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Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

A Randomized Controlled Trial

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Importance Systematic reviews suggest adult patients in intensive care units (ICUs) with relative contraindications to early enteral nutrition (EN) may benefit from parenteral nutrition (PN) provided within 24 hours of ICU admission.

Objective To determine whether providing early PN to critically ill adults with relative contraindications to early EN alters outcomes.

Design, Setting, and Participants Multicenter, randomized, single-blind clinical trial conducted between October 2006 and June 2011 in ICUs of 31 community and tertiary hospitals in Australia and New Zealand. Participants were critically ill adults with relative contraindications to early EN who were expected to remain in the ICU longer than 2 days.

Interventions Random allocation to pragmatic standard care or early PN.

Main Outcomes and Measures Day-60 mortality; quality of life, infections, and body composition.

Results A total of 1372 patients were randomized (686 to standard care, 686 to early PN). Of 682 patients receiving standard care, 199 patients (29.2%) initially commenced EN, 186 patients (27.3%) initially commenced PN, and 278 patients (40.8%) remained unfed. Time to EN or PN in patients receiving standard care was 2.8 days (95% CI, 2.3 to 3.4). Patients receiving early PN commenced PN a mean of 44 minutes after enrollment (95% CI, 36 to 55). Day-60 mortality did not differ significantly (22.8% for standard care vs 21.5% for early PN; risk difference, −1.26%; 95% CI, −6.6 to 4.1; $P=.60$). Early PN patients rated day-60 quality of life (RAND-36 General Health Status) statistically, but not clinically meaningfully, higher (45.5 for standard care vs 49.8 for early PN; mean difference, 4.3; 95% CI, 0.95 to 7.58; $P=.01$). Early PN patients required fewer days of invasive ventilation (7.73 vs 7.26 days per 10 patient × ICU days, risk difference, −0.47; 95% CI, −0.82 to −0.11; $P=.01$) and, based on Subjective Global Assessment, experienced less muscle wasting (0.43 vs 0.27 score increase per week; mean difference, −0.16; 95% CI, −0.28 to −0.038; $P=.01$) and fat loss (0.44 vs 0.31 score increase per week; mean difference, −0.13; 95% CI, −0.25 to −0.01; $P=.04$).

Conclusions and Relevance The provision of early PN to critically ill adults with relative contraindications to early EN, compared with standard care, did not result in a difference in day-60 mortality. The early PN strategy resulted in significantly fewer days of invasive ventilation but not significantly shorter ICU or hospital stays.

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PARENTERAL NUTRITION HAS BEEN in common use since the 1960s[1] and is accepted as the standard of care for patients with chronic nonfunctioning gastrointestinal tracts.[2] In critical illness, controversy surrounds the appropriate use of parenteral nutrition,[3] but large-scale trials have begun to answer important questions.

Published in 2011, EPaNIC (Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients)[4] enrolled 4640 critically ill patients to investigate the effects of using parenteral nutrition when enteral nutrition failed to reach a caloric target. EPaNIC did not find any benefits from using additional parenteral nutrition in patients who could receive enteral nutrition[5]; however, many other important questions regarding parenteral nutrition remain.

For editorial comment see p 2165.

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For example, key questions were raised by a systematic review that reported benefits associated with parenteral nutrition use in patients with relative contraindications to early enteral nutrition.[6] In contrast to EPaNIC, which targeted a wide spectrum of patients who were eligible to receive enteral nutrition, this systematic review focused on clinical trials that enrolled a narrow subset of critically ill patients, those with short-term relative contraindications to enteral nutrition. When these patients were randomized to receive standard care (unfed for 2-5 days) or parenteral nutrition within the first 24 hours of intensive care unit (ICU) admission, mortality was significantly reduced in the group receiving parenteral nutrition. However, infection rates increased.

Because the small size of the clinical trials included in this systematic review led to uncertainty surrounding the clinical importance of increased infections, some authors expressed reluctance to use parenteral nutrition in patients with short-term relative contraindications to enteral nutrition.[7] This uncertainty is mirrored by major practice guidelines, some of which recommend parenteral nutrition within 24 to 48 hours of ICU admission if enteral nutrition is contraindicated,[8,9] and other guidelines recommending parenteral nutrition only after 7 to 14 days of starvation.[10]

We conducted a multicenter clinical trial (the Early PN Trial) to assess the effects of providing parenteral nutrition within 24 hours of ICU admission to adult critically ill patients who would not otherwise receive nutrition therapy because of short-term relative contraindications to enteral nutrition.

METHODS

Adult patients were eligible for enrollment within 24 hours of ICU admission if they were expected to remain in the ICU on the calendar day after enrollment, were considered ineligible for enteral nutrition by the attending clinician due to a short-term relative contraindication and were not expected to receive parenteral or oral nutrition on the day of enrollment or the day after enrollment, and had a central venous line through which parenteral nutrition could be delivered. Patients who were moribund and not expected to survive 24 hours, who were to receive palliative care only, or who had a licensing/labeling contraindication to the study parenteral nutrition (eg, known pregnancy, documented allergy, etc) were excluded. (See eTable 1, available at http://www.jama.com, for complete eligibility criteria.) Approval was obtained from each participating site's human research ethics committee. Written consent was documented in accordance with local and national laws.

