Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2)

Jean Reignier, Julie Boisramé-Helms, Laurent Brisard, Jean-Baptiste Lascarrou, Ali Ait Hssain, Nadia Anguel, Laurent Argaud, Karim Asehnoune, Pierre Asfar, Frédéric Bellec, Vlad Botoc, Anne Bretagnol, Hoang-Nam Bui, Emmanuel Canet, Daniel Da Silva, Michael Darmon, Vincent Das, Jérôme Devaquet, Michel Djibre, Frédérique Ganster, Maité Garrouste-Orgeas, Stéphane Gaudry, Olivier Gontier, Claude Guérin, Bertrand Guidet, Christophe Guitton, Jean-Etienne Herbrecht, Jean-Claude Lacherade, Philippe Letocart, Frédéric Martino, Virginie Maxime, Emmanuelle Mercier, Jean-Paul Mira, Saad Nseir, Gael Piton, Jean-Pierre Quenot, Jack Richecoeur, Jean-Philippe Rigaud, René Robert, Nathalie Rolin, Carole Schwebel, Michel Sirodot, François Tinturier, Didier Thévenin, Bruno Giraudeau, Amélie Le Gouge, for the NUTRIREA-2 Trial Investigators and the Clinical Research in Intensive Care and Sepsis (CRICS) group

Summary

Background Whether the route of early feeding affects outcomes of patients with severe critical illnesses is controversial. We hypothesised that outcomes were better with early first-line enteral nutrition than with early first-line parenteral nutrition.

Methods In this randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2 trial) done at 44 French intensive-care units (ICUs), adults (18 years or older) receiving invasive mechanical ventilation and vasopressor support for shock were randomly assigned (1:1) to either parenteral nutrition or enteral nutrition, both targeting normocaloric goals (20–25 kcal/kg per day), within 24 h after intubation. Randomisation was stratified by centre using permutation blocks of variable sizes. Given that route of nutrition cannot be masked, blinding of the physicians and nurses was not feasible. Patients receiving parenteral nutrition could be switched to enteral nutrition after at least 72 h in the event of shock resolution (no vasopressor support for 24 consecutive hours and arterial lactate <2 mmol/L). The primary endpoint was mortality on day 28 after randomisation in the intention-to-treat-population. This study is registered with ClinicalTrials.gov, number NCT01802099.

Findings After the second interim analysis, the independent Data Safety and Monitoring Board deemed that completing patient enrolment was unlikely to significantly change the results of the trial and recommended stopping patient recruitment. Between March 22, 2013, and June 30, 2015, 2410 patients were enrolled and randomly assigned; 1202 to the enteral group and 1208 to the parenteral group. By day 28, 443 (37%) of 1202 patients in the enteral group and 422 (35%) of 1208 patients in the parenteral group had died (absolute difference estimate 2·0%; [95% CI –1·9 to 5·8]; p=0·33). Cumulative incidence of patients with ICU-acquired infections did not differ between the enteral group (173 [14%]) and the parenteral group (194 [16%]; hazard ratio [HR] 0·89 [95% CI 0·72–1·09]; p=0·25). Compared with the parenteral group, the enteral group had higher cumulative incidences of patients with vomiting (406 [34%] vs 246 [20%]; HR 1·89 [1·62–2·20]; p<0·0001), diarrhoea (432 [36%] vs 393 [33%]; 1·20 [1·05–1·37]; p=0·009), bowel ischaemia (19 [2%] vs five [<1%]; 3·84 [1·43–10·3]; p=0·007), and acute colonic pseudo-obstruction (11 [1%] vs three [<1%]; 3·7 [1·03–13·2; p=0·04).

Interpretation In critically ill adults with shock, early isocaloric enteral nutrition did not reduce mortality or the risk of secondary infections but was associated with a greater risk of digestive complications compared with early isocaloric parenteral nutrition.

Funding La Roche-sur-Yon Departmental Hospital and French Ministry of Health.

Introduction

Acute critical illness requiring mechanical ventilation carries a risk of severe malnutrition, whose adverse effects include infections, muscle wasting, delayed recovery, and increased mortality.[1] Nutritional support is therefore crucial. Guidelines recommend early enteral feeding supplying 20–25 kcal/kg per day during the acute phase of critical illness,[2,3] but rest on a low level of evidence. Whether timing, route, or dose of nutritional support affects the outcomes of critically ill patients remains unclear.[4]

Compared with parenteral nutrition, enteral nutrition was associated with improvements in gastrointestinal mucosa integrity, immune function, and tissue repair responses, which translated into decreases in nosocomial infections, hospital and intensive-care unit (ICU) stay lengths, and health-care costs.[5–11] Early initiation of enteral nutrition (within 24–48 h after ICU admission) might enhance these beneficial effects and decrease mortality rates,[3,12–15] but has been reported to induce gastrointestinal intolerance with vomiting in

France (Prof P Asfar MD);
Laboratoire de Biologie
Neurovasculaire et
Mitochondriale Intégrée, CNRS
UMR 6214 - INSERM U1083,
Université Angers, UBL,
Angers, France (Prof P Asfar);
Medical-Surgical Intensive Care
Unit, Centre Hospitalier de
Montauban, Montauban,
France (F Bellec MD); Medical-
Surgical Intensive Care Unit,
Centre Hospitalier de
Saint-Malo, Saint-Malo, France
(V Botoc MD); Medical Intensive
Care Unit, CHR Orléans,
Orléans, France
(A Bretagnol MD); Medical
Intensive Care Unit, Hôpital
Pellegrin, CHU Bordeaux,
Bordeaux, France (H-N Bui MD);
Medical Intensive Care Unit,
Saint Louis University Hospital,
Assistance Publique-Hôpitaux
de Paris (AP-HP), Paris, France
(E Canet MD); Medical-Surgical
Intensive Care Unit, Centre
Hospitalier de Saint-Denis,
Saint-Denis, France
(D Da Silva MD); Medical-
Surgical Intensive Care Unit,
University Hospital,
Saint Etienne, France
(Prof M Darmon MD); Medical-
Surgical Intensive Care Unit,
Centre Hospitalier
Intercommunal André
Grégoire, Montreuil, France
(V Das MD); Medical-Surgical
Intensive Care Unit, Hôpital
Foch, Suresnes, France
(J Devaquet MD); Medical-
Surgical Intensive Care Unit,
Tenon University Hospital,
Assistance Publique-Hôpitaux
de Paris (AP-HP), Paris, France
(M Djibre MD); Medical
Intensive Care Unit, Hôpital
Emile Muller, Mulhouse, France
(F Ganster MD); UMR 1137,
IAME Team 5, Decision Sciences
in Infectious Diseases (DeSCID),
Control and Care, Sorbonne
Paris Cité, Inserm-Paris Diderot
University, Paris, France
(M Garrouste-Orgeas MD);
Medical-Surgical Unit, Hôpital
Saint-Joseph, Paris France
(M Garrouste-Orgeas MD);
Medical Unit and Palliative
Research Group, French and
British Institute, Levallois-
Perret, France; OUTCOMEREA
Research Group, Drancy, France
(M Garrouste-Orgeas MD);
Medical-Surgical Intensive Care
Unit, Hôpital Louis Mourier,
Assistance Publique-Hôpitaux
de Paris (AP-HP), Colombes,
France (S Gaudry MD);
Université Paris Diderot,

