range from 0 to 100, with higher scores indicating a greater severity of illness. This score was based on data regarding physiological function that were obtained during the first 24 hours after admission to the ICU.

‖ There were insufficient data to calculate the predicted risk of death for one patient in the parenteral group.

** Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. The SOFA score was calculated with the use of data obtained within 24 hours before randomization.

†† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. This value was based on estimated weight or height for 1552 patients (780 in the parenteral group and 772 in the enteral group) and was not available for 24 patients (14 in the parenteral group and 10 in the enteral group).

‡‡ A high degree of malnutrition was defined as a BMI of less than 18.5 or a weight loss of more than 10% over the previous 6 months, and a moderate degree of malnutrition was defined as a BMI of less than 20 and a weight loss of more than 5%.

Table 2. Nonadherence, Clinical Management, and Serious Adverse Events.*

Variable	Parenteral Group (N=1191)	Enteral Group (N=1197)
Any nonadherence to delivery of nutritional support during intervention period — no. (%)	150 (12.6)	127 (10.6)
Median time from ICU admission to initiation of early nutritional support (IQR) — hr	24 (17–30)	22 (16–28)
Total calories received during intervention period — kcal/kg	89±44	74±44
Total protein received during intervention period — g/kg	3±2	3±2
Gastric residual volume — ml†		
Total aspirated during intervention period	35±265	958±1312
Total replaced during intervention period	24±170	618±863
Patients receiving prokinetic drug during intervention period — no. (%)†	26 (2.2)	426 (35.6)
Blood glucose during intervention period — mg/dl		
Daily lowest	127±25	118±26
Daily highest	183±43	181±45
Patients receiving insulin during intervention period — no./total no. (%)	694/1184 (58.6)	668/1191 (56.1)
Patients receiving vasoactive agents during intervention period — no./total no. (%)	958/1184 (80.9)	1007/1191 (84.6)
Median no. of days from randomization to initiation of exclusive oral feeding (IQR)	14 (5–36)	13 (5–32)
Serious adverse events — no. (%)‡		
Any	58 (4.9)	58 (4.8)
Specified§		
Abdominal distention	1 (0.1)	2 (0.2)
Electrolyte disturbance	8 (0.7)	5 (0.4)
Hypoglycemic episode	5 (0.4)	3 (0.3)
Ischemic bowel	8 (0.7)	11 (0.9)
Jaundice	1 (0.1)	1 (0.1)
Pneumothorax	1 (0.1)	1 (0.1)
Elevated liver enzymes	3 (0.3)	7 (0.6)
Regurgitation or aspiration	2 (0.2)	4 (0.3)
Vomiting	1 (0.1)	1 (0.1)
Unspecified¶	39 (3.3)	30 (2.5)

* Plus–minus values are means ±SD. Data completeness for nutritional support ranged from 97 to 100%. The intervention period extended from the initiation of nutritional support to 120 hours or until transition to exclusive oral feeding, discharge from the ICU, or death.

† Data in this category were recorded only for patients receiving nutritional support through the enteral route, including patients who crossed over from the parenteral group.

‡ Adverse events were assessed as serious if they involved prolonging of hospitalization, resulted in persistent or substantial disability or incapacity, or were life-threatening or fatal. P=1.00 for the between-group difference.

§ The following specified serious adverse events did not occur in either study group: abdominal pain, hemopneumothorax, hepatomegaly, hyperosmolar syndrome, hypersensitivity reaction (anaphylactic reaction), nausea requiring treatment, or vascular catheter-related infection.

¶ A list of individual unspecified serious adverse events is provided in Table S7 in the Supplementary Appendix.

SUBGROUP AND SECONDARY ANALYSES

There were no significant interactions between study group and any prespecified subgroup with respect to 30-day mortality (P=0.15 to P=0.83) (Fig. S4 in the Supplementary Appendix). The results were similar after adjustment for nonadherence (relative risk of death at 30 days, 0.96; 95% CI, 0.85 to 1.09; P=0.55).