Allocation concealment was maintained by use of a central randomization web server. Randomization was stratified within site by age and body mass index (BMI) using permuted blocks of variable sizes and random seeds. Use of a small number of odd-sized permuted blocks (size = 1), referred to as random seeds, increases the difficulty of counting into the allocation sequence and helps maintain concealment of upcoming group assignments.[11] After investigators attended a small-group start-up meeting, a run-in phase allowed them to become familiar with the application of eligibility criteria before they recruited their first patients.[12]

Interventions

Intervention patients received standard parenteral nutrition from a ready-to-mix 3-chamber bag containing amino acids, glucose, lipids, and electrolytes (Kabiven G19%, Fresenius Kabi Australia), with starting rates and rate increases defined by study protocol and trace elements, minerals, and vitamins added as clinically appropriate.[13] Targets were to be achieved by study day 3. The protocol reminded clinicians to consider additional vitamins and minerals on each study day and to consider enteral or oral nutrition on study day 3. The protocol also defined timing and rates for parenteral nutrition discontinuation.

Energy targets were calculated using the Harris-Benedict equation, allowing for stress factors.[14] Targets were capped at 35 kcal/kg/d, and obese patients (BMI ≥30) were fed to their ideal body weight (BMI = 21). (BMI is calculated as weight in kilograms divided by height in meters squared.) Total energy content (including amino acids) of the study parenteral nutrition was used in all calculations. Protein targets were not set independently of calculated energy targets. Malnourished patients (BMI <17 or clinical diagnosis) were assigned to a parenteral nutrition protocol designed to reduce the risk of refeeding syndrome. eTable 2 and eTable 3 present complete study parenteral nutrition protocols and Harris-Benedict equations, respectively.

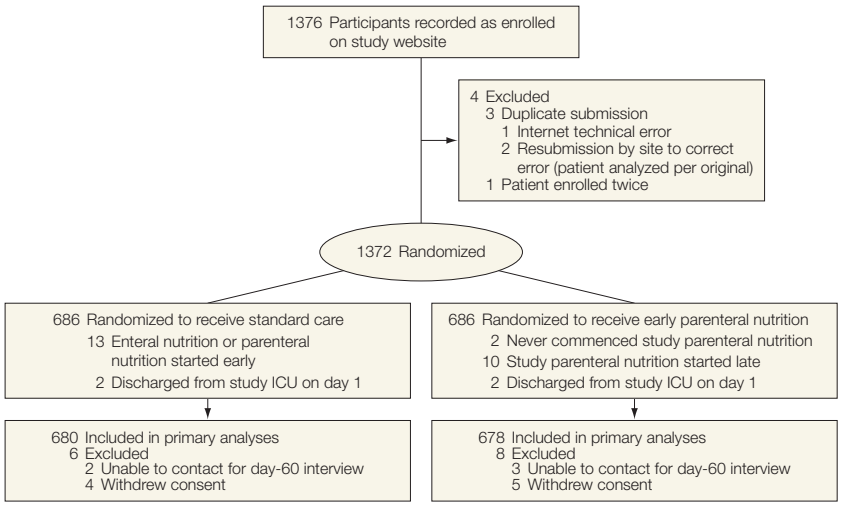
Standard care was defined pragmatically and was not via protocol. The attending clinician selected the route, starting rate, metabolic targets, and composition of nutrition to be provided to patients receiving standard care based on current practice in their ICU. In Australia and New Zealand, it is not an accepted routine practice to infuse isolated glucose solutions to provide caloric intake prior to initiating enteral, parenteral, or oral nutrition.

For all enrolled patients, regardless of group, an insulin infusion was recommended if blood glucose levels exceeded 180 mg/dL to achieve peak glucose levels less than 180 mg/dL. (To convert glucose to mmol/L, multiply by 0.0555.)

Outcomes

The primary outcome was death by study day 60. Secondary outcomes, including quality of life and physical function measures (RAND-36 general health status and physical function[15] plus Eastern Collaborative Oncology Group performance status[16]), were ascertained by unblinded site investigators using scripted telephone or face-to-face interviews at study day 60. Tertiary outcomes included days of clinically significant organ failure,[17] infection rates,[18,19] ICU and hospital stay, vital status at ICU and hospital discharge, days

Figure 1. Patient Recruitment Flow Diagram



The study budget was not sufficient to support the collection of complete information on all patients screened for eligibility into the trial at each site. The total number of screened patients, and reasons they were not enrolled, are not available. ICU indicates intensive care unit.

of invasive mechanical ventilation, days of renal replacement therapy, days of treatment for pressure ulcers, days of antibiotic usage, plus others.[13]

Twice each week while the patient was in the study ICU, trained site investigators assessed mid-arm muscle circumference, the Subjective Global Assessment (SGA)[20] item scoring muscle wasting, and the SGA item scoring fat loss.[21] These SGA items assess muscle wasting and fat loss on scales ranging from 1 to 4, with higher scores indicating greater muscle loss or fat loss (1, no obvious loss; 2, mild loss; 3, moderate loss; and 4, severe loss).[20]

