

EDITORIAL



The Route of Early Nutrition in Critical Illness

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Randomized trials may be broadly categorized as explanatory or pragmatic. Explanatory trials address the question, “Can this intervention work under ideal conditions?” Pragmatic trials ask, “Does this intervention work under usual conditions?” Usual conditions, of course, are context-dependent. In the United Kingdom, the CALORIES trial by Harvey et al.¹ reported in the *Journal*, addresses the clinical effectiveness of early enteral nutrition, as compared with early parenteral nutrition, in critically ill patients without contraindications to either route of delivery. This trial, commissioned and sponsored by the Health Technology Assessment Program of the National Institute for Health Research, was pragmatic in design and conduct.

To maximize the detection of differences between groups, investigators who are designing an explanatory trial might select malnourished patients, maintain blinding with the use of a double-dummy technique, establish near-perfect compliance, and minimize random and systemic errors by adjudicating nonmortality outcomes. Although explanatory trials are enlightening, they often overestimate treatment effects observed in practice. Accordingly, the National Health Service sought to understand the real-world consequences of early nutrition versus early parenteral nutrition.

The adage “use the gut when possible” is based on a physiological rationale, including the fact that immune-enhancing benefits of enteral nutrition have been observed in mechanistic studies. In addition, feeding by the enteral route is often more convenient, and indirect evidence suggests that early initiation of enteral nutrition has been associated with fewer infections than late initiation.² However, obstacles to starting and sustaining enteral nutrition abound. Barriers include the tendency for prioritization of other aspects of care over nutrition, shortages of feeding pumps and

enteral formulas in ICUs, blocked feeding tubes, delayed reinsertions, suspension of nutrient delivery on the basis of gastric residual volumes, vomiting or aspiration, challenges in small-bowel access among patients with feeding intolerance, and insufficient consultation with dietitians.³

Might intravenous nutrition be more reliable, better meet caloric needs, and confer better outcomes than enteral nutrition? The association between parenteral nutrition and increased risk of infection may be attenuated today by contemporary management of central venous catheters and avoidance of hyperglycemia. In a meta-analysis of 13 trials of parenteral nutrition, as compared with enteral nutrition provided by Harvey et al. in a Supplementary Appendix to their study, there was no significant reduction in mortality among patients receiving parenteral nutrition (relative risk, 0.82; 95% confidence interval [CI], 0.60 to 1.11),¹ whereas in a meta-analysis of 9 trials in which analyses were performed on the intention-to-treat principle, there was a significant benefit favoring parenteral nutrition (odds ratio, 0.51; 95% CI, 0.27 to 0.97).⁴ Thus, Harvey et al. hypothesized that parenteral nutrition would be superior to enteral nutrition in the CALORIES trial.

There is conspicuous variation among practices regarding the use and timing of parenteral nutrition,⁵ and guidelines provide differing recommendations. European guidelines recommend the initiation of parenteral nutrition within 48 hours after admission if enteral nutrition is contraindicated or in patients with feeding intolerance.⁶ North American guidelines generally recommend the initiation of parenteral nutrition after the first week in the ICU.^{7,8} International guidelines for patients with sepsis suggest the use of enteral nutrition alone rather than parenteral nutrition alone or in conjunction with enteral nutrition during the first week.⁹

In the CALORIES trial, investigators in 33 English ICUs used a 24-hour telephone randomization system, performed analyses based on the intention-to-treat principle, and had excellent follow-up. Staff members monitored nutritional adequacy and nutritional complications using accepted guidelines. Selected sites had established protocols for the use of enteral nutrition and parenteral nutrition that included serum glucose targets (≤ 180 mg per deciliter [10 mmol per liter]) and the use of infection-prevention methods. Sites were committed to protocol adherence, screening logs, and timely data submission, the last of which is imperative for legitimate safety monitoring.

On average, nutritional support was initiated within 24 hours after admission to the ICU. The targeted intake was 25 kcal per kilogram of body weight per day, a goal that was adapted for patients at the extremes of body-mass index (BMI). The amount of protein calories, product selection, and the use of supplements were determined by local practices. Remarkably, sites achieved similar protein and caloric intake, and rates of adherence were similar, although patients in the parenteral group received more micronutrients, especially selenium. However, the premise that parenteral nutrition would secure better nutritional delivery was not realized.