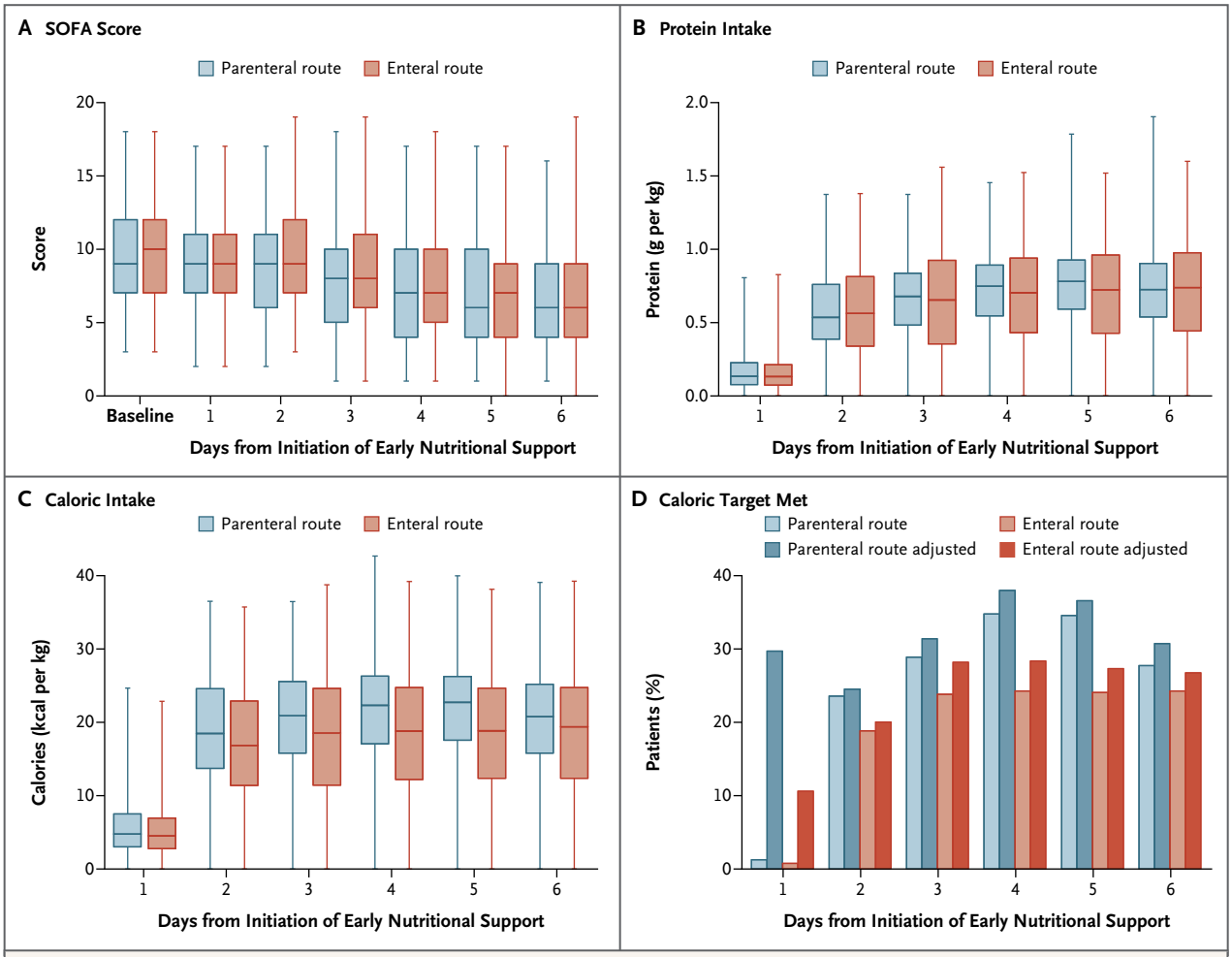

Figure 2. Daily SOFA Score and Protein and Caloric Intake from Days 1 to 6.

Panel A shows the Sequential Organ Failure Assessment (SOFA) scores for the 24 hours before randomization (baseline) and from day 1 to day 6. SOFA scores range from 0 to 24, with higher scores indicating a greater degree of organ failure. Also shown are the total amounts of protein (Panel B) and calories (Panel C) received per kilogram of actual or estimated body weight. Panel D shows the percentage of patients in whom the target of 25 kcal per kilogram of body weight per day was met. The dark-colored bars show the percentage of patients in whom the target was met after adjustment for partial days of feeding (e.g., after the death of a patient). Day 1 data are the values from the time of initiation to the end of the day of initiation of nutritional support. In Panels A to C, the horizontal lines within the boxes indicate medians, the lower and upper ends of the boxes the 25th and 75th percentiles, respectively, and the I bars the 1st and 99th percentiles.