Hospital radiologists' written reports were used to identify new or worsening infiltrates for use in the Clinical Pulmonary Infection Score.[18] Hospital radiologists reviewed chest x-rays unaware of group assignment. The independent safety and data monitoring committee conducted 1 planned blinded interim analysis using Haybittle-Peto stopping rules at mid-recruitment.[22,23]

Sample Size, Power, and Statistical Analysis

Data from the control group of a 27-hospital cluster randomized trial conducted in target participating sites was used to identify potentially eligible patients and estimate expected baseline mortality.[8] Because meta-analyses of small randomized trials may overestimate treatment effects observed in subsequent larger confirmatory trials,[24] the magnitude of the treatment effect reported in a previous meta-analysis on this topic[6] was conservatively deflated by 45%.

Assuming an estimated baseline mortality of 29.7%, we calculated 1470 patients would need to be enrolled to provide 90% power to detect a 7.7% risk difference (RD) between groups.[25] Complete details regarding the assumptions underlying the sample size calculation are provided in the statistical analysis plan.[13]

A detailed intention-to-treat analysis plan is published elsewhere.[13] Crude (unadjusted) analysis of the effect of treatment on the primary outcome, and all other dichotomous outcomes, was conducted using an exact Pearson χ^2 test, with unconditional exact 95% confidence intervals calculated around the RD and the odds ratio metrics.

Outcomes based on count data (eg, length of stay, days of clinically significant organ failure, etc) were analyzed using Poisson regression. If the scaled deviance exceeded 1.4 units per degree of freedom, a conservative negative-binomial model was used instead. An offset term (ICU length of stay) was used to account for time at risk where appropriate. Changes in body composition over time (mid-arm muscle circumference, SGA muscle, and SGA fat stores) were assessed using fully factorial nested analysis of variance.

A prespecified algorithm was used to identify baseline characteristics for inclusion in a covariate-adjusted logistic regression model to control confounding on the primary outcome.[13] A covariate-adjusted average risk difference and appropriate 95% CI were also calculated.[26] Four a priori defined subgroup analyses were conducted (BMI <18.5, BMI ≥ 30, age >70 years, and chronic insulin-treated diabetes) based on logistic regression tests of interaction.[13] Missing data were accepted to be missing at random unless prespecified thresholds were exceeded. If thresholds were exceeded, missing values were imputed as study group–specific pooled mean values.[13] Two-sided 5% significance levels were used to identify statistically significant results. All analyses were conducted in SAS version 9.2 (SAS Institute).

RESULTS

From October 19, 2006, to June 30, 2011, 1376 submissions were received by the study website from 31 participating ICUs throughout Australia and New Zealand (FIGURE 1). Three submissions represented duplicate patient data (1 internet failure, 2 attempts to correct data at time of enrollment), and 1 submission represented a patient enrolled on consecutive days by different research team members. All randomized patients were analyzed in the groups to which they were initially allocated except if consent was withdrawn.

Of the 1372 unique patients enrolled, 686 were randomized to receive pragmatic standard care and 686

were randomized to receive early parenteral nutrition. Nine patients withdrew consent (4 standard care and 5 early parenteral nutrition), and 5 could not be contacted at day 60 (2 standard care and 3 early parenteral nutrition). The mean time from ICU admission to enrollment was 13.8 hours (95% CI, 13.6-14.5, standard care, vs 95% CI, 13.2-14.1, early parenteral nutrition).

TABLE 1 presents baseline characteristics. Covariate-adjusted day-60 mortality was controlled for age, gender, BMI, Acute Physiology and Chronic Health Evaluation (APACHE) II score, chronic liver disease, chronic lung disease, and source of admission to ICU.

At least 1 component of the baseline APACHE II score was missing in 57 of 1363 patients (4.18%). No other baseline variables required imputation. Outcome variables were not imputed.

Measures of Nutrition Therapy

A mean of 1.98 days (95% CI, 1.43-2.78) after enrollment, 199 of 682 patients receiving standard care (29.2%) were given enteral nutrition. Of these 199 patients, 48 (24%) eventually received supplemental parenteral nutrition, which was commenced a mean of 5.58 days (95% CI, 3.9-7.96) after enteral nutrition. An additional 27.3% of patients receiving standard care (186/682) started parenteral nutrition first, with a mean time to start of 1.99 days (95% CI, 1.45-2.70) after enrollment. Enteral and parenteral nutrition was started at the same time in 19 of 682 standard care patients (2.8%), with a mean time from enrollment to start of 5.58 days (95% CI, 3.90-7.96). The remaining 278 of 682 standard care patients (40.8%) never received enteral or parenteral nutrition during their 3.72-day (95% CI, 2.65-5.20) ICU stay. Of all patients allocated to standard care, 298 of 682 patients (43.7%) received enteral nutrition at some time during their ICU stay. Thirteen standard care patients received enteral nutrition, parenteral nutrition, or oral intake within 24 hours of ICU admission. Overall, standard care patients remained unfed for a mean of 2.8 days after randomization (95% CI, 2.3-3.4). Standard care patients received 2.9 days of parenteral nutrition (95% CI, 2.7-3.1) and 4.0 days of enteral nutrition (95% CI, 3.6-4.6) while in the study ICU.