Research in context

Evidence before this study

We searched PubMed without date or language restrictions for studies assessing enteral and parenteral nutritional support in critically ill patients. We also screened the reference lists in published guidelines, meta-analyses, and reviews. At the time our trial was designed, published studies including meta-analyses indicated reduced infectious complications and improved prognosis with enteral feeding compared to parenteral feeding. Observational studies suggested that factors associated with greater benefits from enteral nutrition might have worse critical illness severity and earlier compared with delayed enteral feeding. Recently, during the course of the NUTRIREA-2 study, the multicentre randomised CALORIES trial in an unselected population of critically ill patients was published. The results showed no differences in outcome or infectious complications between early enteral and early parenteral nutrition. A meta-analysis including the CALORIES trial and previous published studies found no difference in mortality; although early enteral nutrition was associated with shorter intensive-care unit (ICU) stay lengths and fewer infectious complications compared with early parenteral nutrition, subgroup analyses suggested that these effects might be limited to trials in which the energy intake was lower with enteral than with parenteral nutrition. The most recently published guidelines recommend early enteral feeding, at the early stage of critical illness. Thus, whether the route of early feeding influences outcomes of patients with severe critically illnesses remains controversial.

Added value of this study

The NUTRIREA-2 study is the second, large, randomised, controlled trial assessing the effect of the route of nutritional support in critically ill adults without contraindications to enteral or parenteral nutrition. By contrast with the CALORIES trial, NUTRIREA-2 focused on patients treated with invasive

mechanical ventilation and vasopressor support for shock, because previous studies suggested that mechanically ventilated patients in ICU with haemodynamic instability might have better survival when early nutrition is given enterally rather than parenterally. In the NUTRIREA-2 trial, nutrition delivery was adapted according to a predetermined definition of the acute phase of critical illness. Furthermore, nutritional intakes were far closer to targets than in the CALORIES trial. The groups given early normocaloric enteral versus parenteral nutrition showed no significant differences in day 28 mortality; frequency of infectious complications; organ failure severity or duration; life support duration; ICU and hospital stay lengths; and ICU, hospital, or day 90 mortality. Compared with the parenteral route, the enteral route was associated with slightly lower calorie and protein intakes and with higher frequencies of hypoglycaemia. Proportions of patients with bowel ischaemia and colonic pseudo-obstruction were higher in the enteral group than in the parenteral group.

Implications of all the available evidence

The findings of NUTRIREA-2 are to some extent consistent with those of the CALORIES trial but not with those of meta-analyses suggesting benefits from the enteral route compared with the parenteral route. However, whereas the CALORIES trial also showed no outcome differences between feeding routes, NUTRIREA-2 raises concern about a rare but major complication of enteral feeding in patients with severe critical illness. Our data do not support a preference for early enteral compared with parenteral nutrition during the acute phase of critical illness in patients who have no contraindications to enteral or parenteral nutrition and who are receiving mechanical ventilation and vasopressor support for shock. Furthermore, our data suggest potential harmful effects on the gut of enteral nutrition with a normocaloric target.

30–70% of ICU patients, raising concerns about ventilator-associated pneumonia and undernutrition.[16–20] Enteral nutrition was also associated with gut ischaemia in critically ill patients with shock.[21–24] Thus, whether enteral feeding has protective or deleterious effects on the gut remains controversial.[21,25] Meta-analyses provided conflicting results on the effect of feeding route on patient outcomes but included studies with hetero-geneous designs, sample sizes, and illness severity.[26,27] Guidelines recommend postponing enteral nutrition in patients with shock until full resuscitation with haemodynamic stability is achieved.[2,3] Nevertheless, numerous studies suggest that mechanically ventilated ICU patients with haemodynamic instability might have better survival when early nutrition is given enterally rather than parenterally.[12,14,23,24,28–32]

We aimed to investigate whether early first-line enteral nutrition had beneficial clinical effects compared with early first-line parenteral nutrition, both targeting

normocaloric goals, in patients requiring invasive mechanical ventilation and vasopressor support for shock.

Methods

Study design and participants

The NUTRIREA-2 trial was a randomised, controlled, multicentre, open-label, parallel-group study done in 44 French ICUs, including 28 (64%) in university hospitals.[33]

Adults (18 years or older) admitted to any of the participating ICUs were eligible if they were expected to require more than 48 h of invasive mechanical ventilation, concomitantly with vasoactive therapy (adrenaline, dobutamine, or noradrenaline) via a central venous catheter for shock and to be started on nutritional support within 24 h after endotracheal intubation (or within 24 h after ICU admission if intubation occurred before ICU admission). Exclusion criteria were invasive mechanical ventilation started more than 24 h earlier; surgery on the

gastrointestinal tract within the past month; history of gastrectomy, oesophagectomy, duodeno-pancreatectomy, bypass surgery, gastric banding, or short bowel syndrome; gastrostomy or jejunostomy; specific nutritional needs, such as pre-existing long-term home enteral or parenteral nutrition; active gastrointestinal bleeding; treatment-limitation decisions; adult under legal guardianship; pregnancy; breastfeeding; current inclusion in a randomised trial designed to compare enteral nutrition to parenteral nutrition; contraindication to parenteral nutrition (known hypersensitivity to egg or soybean proteins or to another component, inborn error in aminoacid metabolism, or severe familial dyslipidaemia affecting triglyceride levels).