DISCUSSION

Our study showed that among adults with an unplanned ICU admission for whom early nutritional support could be provided through either the parenteral or the enteral route, there was no significant difference in mortality at 30 days according to the route of delivery. In addition, there was no significant interaction on the basis of age, the degree of existing malnutrition, the severity of illness, or the timing of the initiation of nutritional support. The enteral route was associated with significantly more episodes of hypoglycemia and vomiting, but there were no significant between-group differences in the duration of organ support, the number of infectious complications, the length of stay in the ICU or total hospital stay, or the duration of survival up to

Table 3. Primary and Secondary Outcomes.*

Outcome	Parenteral Group (N=1191)	Enteral Group (N=1197)	Absolute Difference between Groups (95% CI)	Relative Risk (95% CI)	P Value
Primary outcome: death within 30 days — no./total no. (%)	393/1188 (33.1)	409/1195 (34.2)	1.15 (–2.65 to 4.94)†	0.97 (0.86 to 1.08)‡	0.57§
Secondary outcomes					
No. of days alive and free of specified organ support up to 30 days¶					
Free of advanced respiratory support	14.3±12.1	14.3±12.2	0.04 (–0.94 to 1.01)		0.94
Free of advanced cardiovascular support	18.9±13.5	18.5±13.6	0.41 (–0.63 to 1.53)		0.44
Free of renal support	19.1±13.9	18.8±14.0	0.26 (–0.85 to 1.47)		0.66
Free of neurologic support	19.2±13.8	18.9±14.0	0.34 (–0.81 to 1.36)		0.57
Free of gastrointestinal support	13.0±11.7	13.2±11.8	–0.12 (–1.05 to 0.80)		0.81
No. of treated infectious complications per patient‖	0.22±0.60	0.21±0.56	0.01 (–0.04 to 0.06)		0.72
Noninfectious complications — no./total no. (%)					
Episodes of hypoglycemia	44/1191 (3.7)**	74/1197 (6.2)††	2.49 (0.75 to 4.22)†		0.006§
Elevated liver enzymes	212/1191 (17.8)	179/1197 (15.0)	–2.85 (–5.81 to 0.12)†		0.07§
Nausea requiring treatment	44/1191 (3.7)	53/1197 (4.4)	0.73 (–0.85 to 2.32)†		0.41§
Abdominal distention	78/1191 (6.5)	99/1197 (8.3)	1.72 (–0.38 to 3.82)†		0.12§
Vomiting	100/1191 (8.4)	194/1197 (16.2)	7.81 (5.20 to 10.43)†		<0.001§
New or substantially worsened pressure ulcers	181/1190 (15.2)	179/1195 (15.0)	–0.23 (–3.10 to 2.64)†		0.91§
Median no. of days in the ICU (IQR)‡‡	8.1 (4.0–15.8)	7.3 (3.9–14.3)			0.15
Median no. of days in acute care hospital (IQR)§§	17 (8–34)	16 (8–33)			0.32
Death — no./total no. (%)¶¶					
In the ICU	317/1190 (26.6)	352/1197 (29.4)		0.91 (0.80 to 1.03)	0.13§
In acute care hospital	431/1185 (36.4)	450/1186 (37.9)		0.96 (0.86 to 1.06)	0.44§
By 90 days	442/1184 (37.3)	464/1188 (39.1)		0.96 (0.86 to 1.06)	0.40§

* Plus–minus values are means ±SD.
† This value is the absolute risk reduction between event rates.
‡ The adjusted odds ratio from multiple logistic regression was 0.95 (95% CI, 0.79 to 1.13; P=0.55).
§ This P value was calculated with the use of Fisher's exact test.
¶ Data on the number of days alive and free of organ support were not available for 5 patients in the parenteral group and 2 in the enteral group.
‖ Infectious complications in 224 of 262 patients (85.5%) in the parenteral group and in 215 of 253 patients (85.0%) in the enteral group were confirmed on laboratory testing.
** A total of 25 these episodes occurred during the first 6 days, and the mean (±SD) of the lowest blood glucose levels was 57±15 mg per deciliter (3.2±0.8 mmol per liter).
†† A total of 48 of these episodes occurred during the first 6 days, and the mean of the lowest blood glucose levels was 54±15 mg per deciliter (3.0±0.8 mmol per liter).
‡‡ The number of days in the ICU was not available for 1 patient in the parenteral group.
§§ The numbers of days in an acute care hospital were not available for 6 patients in the parenteral group and 11 in the enteral group.
¶¶ The adjusted odds ratios from multiple logistic regression were 0.86 (95% CI, 0.71 to 1.04; P=0.12) for death in the ICU, 0.93 (95% CI, 0.78 to 1.11; P=0.43) for death in an acute care hospital, and 0.93 (95% CI, 0.77 to 1.11; P=0.39) for death by 90 days.