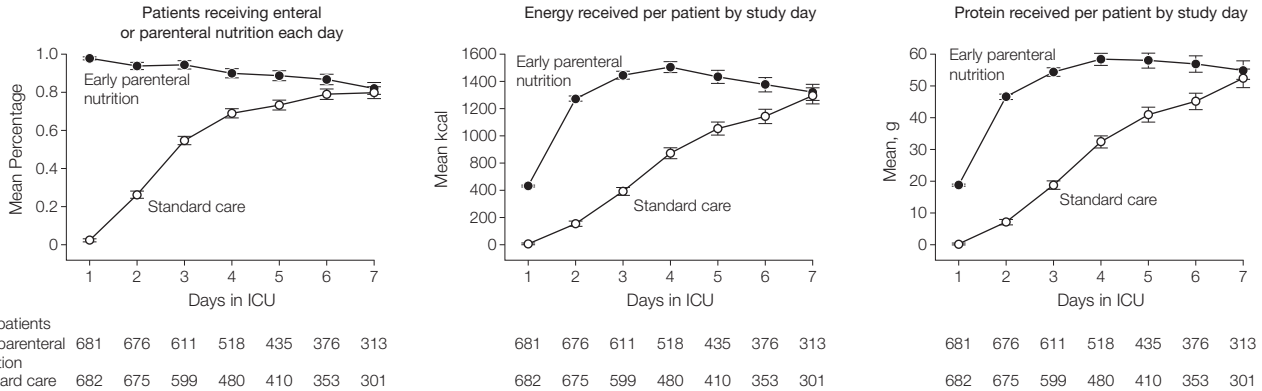
Two early parenteral nutrition patients never received any parenteral nutrition and 10 had parenteral nutrition started later than 24 hours after ICU admission. Parenteral nutrition was

Table 1. Patient Characteristics and Baseline Balance

Baseline Characteristics	Standard Care (n = 682)	Early PN (n = 681)
Age, mean (SD), y	68.6 (14.3)	68.4 (15.1)
Female gender, No. (%)	262 (38.4)	281 (41.3)
BMI, mean (SD)[a,b]	28.5 (6.9)	27.9 (6.8)
BMI ≥30, No. (%)[c]	224 (32.8)	190 (27.9)
BMI <18.5, No. (%)	20 (2.9)	26 (3.8)
Mid-arm muscle circumference, mean (SD), cm	27.2 (4.3)	26.8 (4.3)
SGA muscle wasting, mean (SD)[d]	1.36 (0.69)	1.39 (0.72)
SGA fat loss, mean (SD)[d]	1.37 (0.67)	1.40 (0.37)
APACHE II score, mean (SD)[c,e]	21.5 (7.8)	20.5 (7.4)
Mechanically ventilated, No. (%)	549 (80.6)	572 (83.9)
Chronic health states, No. (%)		
Insulin-treated diabetes	50 (7.3)	57 (8.4)
Immunocompromised[f]	30 (4.4)	33 (4.8)
Respiratory disease[f]	34 (5.0)	27 (4.0)
Cardiovascular disease[f]	23 (3.4)	25 (3.7)
Hepatic cirrhosis[f]	12 (1.8)	4 (0.6)
Chronic dialysis[f]	8 (1.2)	7 (1.0)
Source of admission to ICU, No. (%)[b]		
Operating room	430 (63.0)	464 (68.1)
Other hospital	91 (13.3)	70 (10.3)
Emergency department	88 (12.9)	70 (10.3)
Hospital ward	71 (10.4)	72 (10.6)
Transfer from ICU	2 (0.3)	5 (0.7)
ICU readmission	0	0
Surgical admission, No. (%)[b]		
Emergency surgery	305 (44.7)	320 (47.0)
Elective surgery	125 (18.3)	144 (21.5)
APACHE III admission diagnosis		
Gastrointestinal	412 (60.4)	409 (60.0)
Cardiovascular	126 (18.5)	145 (21.3)
Sepsis	54 (7.9)	43 (6.3)
Respiratory	48 (7.0)	30 (4.4)
Trauma	19 (2.8)	21 (3.1)
Neurological	9 (1.3)	8 (1.1)
Renal	4 (0.6)	5 (0.7)
Metabolic	3 (0.4)	4 (0.6)
Hematological	0	2 (0.3)
Gynecological	0	2 (0.3)
Orthopedic surgery	0	1 (0.1)
Other	7 (1.0)	11 (1.6)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit; PN, parenteral nutrition; SGA, Subjective Global Assessment.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Potential confounder due to imbalance ($P<.15$).
[c] Potential confounder due to imbalance ($P<.05$).
[d] Scored twice a week while patient was in the study ICU. Scores ranged from 1 to 4, with higher scores indicating greater loss.
[e] Fifty-seven patients (4.2%) had ≥1 missing APACHE II physiology variables, which were imputed with average values. No other data were imputed.
[f] Defined using APACHE II criteria. Scores range from 0 to 71. APACHE scores have a nonlinear relationship with the risk of death. Higher scores indicate more severe disease, associated with a higher risk of death. Scores in excess of 37 have been associated with a greater than 99.9% risk of subsequent death in-hospital.