The study protocol was approved by the ethics committee of the French Intensive Care Society and appropriate French authorities (Comité de Protection des Personnes de Poitiers). According to French law, because the treatments and strategies used in the study were classified as standard care, there was no requirement for signed consent, but the patients or next of kin were informed about the study before enrolment and confirmed this fact in writing. In compliance with French law, the electronic case-record form and database organisation were approved by the appropriate committees. The study protocol has been published[33] (appendix).

Randomisation and masking

All patients treated with invasive mechanical ventilation and vasopressor support for shock within 24 h after ICU admission were screened for eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a week. Using a secure, computer-generated, interactive, web-response system available at each study centre, consecutive eligible patients were randomly assigned (1:1) to one of the two treatment groups (early enteral or parenteral nutrition). Randomisation was stratified by centre using permutation blocks of variable sizes. Investigators had no access to the randomisation list and were not aware of the size of the randomisation blocks. Given that route of nutrition cannot be masked, blinding of the physicians and nurses was not feasible.

The electronic case-record form was a secure, interactive, web-response system available at each study centre, provided and managed by the biometrical unit of the Tours University Hospital (CIC INSERM 1415, Tours, France), which was not involved in patient recruitment.

Procedures

All participating ICU staff members attended training in the study procedures and protocols for providing nutritional support and managing intolerance to enteral nutrition (appendix p 7).[33]

In the parenteral group, all patients received only parenteral nutrition via a central venous catheter for at least 72 h after randomisation. Subsequently, the route used until day 8 depended on the results of daily haemodynamic assessments. When the patient met predefined criteria for haemodynamic stability (no vasopressor support for 24 consecutive hours and arterial blood lactate concentration less than 2 mmol/L), parenteral nutrition was stopped and immediately replaced by enteral nutrition at the flow rate needed to achieve the predefined calorie target. Otherwise, parenteral nutrition was continued for a total of 7 days. On day 8, in the absence of contraindications, the patient was switched to enteral nutrition regardless of haemodynamic status.

In the enteral group, patients received first-line enteral nutrition. In the event of persistent gastrointestinal intolerance precluding achievement of the predefined calorie targets, supplemental parenteral nutrition could be added on day 8 at the earliest.[3,34] Gastric residual volumes were not monitored and minor regurgitation was not considered a reason to stop feeding. Isosmotic, isocaloric, normal-protein, polymeric preparations were used during the first week, after which the choice of the preparation was at the discretion of the bedside physician.

In both groups, nutritional support was started as soon as possible after randomisation and no later than 24 h after intubation (or after ICU admission in patients intubated before ICU admission). Nutritional support was prescribed as flow rate (in mL per h) and started at the flow rate required to achieve the calorie target on day 1. The recommended daily calorie target in kcal/kg of actual bodyweight was 20–25 during the first 7 days then 25–30 from day 8 to extubation. From day 8, supplemental parenteral nutrition could be added in patients with persistent intolerance to enteral nutrition precluding achievement of the predefined calorie target. Patients who were reintubated within 7 days after trial inclusion were managed until day 8 according to the group they were randomised to during the first intubation period. Patients reintubated after day 7 received enteral nutrition if they had no contraindications. Additional water, electrolytes, intravenous vitamins, and trace elements were given as needed, as assessed by the bedside physician, using standard preparations and protocols available in each study ICU.

Outcomes

The primary outcome was day 28 all-cause mortality. Secondary outcomes were the Sequential Organ Failure Assessment (SOFA) score;[35] bodyweight; amounts of calories and proteins delivered; vomiting; prokinetic drugs; stool; blood glucose; insulin treatment; blood concentrations of lactate, bilirubin, alanine aminotransferase, and aspartate aminotransferase; antiulcer prophylaxis; anti-infectious treatments; prone position; dialysis during the intervention period; day 90 mortality; ICU mortality; hospital mortality; ICU stay length; acute-care hospital stay length; days without life-support; ICU-acquired infections; and non-infectious complications.

Baseline characteristics were recorded at inclusion. The Simplified Acute Physiology Score (SAPS II) was