Today, many nutrition trials evaluate mortality and acquired infections, which are the most commonly used primary outcomes in randomized trials conducted in ICUs since 2007.¹⁰ In the CALORIES trial, no significant between-group difference was observed in the rate of infection or death at each prespecified time point up to 90 days. Predictably, patients in the enteral group had more frequent vomiting, had a higher mean gastric residual volume, and received more prokinetic drugs.

Could the profile of the study population explain the similar findings in the two groups? Although patients were at high risk for death (80% received mechanical ventilation or vasopressors), 90% had no malnutrition, as defined on the basis of the BMI and recent weight loss; subjectively, 13% were malnourished. The use of a scoring system to identify patients who may be most nutrition-responsive may serve in future explanatory trials. However, the administration of nutrition — an archetypal basic life support — clearly needs to be evaluated in more pragmatic trials.

The CALORIES trial weaves an important thread into the complex tapestry of evidence that informs the practice of nutritional support in the ICU. Among patients without contraindications to either route of delivery, when enteral nutrition and parenteral nutrition are initiated early and with similar caloric and protein doses, clinical outcomes appear to be similar. The lack of benefit associated with exclusive early parenteral nutrition raises questions about inflated estimates of benefit in previous smaller trials. Meanwhile, bedside decisions about the route of nutritional support during critical illness will probably continue to be influenced by availability, access, assessment of individualized nutritional needs, perceived costs, and prevailing practices.

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

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ORIGINAL ARTICLE

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

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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.)

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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 patients¹⁻³ 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 nutrition⁶ 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

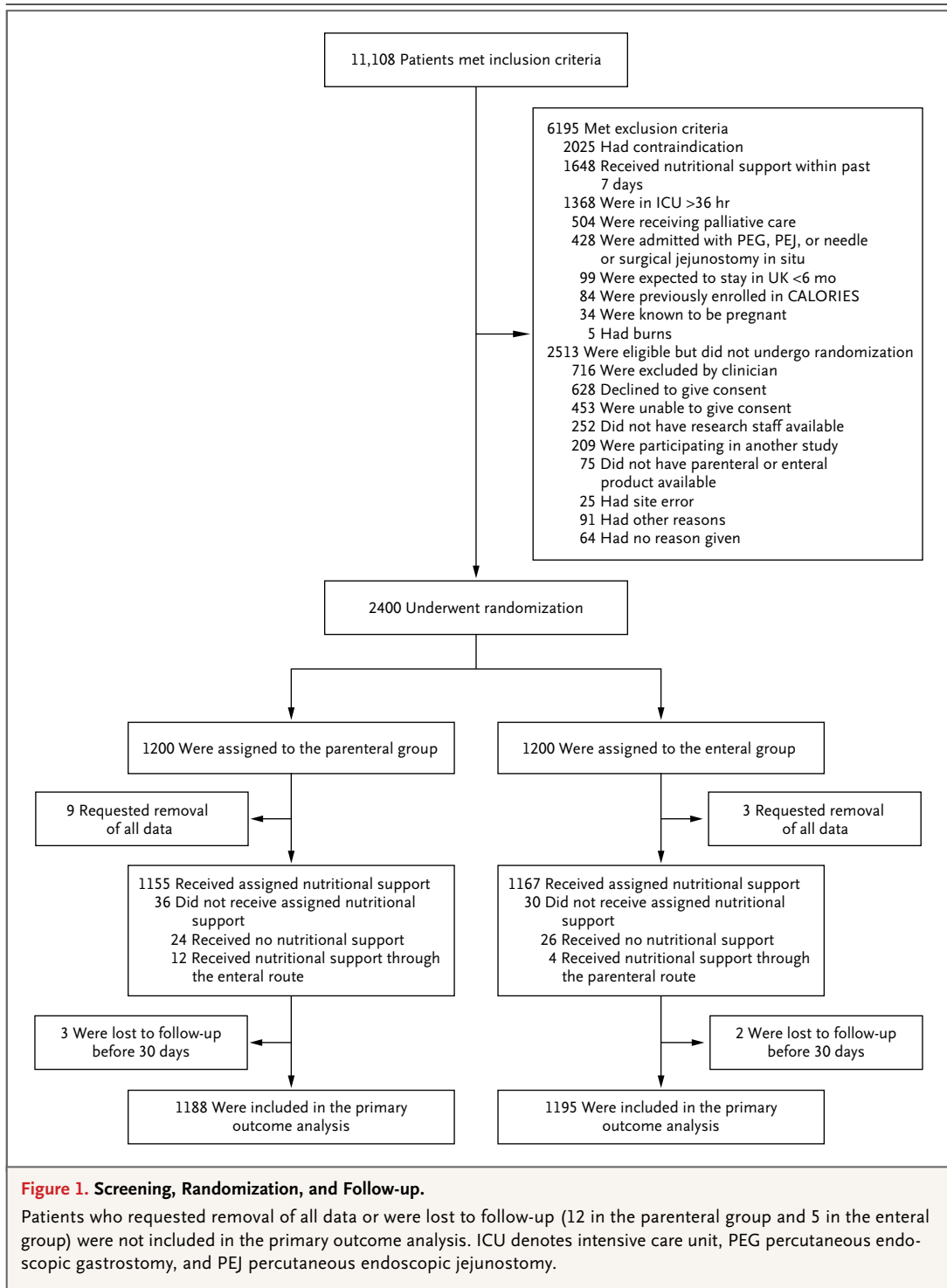
A single, planned interim analysis was performed and was reviewed by the data and safety monitoring committee at the point when 30-day outcomes for the first 1200 patients were available. A Haybittle–Peto stopping rule ($P < 0.001$) was used to guide recommendations for early termination.¹⁸