Figure 2. Enteral and Parenteral Nutrition Delivery Process Measures for Patients Remaining in the Study ICU



Day 1 is the day of study enrollment. Energy received was calculated from enteral nutrition, parenteral nutrition, and intravenous infusions with ≥10% glucose. Error bars indicate standard error; ICU, intensive care unit.

begun a mean of 44 minutes after randomization (95% CI, 36-55), with additional vitamin supplementation commencing 2.8 days after study parenteral nutrition initiation (95% CI, 2.7-3.0) and additional mineral/trace element supplementation starting 2.2 days after study parenteral nutrition initiation (95% CI, 2.1-2.3). Of all patients allocated to early parenteral nutrition, 274 of 681 patients (40.2%) received enteral nutrition at some time during their ICU stay. Early parenteral nutrition patients received a mean of 6.0 days of parenteral nutrition (95% CI, 5.6-6.4) and 3.1 days of enteral nutrition (95% CI, 2.8-3.5) while in the study ICU. There were no study intervention–related serious adverse events reported.

FIGURE 2 presents nutrition delivery over the first 7 ICU days. Additional information regarding nutrition therapy provided to patients in both groups of the trial is reported in eTable 4 and eFigure 1.

Primary and Secondary Outcomes

Crude day-60 mortality (22.8% [155/680] for standard care vs 21.5% [146/678] for early parenteral nutrition; RD, −1.3; 95% CI, −6.6% to 4.1%; *P*=.60) and covariate-adjusted day-60 mortality, controlled for age, gender, BMI, APACHE II score, chronic liver disease, chronic lung disease, and source of ICU admission, were not found to be significantly different between groups (adjusted RD, 0.0%; 95% CI, −4.2% to 4.3%; *P*=.99).

A statistically significant improvement in quality of life (RAND-36 General Health Status)[15] (45.5 for standard care vs 49.8 for early parenteral nutrition; mean difference, 4.3; 95% CI, 0.95 to 7.58; *P*=.01) was detected in favor of patients receiving early parenteral nutrition; however, the magnitude of the difference did not exceed one-half the standard deviation,[27] which was defined a priori as clinically meaningful to patients.[13]

Additional details regarding physical function are reported in TABLE 2.

Tertiary Outcomes

Details regarding vital status at ICU discharge and hospital discharge, along with lengths of stay, are reported in Table 2.

Adjusted for time at risk (ICU stay), patients receiving early parenteral nutrition required significantly fewer days of invasive mechanical ventilation (−0.47 days per 10 patient × ICU days; 95% CI, −0.82 to −0.11; *P*=.01) and experienced fewer days with clinically significant coagulation failure[17] (−0.34 days per 10 patient × ICU days; 95% CI, −0.57 to −0.08; *P*=.01). Expressed as crude day counts, the magnitude of these differences were 1.07 fewer days of invasive mechanical ventilation (95% CI, −1.77 to −0.29) and 0.43 fewer days of coagulation failure (95% CI, −0.62 to −0.21) attributable to early parenteral nutrition (eTable 5). There were no other significant differences (TABLE 3).

There were no significant differences between groups in rates of new infection (TABLE 4).

Standard care patients experienced significantly greater muscle wasting (0.43 vs 0.27 increase in SGA score per week; mean difference, 0.16; 95% CI, 0.038 to 0.28; *P*=.01) and significantly greater fat loss (0.44 vs 0.31 increase in SGA score per week; mean difference, 0.13; 95% CI, 0.01 to 0.25; *P*=.04) over the duration of their ICU stay. Changes in mid-arm muscle circumference were evident between groups by day 2 (0.2-cm loss for standard care vs 0.0-cm loss for early parenteral nutrition over 2 days; mean difference, −0.2; 95% CI, −0.39 to −0.01; *P*=.04); however, these early mid-arm muscle circumference differences did not remain significant over the entire ICU stay (0.8-cm loss vs 0.4-cm loss per week; mean difference, −0.4; 95% CI, −1.2 to 0.3; *P*=.28).

Subgroup Analyses

There were no significant differences in day-60 mortality between a priori defined subgroups (BMI <18.5, *P*=.75 for interaction; BMI ≥30, *P*=.66 for interaction; age >70 years, *P*=.15 for interaction; and chronic insulin-treated diabetes, *P*=.80 for interaction).

DISCUSSION

The provision of parenteral nutrition within 24 hours of ICU admission to critically ill patients with short-term relative contraindications to enteral nutrition did not result in significant differences in day-60 all-cause landmark mortality or ICU infection rates. Patients who received early parenteral nutrition required significantly fewer days of invasive mechanical ventilation, but this did not result in a statistically significant shortening of ICU or hospital length of stay. No harm was attributable to the use of early parenteral nutrition in this trial.