ECEVE, UMR 1123, Sorbonne Paris Cité, Paris, France (S Gaudry); **Medical-Surgical Intensive Care Unit, Hôpital de Chartres, Chartres, France** (O Gontier MD); **Medical Intensive Care Unit, Groupement Hospitalier Nord, Hospices Civils de Lyon, Lyon, France** (Prof C Guérin MD); **Université de Lyon, IMRB INSERM 955, Lyon, France** (Prof C Guérin); **Medical Intensive Care Unit, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France** (Prof B Guidet MD); **Sorbonne Université, UPMC Université Paris 06, INSERM, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe: Epidémiologie Hospitalière Qualité et Organisation des Soins, Paris, France** (Prof B Guidet); **Medical-Surgical Intensive Care Unit, Hôpital du Mans, Le Mans, France** (C Guitton MD); **Medical Intensive Care Unit, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, Strasbourg, France** (J-E Herbrecht MD); **Faculté de Médecine U1121, Université de Strasbourg, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Strasbourg, France** (J-E Herbrecht); **Médecine Intensive Réanimation, Centre Hospitalier Départemental de la Vendée, La Roche sur Yon, France** (J-C Lacherade MD); **Medical-Surgical Intensive Care Unit, Hôpital Jacques Puel, Rodez, France** (P Letocart MD); **Medical-Surgical Intensive Care Unit, CHU de Pointe-à-Pitre, Pointe-à-Pitre, France** (F Martino MD); **Medical-Surgical Intensive Care Unit, Hôpital Raymond Poincaré, Assistance Publique-Hôpitaux de Paris (AP-HP), Garches, France** (V Maxime MD); **Médecine Intensive Réanimation, Hôpital Bretonneau, CHU Tours, Tours, France** (E Mercier MD); **Medical Intensive Care Unit, Cochin University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France** (Prof J-P Mira MD); **Medical Intensive Care Unit, CHU Lille, Lille, France** (Prof S Nseir MD); **Université Lille, Medicine School, Lille, France** (Prof S Nseir); **Medical Intensive**
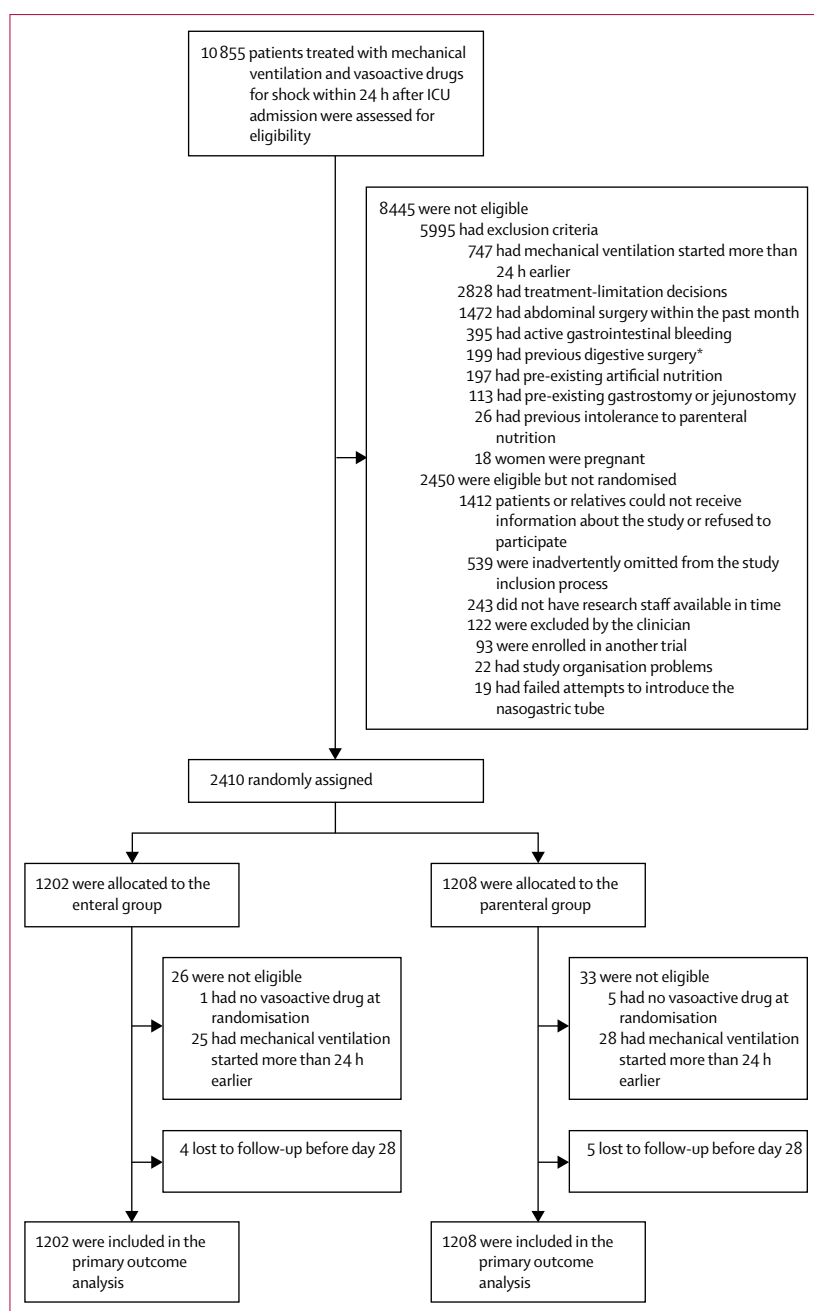
Figure 1: Trial profile
ICU=intensive-care unit. *Gastrectomy, oesophagectomy, duodeno-pancreatectomy, bypass surgery, gastric banding, or short bowel syndrome.

complications were diagnosed according to predefined criteria.[33] Bowel ischaemia was defined as any of the following: absent blood flow in one of the main arteries supplying the bowel (superior mesenteric artery, inferior mesenteric artery, or cOeliac artery) with evidence of bowel wall compromise on an imaging study (CT angiography, angiography, or magnetic resonance angiography), presence of endoscopy criteria for colonic ischaemia according to the Favier classification system (stage I, petechiae; stage II, petechiae and superficial ulcers; and stage III, necrotic ulcers and polypoid lesions); and evidence of bowel ischaemia during surgery. Ventilator-associated pneumonia diagnoses were adjudicated by an independent blinded committee, based on all available clinical, radiological, and bacteriological data. All the study data were stored in a logged database that was closed on Jan 12, 2016, after the site investigators had responded to all the queries made by the database managers.

Statistical analysis

Two interim analyses were scheduled, after enrolment of 1000 and 2000 patients, respectively. The independent Data Safety and Monitoring Board was composed of two physicians and one biostatistician not otherwise involved in the trial, who had access, for both interim analyses, to unblinded results on day 28 mortality, variations in SOFA score from day 1 to day 7, blood bilirubin values, and proportions of patients with ICU-acquired infections. According to French laws on studies of standard care, the protocol prespecified that enrolment would continue during the interim analyses. The interim analysis results were not disclosed to the investigators, who were told only whether the study would be stopped or continued.

To estimate the sample size, we used mortality rates found in our NUTRIREA-1 randomised trial.[37] Assuming a 37% day 28 mortality rate in the parenteral group and a 5% decrease in mortality in the enteral group, with a 4·9% two-sided type I error rate and 80% power, 2854 patients were required. According to Peto's method, a 4·9% two-sided type I error rate was used because of the two planned interim analyses.[38] The p value cutoff selected to guide recommendations for early study termination after interim analyses was less than 0·001. No specific futility analysis was planned.