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 latter²²), 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



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

model²⁴ 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).

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.

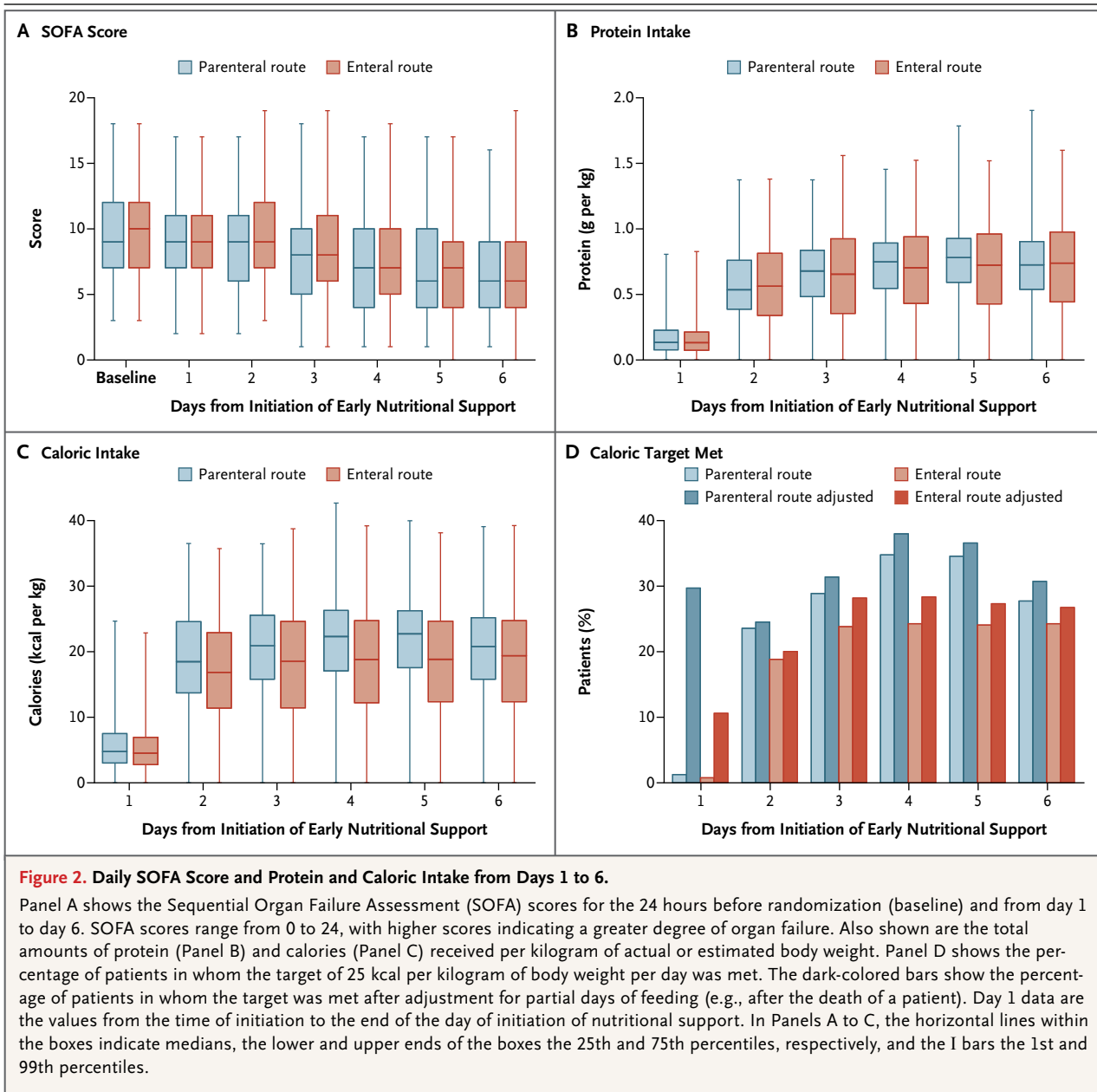
§ The following specified serious adverse events did not occur in either study group: abdominal pain, hemopneumothorax, hepatomegaly, hyperosmolar syndrome, hypersensitivity reaction (anaphylactic reaction), nausea requiring treatment, or vascular catheter-related infection.