Trial Execution

Patients who received early parenteral nutrition had significantly higher energy and amino acid/protein intakes on each of the first 6 days of ICU stay after study enrollment. Considering the magnitude of nutritional differences reported in previous trials[8,28] and the in-

Table 2. Mortality, Quality of Life, and Length of Stay

	Standard Care (n = 680)[a]	Early PN (n = 678)[a]	Risk Difference, % (95% CI)	Odds Ratio (95% CI)	*P* Value
Deaths before study day 60, No. (%)	155 (22.8)	146 (21.5)	−1.26 (−6.6 to 4.1)	0.93 (0.71 to 1.21)	.60
Covariate-adjusted deaths before study day 60[b]			0.04 (−4.2 to 4.3)	1.00 (0.76 to 1.31)	>.99
Quality of life and physical function, mean (SD)[c]	(n = 525)	(n = 532)	Difference (95% CI)		
RAND-36 general health status[d]	45.5 (26.8) (n = 516)	49.8 (27.6) (n = 525)	4.3 (0.95 to 7.58)		.01
ECOG performance status[e]	1.53 (1.1) (n = 516)	1.51 (1.1) (n = 525)	−0.02 (−0.15 to 0.11)		.70
RAND-36 physical function[f]	40.7 (29.6) (n = 513)	42.5 (30.8) (n = 524)	1.8 (−1.85 to 5.52)		.33
Discharge status and length of stay	(n = 682)	(n = 681)	Difference (95% CI)		
ICU stay, mean (95% CI), d	9.3 (8.9 to 9.7)	8.6 (8.2 to 9.0)	−0.75 (−1.47 to 0.04)		.06
Deaths before ICU discharge, No. (%)	100 (14.66)	81 (11.89)	−2.77% (−8.08% to 2.52%)		.15
Hospital stay, mean (95% CI), d	24.7 (23.7 to 25.8)	25.4 (24.4 to 26.6)	0.7 (−1.4 to 3.1)		.50
Deaths before hospital discharge, No. (%)	151 (22.1)	140 (20.6)	−1.58% (−6.91% to 3.69%)		.51

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ECOG, Eastern Collaborative Oncology Group; ICU, intensive care unit; PN, parenteral nutrition.
[a] Five patients (2 standard care, 3 early PN) who were alive at hospital discharge prior to day 60 could not be contacted on study day 60 to determine vital status. These patients were considered "missing at random" for the intention-to-treat primary and adjusted primary outcome analysis.
[b] Covariate model controlled for confounding due to age, gender, body mass index, APACHE II score, chronic liver disease, chronic respiratory disease, and source of admission.
[c] Responses available for analysis as reported by survivors at day-60 interview.
[d] Scored on a scale from 0 to 100, with higher scores indicating better general health status.
[e] Scores range from 0 to 4, with lower scores indicating fewer physical limitations.
[f] Scored on a scale from 0 to 100, with higher scores indicating better physical function.

Table 3. Clinically Significant Organ Failure and Concomitant Interventions, Adjusted for Time at Risk (ICU Stay)[a]

	Mean (95% CI), Days per 10 Patient × ICU Days		Mean Difference (95% CI), Days per 10 Patient × ICU Days	*P* Value[b]
	Standard Care (n = 682)	Early PN (n = 681)		
Organ system failures[c]				
Renal	1.66 (1.51 to 1.82)	1.65 (1.51 to 1.81)	−0.01 (−0.28 to 0.33)	.98
Pulmonary	8.51 (8.34 to 8.69)	8.54 (8.37 to 8.71)	0.03 (−0.31 to 0.37)	.88
Hepatic	1.14 (1.09 to 1.20)	1.08 (1.03 to 1.14)	−0.06 (−0.16 to 0.06)	.15
Coagulation	2.23 (2.09 to 2.38)	1.89 (1.78 to 2.02)	−0.34 (−0.57 to −0.08)	.01
Cardiovascular	1.16 (1.05 to 1.27)	0.99 (0.89 to 1.09)	−0.17 (−0.34 to 0.04)	.11
MODs	4.04 (3.85 to 4.25)	3.93 (3.74 to 4.13)	−0.11 (−0.48 to 0.29)	.59
No. of organ failures[d]	1.47 (1.44 to 1.51)	1.42 (1.39 to 1.46)	−0.05 (−0.12 to 0.02)	.12
Concomitant therapies and tertiary outcomes				
Renal replacement therapy	0.99 (0.82 to 1.81)	0.80 (0.67 to 0.96)	−0.19 (−0.42 to 0.16)	.25
Invasive mechanical ventilation	7.73 (7.55 to 7.92)	7.26 (7.09 to 7.44)	−0.47 (−0.82 to −0.11)	.01
Pressure ulcer treatment[e]	0.87 (0.74 to 1.02)	0.78 (0.67 to 0.92)	−0.09 (−0.30 to 0.22)	.54
Low serum albumin (<2.5 g/dL)	5.47 (5.28 to 5.67)	5.76 (5.56 to 5.97)	0.29 (−0.10 to 0.71)	.15
Systemic antibiotic use	7.95 (7.78 to 8.12)	8.05 (7.88 to 8.22)	0.10 (−0.23 to 0.45)	.55
Witnessed aspiration[f]	1.59 (0.98 to 2.54)	1.96 (1.21 to 3.13)	0.37 (−0.80 to 3.45)	.66
With new pulmonary infiltrates[f]	0.48 (0.20 to 1.15)	0.71 (0.30 to 1.72)	0.23 (−0.36 to 0.37)	.65