All statistical analyses followed a prespecified statistical analysis plan, with the intention-to-treat approach. p values of 0·049 or less were taken as indicating a significant difference in the primary outcome because of the two planned interim analyses and values of 0·05 or less as indicating statistical significance for the secondary outcomes. Categorical variables were summarised as frequencies and percentages and continuous variables as medians (IQRs) or means (SD). No statistical test was done to compare baseline characteristics between groups. The day 28 mortality rate (primary outcome) was reported as the point estimate in each group with the 95% CI and compared using the χ^2 test. For missing

Care Unit, CHRU Besançon, Besançon, France (G Piton MD); EA3920, Université de Franche Comté, Besançon, France (G Piton); Medical-Surgical Intensive Care Unit, François Mitterrand University Hospital, Dijon, France (Prof J-P Quenot MD); Lipness

computed 24 h after ICU admission.[36] After the initiation of nutritional support via the route allocated at random, nutritional data, treatments, nosocomial infections, abdominal complications, laboratory data, and invasive devices were recorded daily until hospital discharge or day 90, whichever occurred first. Vital status was recorded at ICU discharge, at hospital discharge, on day 28, and on day 90. Gastrointestinal complications and infection

	Enteral group (n=1202)	Parenteral group (n=1208)
Age (years)	66 (14)	66 (14)
Sex		
Men	809 (67%)	815 (67%)
Women	393 (33%)	393 (33%)
McCabe score		
(0) No fatal underlying disease	741 (62%)	750 (62%)
(1) Death expected within 5 years	402 (33%)	394 (33%)
(2) Death expected within 1 year	57 (5%)	62 (5%)
Pre-existing illness at ICU admission	869 (72%)	880 (73%)
Chronic renal failure	161 (13%)	161 (13%)
Liver disease	94 (8%)	112 (9%)
Cardiovascular disease	276 (23%)	274 (23%)
Chronic respiratory failure	184 (15%)	169 (14%)
Neurological disease	160 (13%)	159 (13%)
Cancer or immune deficiency	346 (29%)	352 (29%)
Oesophageal, gastric, or duodenal ulcer	77 (6%)	75 (6%)
Diabetes	298 (25%)	338 (28%)
Weight (kg)	79·4 (20·5)	79·2 (20·3)
BMI (kg/m²)	28·0 (7·2)	27·7 (6·8)
SAPS II	59 (19)	61 (20)
SOFA at baseline	11 (3)	11 (3)
Medical diagnosis at admission	1104 (92%)	1127 (93%)
Acute illness at ICU admission		
Cardiac arrest	121 (10%)	137 (11%)
Acute heart failure	259 (22%)	228 (19%)
Acute CNS failure	94 (8%)	91 (8%)
Acute respiratory failure	589 (49%)	613 (51%)
Trauma	27 (2%)	25 (2%)
Miscellaneous	110 (9%)	112 (9%)
Cause of shock		
Cardiac	229 (19%)	227 (19%)
Sepsis	728 (61%)	776 (64%)
Other	243 (20%)	203 (17%)
	(Table 1 continues in next column)	

	Enteral group (n=1202)	Parenteral group (n=1208)
(Continued from previous column)		
Ongoing treatments		
Prone position	44 (4%)	59 (5%)
Sedative drugs	1038 (86%)	1036 (86%)
NMB drugs	351 (29%)	357 (30%)
Insulin	469 (39%)	482 (40%)
Antiulcer medication	485 (40%)	531 (44%)
Prokinetic drugs*	27 (2%)	15 (1%)
Anti-infectious treatment	1012 (84%)	1000 (83%)
Dialysis	189 (16%)	183 (15%)
Vasopressor support		
Norepinephrine alone	978 (81%)	973 (81%)
Epinephrine alone	43 (4%)	48 (4%)
Dobutamine alone	28 (2%)	37 (3%)
At least two drugs	144 (12%)	138 (11%)
Norepinephrine dose (μg/kg per min)	0·56 (0·30–1·20)	0·50 (0·25–1·03)
FiO₂	55 (23)	55 (23)
PEEP (cmH₂O)	7 (3)	7 (3)
Glucose (mmol/L)	10·2 (5·5)	11·0 (8·2)
Serum creatinine (μmol/L)	189·4 (168·2)	190·4 (156·9)
Lactate (mEq/L)	3·8 (3·5)	3·9 (3·5)
C reactive protein (mg/dL)	170·3 (138·3)	159·2 (130·6)
Serum albumin (g/L)	25·5 (7·0)	25·8 (6·8)
Time from intubation to randomisation (h)	15 (7–20)	15 (7–21)

Data are n (%), mean (SD), or median (IQR). SAPS II scores can range from 0 (lowest level of critical illness) to 163 (most severe level of critical illness with 100% predicted mortality). A score of 50 predicts a 46·1% risk of death. SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multiorgan failure). Subscores of the SOFA score at ICU admission are detailed in the appendix (p 13). Demographic characteristics were recorded at study inclusion. SAPS II was calculated 24 h after ICU admission. Anti-infectious treatments included antibiotics, antiviral agents, and antifungal agents. Anti-ulcer treatments included proton-pump inhibitors and histamine 2 receptor antagonists. Prokinetic drugs were metoclopramide and erythromycin. SI conversion factors: to convert glucose values to mg/dL, multiply by 18·02; to convert creatinine values to mg/dL, multiply by 0·113. ICU=intensive-care unit. BMI=body-mass index. SAPS II=Simplified Acute Physiologic Score.[36] SOFA score=Sequential Organ Failure Assessment score.[35] NMB=neuromuscular blockade. FiO₂=inspired fraction of oxygen. PEEP=positive end-expiratory pressure.

Table 1: Baseline characteristics of the participants

data, single imputation was done by assuming that patients with missing data had died. A sensitivity analysis was performed on patients without missing data. A post-hoc sensitivity analysis to look for a centre effect was also performed using mixed effects logistic regression with centre as a random effect. Secondary outcomes expressed as proportions were compared between the two groups using the χ² test. Outcomes reported as cumulative incidences were analysed using the competing risk approach, with death, ICU discharge, or hospital discharge as the competing risks. Changes over time were compared between the two groups using a mixed linear model, after data transformation if necessary. Continuous data were analysed using Student's *t* test or Wilcoxon's non-parametric test, as appropriate.