¶ 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; $P=0.55$).



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 complica- tions 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 access²⁷ 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 enroll-

ment, 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 typi-

cally 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.

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

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CORRESPONDENCE



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

TO THE EDITOR: In reporting the results of the CALORIES trial, Harvey and colleagues (Oct. 30 issue)¹ indicate that the route of delivery of early nutritional support in the intensive care unit (ICU) does not alter patient outcomes. This message contradicts the widely held belief that the enteral route, which is more physiological, is to be preferred. However, we think that there is another implicit message: this study suggests that the role of nutritional support in the ICU should be reconsidered. Past evidence has led researchers to implement an overzealous approach to nutritional support in patients in the ICU. Given the results from the present study, we should probably take a step backward. There is still an unanswered question regarding which critically ill patients should receive early nutritional support. Some recent trials¹⁻³ suggest that such patients may be those with depleted body stores due to malnutrition rather than all those who are at nutritional risk as a consequence of critical illness. We believe that targeting early nutritional support to the right patients constitutes a key point that should be addressed.

Once that question is addressed, we could focus again on timing, the route of delivery, protein and caloric targets, and nutrients that have putative pharmacologic activity.

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TO THE EDITOR: The external validity of the study by Harvey et al. is questionable in our view. The inclusion criteria do not adhere to standards of care^{1,2} based on updated literature (see www.criticalcarenutrition.com). These standards call for the preferential use of enteral nutrition in patients who are able to receive it. The area in which experts and guidelines disagree is the timing of supplemental parenteral nutrition in patients who are unable to receive sufficient enteral nutrition without unacceptable side effects.^{3,4} The lack of advantage of early parenteral nutrition in the CALORIES study is not surprising, given that some patients may not have needed any nutritional support and the most appropriate route was not assessed in other patients in this trial. Both the low protein intake and the low caloric intake, as well as the low number of patients per center, are other major concerns. In our view, the primary outcome, all-cause mortality at 30 days, was also unlikely to be related to the efficacy of

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the therapeutic interventions. The contribution of this study would have been much more valuable after a selection of patients in whom the adequacy of nutrition mattered and could be properly evaluated.