90 days. The target delivery of 25 kcal per kilogram per day was not reached in a majority of the patients in each study group.

There is debate about both the route of delivery and the dose of clinically supplied nutrition, and the aim of our study was to address solely the question of route. Set in a real-world context, our study had two major findings. First, there was no significant difference in outcome between the two study groups. Although there was a trend toward more gastrointestinal side effects with the enteral route, the reported increase in infectious complications that have been associated with the parenteral route was not observed. Possible contributory reasons are improvements in current management of vascular access[27] and prevention of ventilator-associated pneumonia,[28] as well as developments in feeding technology. Second, there was no significant difference in effective nutritional delivery, since patients in the two groups did not receive the caloric targets. Although these findings are consistent with those of previous trials evaluating the enteral route in critically ill patients,[6,7] the presumption is that the parenteral route is more reliable in guaranteeing delivery.[10,11] Possible contributory reasons as to why the parenteral route did not meet its caloric target include lack of availability of nutritional product, content (the use of commercially available rather than individually titrated product), delivery (delays or interruptions in delivery for procedures, transfers, patient factors, etc.), and clinical preference. However, the amount of nutrition that was delivered was consistent with amounts in previous studies in which delivery also fell short of the target in this population, suggesting that there are substantial practical and organizational impediments for both routes of delivery, at least during an initial 5-day period. However, the similar between-group caloric intake reinforces the design of our study to focus on the evaluation of the delivery route uncomplicated by dose.

Our study was conducted in ICUs in England that had preexisting, established protocols for the delivery of parenteral and enteral nutrition, prevention of bloodstream infections and ventilator-associated pneumonia, and glycemic control. It was designed as a pragmatic effectiveness study and represents the reality of current critical care practice in the English National Health Service. Although the study had a large enrollment, the results are generalizable only to the specific population that we studied. It was rigorously conducted, with the study groups well balanced at baseline and early initiation of nutritional support, as intended. Blinding was deemed to be impractical and, although the primary outcome was objective, some of the secondary outcomes, though defined and objectively assessed, may have been more vulnerable to observer bias. We selected an objective, documented clinical definition of a new infection — one that was laboratory-confirmed or for which there was sufficient conviction to treat the patient. Though the measurement of the residual gastric volume has recently been questioned,[29] the overall feeding performance through the enteral route in our study was similar to their findings, and the rates of vomiting and infectious complications in our study were lower.

How do our findings compare with those in other recent trials on nutritional support in the critically ill? In the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial,[10] which was conducted in two hospitals (seven units) recruiting patients who required parenteral nutrition and using tight glycemic control, investigators found an association between supplemental parenteral nutrition delivered within 48 hours after presentation and an increased number of infectious episodes and days of mechanical ventilation, less hypoglycemia, and no difference in 90-day mortality. These differences were found for subgroups of cardiac surgical patients and other critically ill patients. Post hoc analyses suggested a dose–response relationship between an increased amount of parenteral nutrition and an increased rate of infectious episodes.[30] Despite important differences between our study and the EPaNIC trial and between the two study groups in EPaNIC, our results potentially support their hypothesis that among patients receiving early supplemental parenteral nutrition, the dose is more associated with harm than is the route of delivery. In a trial conducted at two sites, Heidegger et al.[11] found no difference in the rate of infection between day 8 and day 28 among patients who started receiving individually optimized parenteral nutrition to supplement inadequate enteral intake on day 4 and patients receiving only enteral nutrition.[11] In a trial conducted at 31 sites involving patients with relative

contraindications to enteral nutrition, Doig et al.[31] found no differences in 60-day mortality and the number of infectious episodes but fewer days of mechanical ventilation in patients receiving early parenteral nutrition, as compared with standard care. However, in the standard-care group, 27% of patients received early parenteral nutrition and 41% received no nutritional support.[31] In drawing any comparison, it must be noted that in our study, we asked a different research question in a different population of critically ill patients.