Data were analysed with SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.3.1 were used for the statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT01802099.

Role of the funding source

The funders of the study had no role in the study design; data collection, analysis, or interpretation; writing of the report; or decision to submit for publication. The

Team, INSERM UMR 866 and LabExLipSTIC, Université de Bourgogne, Dijon, France (Prof J-P Quenot); **Medical-Surgical Intensive Care Unit, Hôpital de Beauvais, Beauvais, France** (J Richecoeur MD); **Medical-Surgical Intensive Care Unit, Hôpital de Dieppe, Dieppe, France** (J-P Rigaud MD); **Medical Intensive Care Unit, CHU Poitiers, Poitiers, France** (Prof R Robert MD); **Université de Poitiers, INSERM CIC1402, Poitiers, France** (Prof R Robert); **Medical-Surgical Intensive Care Unit, Centre Hospitalier de Melun, Melun, France** (N Rolin MD); **Medical Intensive Care Unit, CHU Albert Michallon Grenoble, Grenoble, France** (Prof C Schwebel MD); **Inserm U1039, Radiopharmaceutiques Bioclinques, Université Grenoble Alpes, La Tronche, France** (Prof C Schwebel); **Medical-Surgical Intensive Care Unit, Centre Hospitalier Annecy-Genevois, Metz-Tessy, Pringy, France** (M Sirodot MD); **Surgical Intensive Care Unit, CHU Amiens Picardie, Amiens, France** (F Tinturier MD); **Medical-Surgical Intensive Care Unit, Centre Hospitalier Docteur Schaffner, Lens, France** (D Thévenin MD); **Inserm CIC 1415, Tours, France; Université de Tours, Tours, France; CHU Tours, Tours, France** (B Giraudeau PhD, A Le Gouge MSc); **and Université François-Rabelais de Tours, PRES Centre-Val de Loire Université, Tours, France** (B Giraudeau)

Correspondence to:
Prof Jean Reignier, Service de Médecine Intensive-Réanimation, Centre Hospitalier Universitaire Hôtel-Dieu, 44093 Nantes cedex 1, France
jean.reignier@chu-nantes.fr

See **Online** for appendix

For **R software** see http://www.r-project.org

	Enteral group (n=1202)	Parenteral group (n=1208)	Hazard ratio (95% CI)	p value
Days with parenteral nutrition	0·0 (0·0–0·0)	4·0 (3·0–6·0)	..	<0·0001
Days with enteral nutrition	6·0 (3·0–8·0)	1·0 (0·0–3·0)	..	<0·0001
Total calories received (kcal/kg)*	113·5 (61·2)	125·7 (61·9)	..	<0·0001
Daily calorie intake (kcal/kg per 24 h)	17·8 (5·5)	19·6 (5·3)	..	<0·0001
Total protein intake (g/kg)	4·1 (2·3)	5·1 (2·5)	..	<0·0001
Daily protein intake (g/kg/d)	0·7 (0·2)	0·8 (0·2)	..	<0·0001
Patients with vomiting*	333 (28%)	158 (13%)	2·37 (1·97–2·84)	<0·0001
Patients receiving prokinetic drugs*	352 (29%)	130 (11%)	3·13 (2·57–3·79)	<0·0001
Absence of stool†	154 (13%)	273 (23%)	..	<0·0001
Blood glucose concentration (mmol/L)				
Daily highest	11·7 (9·4–14·4)	11·7 (9·5–15·1)	..	0·20
Daily lowest	6·2 (5·1–7·5)	6·4 (5·2–7·6)	..	0·01
Patients receiving insulin*	954 (79%)	995 (82%)	0·93 (0·87–0·98)	0·009
Patients with hypoglycaemia*‡	29 (2%)	13 (1%)	2·26 (1·18–4·33)	0·01
Maximum blood lactate level during intervention period (mEq/L)				
Daily highest	3·0 (2·0–5·7)	3·0 (1·9–5·4)	..	0·28
Patients with normalisation of the blood lactate concentration*§	743 (62%)	797 (66%)	0·91 (0·83–0·99)	0·03
Blood bilirubin concentration (μmol/L)				
Daily highest	16·0 (9·0–31·0)	17·0 (9·0–36·0)	..	0·26
Blood alanine aminotransferase concentration (IU/L)				
Daily highest	66 (33–171)	71 (34–185)	..	0·39
Blood aspartate aminotransferase concentration (IU/L)				
Daily highest	37 (23–69)	38·0 (23–69)	..	0·94
Patients receiving antiulcer prophylaxis*	809 (67%)	883 (73%)	0·90 [0·84–0·97]	0·005
Anti-infectious treatment*¶	1147 (95%)	1132 (94%)	1·03 (0·99–1·07)	0·07
Prone position*	161 (13%)	144 (12%)	1·12 (0·89–0·90)	0·30
Dialysis*	407 (34%)	419 (35%)	0·97 (0·86–1·10)	0·67

Data are median (IQR), mean (SD), or n (%), unless otherwise indicated. SI conversion factors: to convert glucose values to mg/dL, multiply by 18·02; to convert bilirubin value to mg/L, multiply by 0·58. Continuous data described as mean (SD) were compared using Student's t tests. Categorical data were reported as median (IQR) and compared by applying Wilcoxon's non-parametric test. Outcomes reported as cumulative incidences were analysed using a competing risk approach, with death and intensive-care unit (ICU) discharge as competing risks. Secondary outcomes expressed as percentages of patients with each outcome were compared between the two groups using the χ^2. The intervention period started with the initiation of nutritional support and ended after day 7 or at ICU discharge or death. *Calories in propofol and dextrose solutions were included in the total calorie count. †Absence of stool was defined as no passage of stools from randomisation to day 6 included. ‡Hypoglycaemia was defined as blood glucose concentration lower than 2·3 mmol/L. §Blood lactate concentration was considered normal when lower than 2 mmol/L. ¶Anti-infectious treatments included antiviral agents, anti-fungal agents, and antibiotics.