Abbreviations: ICU, intensive care unit; MODs, multiple organ dysfunction syndrome; PN, parenteral nutrition.
[a] These measures are reported as crude counts, not adjusted for time at risk (ICU stay), in eTable 5.
[b] *P* values from negative binomial model, controlled for duration of risk (ICU stay).
[c] Organ failure was defined using the following measures: renal failure, creatinine >2.0 mg/dL; pulmonary failure, PaO_2:FiO_2 ratio <301; hepatic failure, total bilirubin >2.0 mg/dL; coagulation failure, platelets <81 x10^9/L; cardiovascular failure, systolic blood pressure <90 mm Hg, not fluid responsive; MODs, ≥2 organ system failures on the same day.
[d] Per patient per ICU day.
[e] Treatment for stage 1 or greater.
[f] Events per 1000 patient × ICU days.

Table 4. New Infections During Study

Patients With New Infections[a]	No. (%) Standard Care (n = 682)	No. (%) Early PN (n = 681)	Risk Difference (Exact 95% CI)	Exact *P* Value[b]
Catheter[c]	32 (4.69)	31 (4.55)	−0.14 (−5.45 to 5.12)	>.99
Catheter tip[c]	28 (4.11)	26 (3.82)	−0.29 (−5.60 to 5.01)	.89
Surgical wound	27 (3.96)	22 (3.23)	−0.73 (−6.04 to 4.57)	.56
Bloodstream	33 (4.84)	39 (5.73)	0.89 (−4.43 to 6.18)	.47
Abdominal	3 (0.44)	6 (0.88)	0.44 (−4.89 to 5.74)	.34
Clinically significant UTI	1 (0.15)	2 (0.29)	0.15 (−5.16 to 5.45)	.62
Airway or lung[d]	123 (18.04)	101 (14.83)	−3.20 (−8.52 to 2.08)	.12
CPIS-probable pneumonia[e]	96 (14.08)	81 (11.89)	−2.18 (−7.50 to 3.11)	.26
CPIS-confirmed pneumonia[f]	45 (6.60)	43 (6.31)	−0.28 (−5.60 to 5.01)	.91
Any major infection[g]	78 (11.4)	74 (10.9)	−0.57 (−5.89 to 4.72)	.80

Abbreviations: CPIS, Clinical Pulmonary Infection Score; ICU, intensive care unit; PN, parenteral nutrition; UTI, urinary tract infection.

[a] Based on cultures obtained in the study ICU.

[b] Exact Pearson χ^2 test.

[c] Venous or arterial catheters.

[d] New or worsening infiltrates/consolidation plus positive respiratory tract culture of likely pathogen sampled on the day of, day before, or day after onset of new or worsening infiltrates/consolidation.

[e] Clinical Pulmonary Infection Score ≥6 plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic lavage fluid or brush catheter specimen), or the presence of a negative lower respiratory tract culture if collected within 72 hours after starting a new antibiotic regimen.[18]

[f] Clinical Pulmonary Infection Score ≥6 (using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable etiologic agent from (1) an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate); (2) the recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (eg, *Mycobacterium tuberculosis*, *Legionella* species, influenza virus, or *Pneumocystis jiroveci [carinii]*); (3) recovery of a likely/possible respiratory pathogen in cultures of a lower respiratory tract sample (endotracheal aspirate, bronchoalveolar lavage, or protected specimen brush); or (4) positive serology.[18]

[g] Attributable excess case mortality >15%.[19]

tended target population,[6] the lack of mortality effect cannot be attributed to unsuccessful implementation of the study intervention.

It is accepted that meta-analyses of small trials often overestimate treatment effects obtained from subsequent large-scale clinical trials.[24] The most unbiased estimate of treatment effect, obtained from the covariate-adjusted model, suggests early parenteral nutrition may have zero effect on mortality. Use of early parenteral nutrition also had no significant effects on infection rates.

Infections

The Early PN Trial provides reliable and precise estimates of infection rates, including catheter-related infections.[5] Previous clinical trials each used different definitions of infections, with some trials reporting only the total number of positive cultures by study group.[6] The Early PN Trial used robust definitions of infections appropriate for a critically ill population,[18] with subjective information (chest x-ray interpretation) obtained from blinded sources.[29] Furthermore, the clinical importance of each infection was graded according to site and organism, with infections having an attributable excess case mortality greater than 15% pooled for analysis as major infections.[19] Despite extensive reporting and analysis, there were no differences in any type of infection between groups.