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DOI: 10.1056/NEJMc1414479

TO THE EDITOR: In my view, the CALORIES trial fails to support the hypothesis that the parenteral route is superior to the enteral route for the delivery of early nutritional support in adults. According to the trial design, even patients who were assigned to the parenteral group received the benefits of enteral nutrition. A significant number of patients in the parenteral group received enteral nutrition both during the 120-hour period and after it. Among 700 patients in the parenteral group, only 13 patients (1.9%) exclusively received parenteral nutrition after the intervention. Extrapolation of such a short duration of parenteral nutrition with or without enteral nutritional support to estimate the effect on mortality at 30 days is not ideal. Data about coexisting diseases such as diabetes mellitus, hypertension, congestive heart failure, and chronic obstructive pulmonary disease — all of which may have an important effect on secondary outcome measures — are not mentioned. The summary of the original protocol (available with the

full text of the article at NEJM.org) mentions a primary objective to estimate the incremental cost-effectiveness of early parenteral nutrition as compared with early enteral nutrition at 1 year. I do not find mention of this in the article.

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THE AUTHORS REPLY: CALORIES was a pragmatic trial evaluating the effectiveness of the parenteral route as compared with the enteral route for early nutritional support in critically ill adults. Nutritional support was initiated within 36 hours after unplanned admission to one of a representative sample of ICUs in England and was used exclusively for 120 hours.

The suggestion by Cereda and Caccialanza that critically ill patients should receive early nutritional support only if they are malnourished is interesting but not directly relevant to our trial. Therefore, we do not believe that our data can be interpreted either to support or to refute their hypothesis, which we agree merits further consideration.

Preiser and colleagues appear to advocate opinion-based guidelines and a meta-analysis of small, older, and methodologically compromised studies, rather than evidence from a large, rigorous, randomized, controlled trial. We disagree with such an approach. Contrary to their assertion, all patients recruited into the CALORIES trial met standard criteria to receive nutritional support, as our article made clear. Moreover, effectiveness, not efficacy, was tested in our pragmatic trial. Despite their belief that mortality was unlikely to be affected by the route of nutritional support, the meta-analysis by Simpson and Doig¹ suggested otherwise. The energy intake and protein intake in our pragmatic trial were similar to or greater than those in other studies of nutritional support in clinical practice.² In addition, the number of eligible patients recruited per center was greater than that in another recent, large, multicenter trial of nutritional support in intensive care.³

Ramamurthy's statement that benefits are associated with the use of the enteral route rather

than the parenteral route is not supported by our trial. Our aim was to evaluate the effect of the route for the delivery of early nutritional support, and the number of patients in the parenteral group who were fed enterally during the 120-hour intervention period was small. Baseline characteristics, including coexisting conditions, were well balanced between the groups and were summarized in Table 1 of our article. A 1-year follow-up study is under way to assess longer-term outcomes and to provide an integrated economic evaluation.

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Since publication of their article, the authors report no further potential conflict of interest.

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Etanercept Tapering in Rheumatoid Arthritis

TO THE EDITOR: The study by Emery et al. (Nov. 6 issue)¹ contravenes the recommendations not to use biologic agents as first-line treatment for rheumatoid arthritis. Furthermore, the study uses biased control groups (methotrexate monotherapy and placebo) and does not compare the combination treatment (etanercept plus methotrexate) with a balanced combination of disease-modifying antirheumatic drugs (DMARDs). Several studies have shown that such a combination is as effective as biologic treatment, especially when combined with a short-term initial course of glucocorticoids.²⁻⁴

Owing to a lack of comparison with DMARD combination therapy, the conclusion of the study is inappropriately biased in favor of etanercept. The correct first-line treatment algorithm for rheumatoid arthritis includes DMARD monotherapy and combination therapy. Biologic agents should be reserved as second-line therapy for patients with rheumatoid arthritis who have an insufficient response to combination DMARD treatment.

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THE AUTHORS REPLY: Graudal and Jürgens contend that our study contravenes recommendations not to use biologic agents as first-line therapy for rheumatoid arthritis. The recommendations of the European League against Rheumatism (EULAR) in 2010,¹ when the study started, stated that biologic agents could be used first in the case of severe disease. In 2013, the recommendations² were modified (not by unanimous decision) to suggest that conventional synthetic DMARDs be used first. Graudal and Jürgens also indicate that a comparison with methotrexate monotherapy rather than with combination DMARDs biased the study. However, the 2013 EULAR recommendations do not endorse initial triple therapy but suggest initial methotrexate monotherapy, albeit plus glucocorticoids.