Table 2: Clinical management and outcome during the intervention period (day 0 through day 7)

corresponding author (JR), BG, and ALG had full access to all the study data. The corresponding author (JR) had final responsibility for the decision to submit for publication.

Results

After the second interim analysis, the independent Data Safety and Monitoring Board deemed that completing patient enrolment was unlikely to significantly change the results of the trial and recommended stopping patient recruitment. The interim analyses are available in the appendix. Between March 22, 2013, and June 30, 2015, 2410 patients were randomised; 1202 to the enteral group and 1208 to the parenteral group (figure 1; appendix p 13). No patients were withdrawn, and all randomised patients were included in the intention-to-treat analysis. Baseline characteristics were similar between groups (table 1; appendix p 14).

By day 28, 443 (37%) of 1202 patients in the enteral group and 422 (35%) of 1208 patients in the parenteral group had died (absolute difference estimate 2·0% [95% CI −1·9 to 5·8]; p=0·33). The results were similar after exclusion of the nine patients with missing data (absolute difference estimate 2·1% [95% CI −1·8 to 5·8; p=0·31) and after the sensitivity analysis to look for a centre effect (odds ratio 1·1 [95% CI 0·9 to 1·3]; p=0·33).

Secondary outcomes on nutritional support are detailed in tables 2 and 3, figure 2, and appendix p 15 and pp 8–9. Median time from intubation to initiation of nutritional support was 16·2 h (IQR 8·9–21·7) in the enteral group and 16·1 h (9·9–22·0) in the parenteral group. Little overlap occurred in feeding routes across groups: 46 (4%) patients in the parenteral group received enteral nutrition during the 72 h period after

	Enteral group (n=1202)	Parenteral group (n=1208)	Absolute difference estimate (95% CI)	Hazard ratio (95% CI)	p value
Primary outcome					
Day 28 mortality	443/1202 (37%)	422/1208 (35%)	2·0 (−1·9 to 5·8)	··	0·33
Secondary outcomes					
Day 90 mortality	530/1185 (45%)	507/1192 (43%)	2·2 (−1·8 to 6·2)	··	0·28
ICU mortality*	429 (33%)	405 (31%)	··	1·10 (0·96 to 1·26)	0·17
Hospital mortality*	498 (36%)	479 (34%)	··	1·08 (0·95 to 1·22)	0·25
ICU length of stay (days)	9·0 (5·0 to 16·0)	10·0 (5·0 to 17·0)	··	··	0·08
Acute-care hospital length of stay (days)	17·0 (8·0 to 32·0)	18·0 (9·0 to 33·0)	··	··	0·11
Days without vasopressor support*	20·0 (0·0 to 25·0)	21·0 (0·0 to 26·0)	··	··	0·10
Days without dialysis*	27·0 (0·0 to 28·0)	27·0 (0·0 to 28·0)	··	··	0·52
Days without mechanical ventilation*	11·0 (0·0 to 23·0)	12·0 (0·0 to 23·0)	··	··	0·54
Infections					
ICU-acquired infection*	173 (14%)	194 (16%)	··	0·89 (0·72 to 1·09)	0·25
Ventilator-associated pneumonia*	113 (9%)	118 (10%)	··	0·96 (0·74 to 1·24)	0·75
Bacteraemia*	38 (3%)	55 (5%)	··	0·69 (0·46 to 1·04)	0·08
CVC-related infection*	29 (2%)	27 (2%)	··	1·07 (0·64 to 1·81)	0·79
Urinary tract infection*	18 (2%)	16 (1%)	··	1·13 (0·58 to 2·21)	0·73
Soft-tissue infection					
Patients (n)	1/1202	6/1208	··	··	··
Other infection*	11 (1%)	21 (2%)	··	0·52 (0·25 to 1·09)	0·08
Gastrointestinal complications					
Vomiting*	406 (34%)	246 (24%)	··	1·89 (1·62 to 2·20)	<0·0001
Diarrhoea*	432 (36%)	393 (33%)	··	1·20 (1·05 to 1·37)	0·009
Bowel ischaemia*	19 (2%)	5 (<1%)	··	3·84 (1·43 to 10·3)	0·007
Acute colonic pseudo-obstruction*	11 (1%)	3 (<1%)	··	3·7 (1·03 to 13·2)	0·04

Data are n/N (%), cumulative incidence (%), and median (IQR). Continuous data described as mean (SD) were compared using Student's t tests and categorical data described as median (IQR) were using Wilcoxon's nonparametric test. Outcomes reported as cumulative incidences were analysed using a competing risk approach, with death and ICU discharge as competing risks; the only exceptions were ICU mortality and hospital mortality, for which competing risks were only ICU discharge and hospital discharge, respectively. ICU-acquired infections included ventilator-associated pneumonia, bacteraemia, urinary tract infections, catheter-related infections, and other infections. Outcomes expressed as percentages of patients with each outcome were compared between the two groups using χ^2 tests. ICU=intensive-care unit. CVC=central venous catheter. *Number of days alive and free of specified organ support up to day 28.

Table 3: Outcomes

randomisation and 70 (6%) patients in the enteral group received parenteral nutrition from day 0 to day 7. During the intervention period, the proportions of patients with vomiting and gastric prokinetic drug therapy were higher in the enteral group than in parenteral group, although the daily calorie intake was near the 20 kcal/kg per day target in both groups. Compared with the enteral group, the parenteral group had higher calorie and protein intakes, a lower frequency of hypoglycaemia, and a higher frequency of blood lactate normalisation (figure 2; table 2, table 3). No significant differences were noted for blood bilirubin, alanine aminotransferase, or aspartate aminotransferase concentrations; serial SOFA scores; C reactive protein; or bodyweight between the two groups (figure 2; table 2, table 3).

Other secondary outcomes are detailed in table 3 and the appendix p 17 and pp 10–12. Differences between groups were not noted for 90 day, ICU, or hospital mortality; days without mechanical ventilation, vasopressor support, or renal replacement therapy; lengths of ICU and acute care hospital stays; frequency of infections; and frequencies of subtypes of ICU-acquired infections. Adverse gastrointestinal events were significantly less common in the parenteral group than in the enteral group (table 3). Median time from initiation of nutritional support to bowel ischaemia diagnosis was 4·0 days (IQR 1·0–12·0) in the enteral group and 3·0 days (1·0–9·0) in the parenteral group; 10 (53%) patients with bowel ischaemia in the enteral group and three (60%) in the parenteral group required surgery (absolute difference estimate −7·4% [95% CI −55·8 to 41·1]). Among the patients with bowel ischaemia, 14 (74%) in the enteral group and four (80%) in the parenteral group died.