Our study leaves unanswered the question of nutritional dose and the determination of energy and protein or amino acid requirements for critically ill patients. We specifically did not compare an individualized enteral feeding regimen (that allows for increased amounts in patients who can tolerate enteral feeding) with its parenteral equivalent (with individualized monitoring of metabolic and protein balance). However, our findings suggest that early nutritional support through the parenteral route, as it is typically administered, is neither more harmful nor more beneficial than such support through the enteral route.

The views expressed in this article are those of the authors and do not necessarily reflect those of the Health Technology Assessment Program of the National Institute for Health Research, National Health Service, or the Department of Health.

Supported by a grant from the Health Technology Assessment Program of the United Kingdom National Institute for Health Research (project no. 07/52/03).

Ms. Bear reports receiving consulting fees from Nutricia, lecture fees from Nestle Nutrition, travel support from Nutricia and Baxter, and grant support through her institution from Corpak MedSystems UK; Ms. Segaran, receiving travel support from Abbott Nutrition; Dr. Beale, receiving consulting and lecture fees from Nestle Nutrition and grant support from Fresenius Kabi (all through his institution), and negotiating an unrestricted research grant from Nestle Nutrition (through the European Society of Intensive Care Medicine); and Dr. Mythen, receiving lecture fees from Fresenius Kabi and Baxter and grant support from Fresenius Kabi and holding a patent related to methods and apparatus for guiding medical care based on detected gastric function through Medical Defence Technologies. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition 2004; 20:843-8.
2. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr 2003;27:355-73.
3. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. Intensive Care Med 2005;31:12-23.
4. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: executive summary. Crit Care Med 2009;37:1757-61.
5. Singer P, Berger MM, Van den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 2009; 28:387-400.
6. De Jonghe B, Appere-De-Vechi C, Fournier M, et al. A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 2001; 29:8-12.
7. Engel JM, Muhling J, Junger A, Menges T, Karcher B, Hempelmann G. Enteral nutrition practice in a surgical intensive care unit: what proportion of energy expenditure is delivered enterally? Clin Nutr 2003;22:187-92.
8. Boitano M, Bojak S, McCloskey S, McCaul DS, McDonough M. Improving the safety and effectiveness of parenteral nutrition: results of a quality improvement collaboration. Nutr Clin Pract 2010;25: 663-71.
9. Naylor CJ, Griffiths RD, Fernandez RS. Does a multidisciplinary total parenteral nutrition team improve patient outcomes? A systematic review. JPEN J Parenter Enteral Nutr 2004;28:251-8.
10. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011; 365:506-17.
11. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381:385-93.
12. Harrison DA, Brady AR, Rowan K. Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the Intensive Care National Audit and Research Centre Case Mix Programme Database. Crit Care 2004;8:R99-R111.
13. High impact intervention no 1: central venous catheter care bundle. London: National Health Service, 2007 (http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_078120.pdf).
14. Reducing the harm caused by misplaced nasogastric feeding tubes — patient safety alert. London: National Patient Safety Agency, February 2005 (http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59794).
15. How to confirm the correct position of nasogastric feeding tubes in infants, children and adults — interim advice for healthcare staff. London: National Patient Safety Agency, 2005 (http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59794).
16. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
17. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 2005;366:472-7.
18. Grant AM, Altman DG, Babiker AB, et al. Issues in data monitoring and interim analysis of trials. Health Technol Assess 2005;9:1-238.
19. Harvey SE, Parrott F, Harrison DA, Mythen M, Rowan KM. The CALORIES trial statistical analysis plan. Crit Care Resusc (in press).

20. Harrison DA, Parry GJ, Carpenter JR, Short A, Rowan K. A new risk prediction model for critical care: the Intensive Care National Audit and Research Centre (ICNARC) model. Crit Care Med 2007;35:1091-8.
21. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18:681-94.
22. Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? BMJ 2000;320:1197-200.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
24. Fischer K, Goetghebeur E, Vrijens B, White IR. A structural mean model to allow for noncompliance in a randomized trial comparing 2 active treatments. Biostatistics 2011;12:247-57.
25. Greenland S. An introduction to instrumental variables for epidemiologists. Int J Epidemiol 2000;29:722-9.
26. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22:707-10.
27. Bion J, Richardson A, Hibbert P, et al. 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf 2013;22:110-23.
28. High impact intervention no 5: care bundle for ventilated patients (or tracheostomy where appropriate). London: National Health Service, 2007 (http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_078124.pdf).
29. Reignier J, Mercier E, Le Gouge A, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA 2013;309:249-56.
30. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187:247-55.
31. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013;309:2130-8.