Body Composition

Previous studies have shown critically ill patients lose 15.5% of their total body protein over the first 3 weeks of their ICU stay, with the majority of total body protein loss coming from skeletal muscle early during the ICU stay (up to 1.2% per day).[30]

We found early administration of parenteral nutrition may be protective against both muscle wasting and fat loss, with significant early benefits appearing to persist over the patient's entire ICU stay. Although preservation of muscle mass might be expected to translate into improved recovery of physical function, measures of physical function obtained 60 days after enrollment did not differ between groups. It is possible the RAND-36 is not sensitive to differences in early recovery, and we strongly recommend longer-term follow-up in future trials in this field.[31] However, liberation from invasive mechanical ventilation may reflect early differences in recovery attributable to maintenance of muscle mass.

Diaphragmatic function is a major determinant of the ability to successfully wean from invasive mechanical ventilation.[32] It is well known that mechanical ventilation itself has adverse effects on the structure and function of the diaphragm, with biopsies demonstrating marked atrophy of myofibers after only 18 hours of mechanical ventilation,[33] characterized by increased catabolic activity.[34] Furthermore, the specific catabolic changes observed in the diaphragm are known to be downregulated by amino acids.[35] It is possible that the overall preservation of muscle mass attributable to early parenteral nutrition resulted in some degree of preservation of diaphragmatic structure and function, leading to improved respiratory mechanics at time of weaning.[36] We strongly recommend future studies investigate the veracity of this mechanistic hypothesis.

Limitations and Strengths

Objective and repeatable eligibility criteria were developed to identify patients with short-term relative contraindications to enteral nutrition within the first 24 hours of ICU admission. It was anticipated this trial would recruit a large proportion of critically ill patients who had multiple surgical procedures scheduled within the first 2 days of ICU admission and patients who were ordered by surgeons not to take oral food or fluids for 48 hours after major surgery. In both types of patients, initial short-term relative contraindications to early enteral nutrition could resolve over time, and under usual care conditions, it would be appropriate to commence enteral nutrition. Indeed, the finding that approximately 40% of

patients in both groups eventually received delayed enteral nutrition suggests our pragmatic approach to standard care resulted in a comparison group that reflects real-world usual-care conditions: as appropriate, some standard care patients received delayed enteral nutrition, others received delayed parenteral nutrition, and some never received enteral or parenteral nutrition during their entire ICU stay.

The Early PN Trial differs from the other major trial in this field with regards to 2 key factors: the patient population targeted and the intervention studied. Whereas EPaNIC targeted critically ill patients regardless of adequacy of planned enteral intake,[6] the Early PN Trial maintained a strict focus on a narrow subset of patients unlikely to receive any early enteral nutrition. Furthermore, it is important to understand that complete nutrition therapy did not commence in either group of the EPaNIC trial until ICU day 3, while the Early PN Trial commenced early parenteral nutrition on the first day of ICU care, relative to a standard care group commencing nutrition therapy on day 3 or later. Although the results of the Early PN Trial apply to a much narrower subset of patients than EPaNIC, the Early PN Trial does address an important question in this narrow subset concerning the timing of the provision of nutrition therapy: if my patient cannot receive early enteral nutrition, should I start feeding my patient immediately with parenteral nutrition?

The Early PN Trial was terminated when 100 patients short of its target of 1470 patients. The decision to terminate was based on financial considerations due to slower-than-expected recruitment and was made without knowledge of treatment effects.[37] Because the 95% CIs for both the crude and covariate-adjusted estimates of treatment effect rule out the presence of a 7.7% RD mortality effect, we conclude it is unlikely that a loss of post hoc power due to early termination, or a lower-than-expected baseline mortality rate, explains our negative findings.[38]

Many aspects of trial conduct were not blinded (study intervention, outcome assessment), so it is possible that preexisting biases influenced concomitant treatment decisions and outcome ascertainment; however, a large body of literature expresses both positive[6,9] and negative[3,10] views on parenteral nutrition use. Based on numerous visits to, and discussions with, clinicians at all 31 study sites, we believe participating clinicians represented a broad spectrum of all possible views and opinions with no evidence of overall net positive or negative personal views on parenteral nutrition use.

A prespecified regression algorithm identified age, gender, BMI, APACHE II score, chronic liver disease, chronic lung disease, and source of ICU admission as potential confounders for inclusion in a covariate-adjusted mortality model. However, we do not recommend this subset of variables for use in prespecified covariate-adjusted models in future studies. There is small likelihood that this subset will completely capture confounding in future studies, and each individual study is likely to require adjustment with a unique subset of alternate confounders.

The major strengths of this trial lie in its rigorous design and conduct. A meaningful difference in nutrition therapy was achieved between groups, with minimal treatment crossovers and minimal loss to follow-up. Conduct at 31 sites throughout 2 countries enhances generalizability to similar health care settings.

CONCLUSIONS

The use of early parenteral nutrition did not result in significant differences in day-60 mortality or infection rates. Early parenteral nutrition resulted in a significant reduction in days of invasive mechanical ventilation, but this did not result in a significant shortening of ICU or hospital length of stay. No harm was associated with the use of early parenteral nutrition in this trial.

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