Discussion
Day 28 mortality did not differ significantly between groups given early normocaloric enteral versus parenteral nutrition during mechanical ventilation and vasoactive drug therapy for shock. Compared with the parenteral route, the enteral route was associated with slightly lower

calorie and protein intakes and with higher frequencies of hypoglycaemia and adverse gastrointestinal events. The groups showed no significant differences for

frequency of infectious complications; organ failure severity or duration; lifeÚ support duration; ICU or hospital stay lengths; or ICU, hospital, or day 90 mortality.

Our data for mortality agree with those of the recent CALORIES trial.[39] CALORIES and NUTRIREA-2 are the only large randomised trials specifically designed to assess the feeding route in critically ill patients. Our trial has substantial differences compared with the CALORIES trial and other studies. NUTRIREA-2 is the first trial focusing on severely ill ICU patients treated with mechanical ventilation and vasopressor support for shock. Patients with severe critical illness might benefit the most from the protective effects of early enteral feeding.[12,14,28] Accordingly, the main hypothesis of our trial was that, compared with early parenteral nutrition, early enteral nutrition might decrease mortality, with normocaloric goal targets for both routes. In our study, patients in the enteral group received slightly fewer calories than those in the parenteral group. This finding is in accordance with previous studies, but not with the CALORIES trial, in which calorie intakes were similar with enteral and parenteral nutrition. It is unlikely that the slightly lower calorie and protein intakes with enteral compared with parenteral nutrition in our study masked beneficial effects of enteral nutrition on mortality. Indeed, both groups received amounts near the predefined 20 kcal/kg per day target, and between-group differences in calorie and protein intakes were very small. A recent large randomised trial showed no deleterious effect of permissive hypocaloric enteral feeding compared with standard enteral feeding in ICU
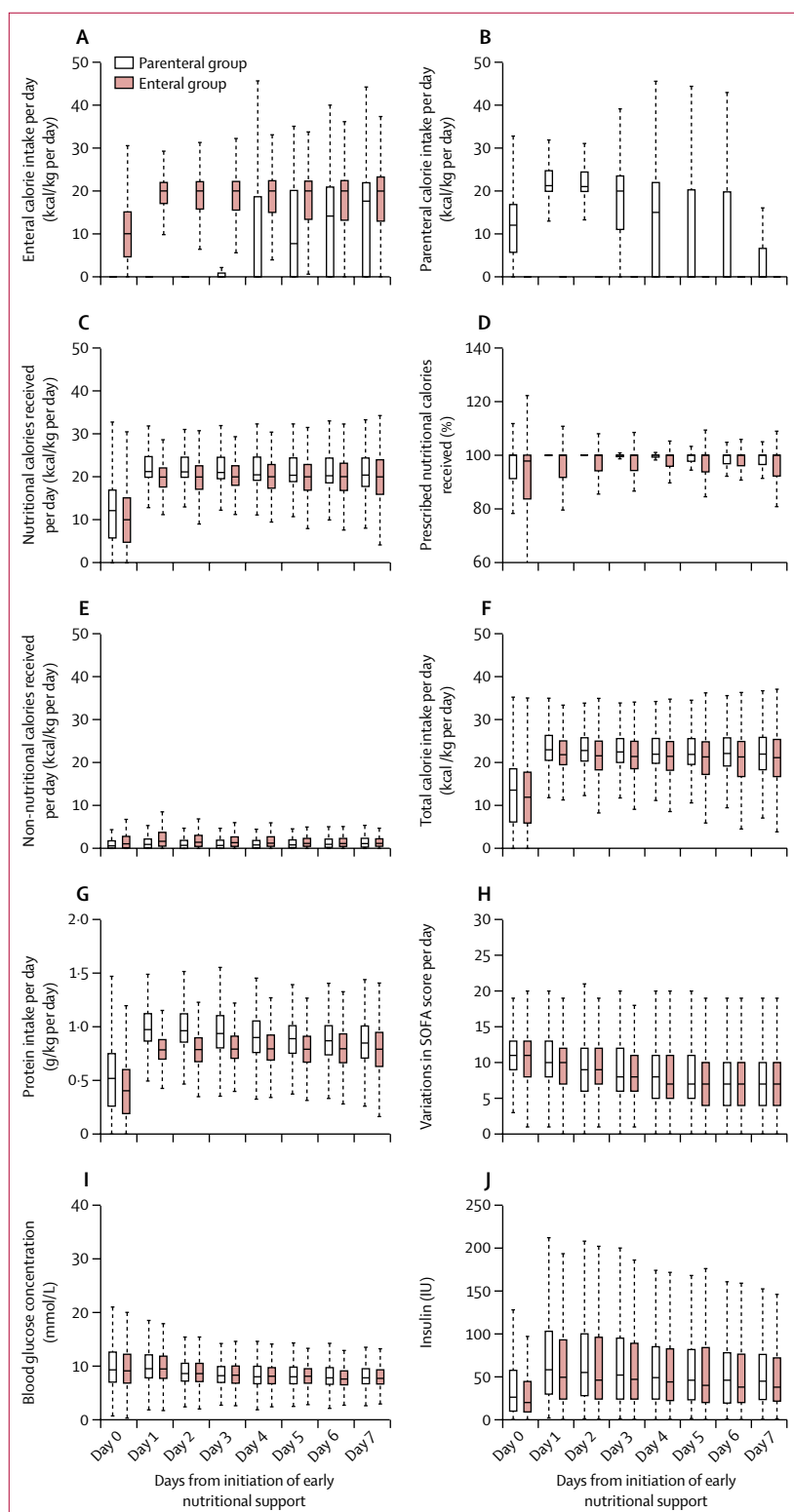

Figure 2: **Daily calorie intake (A–F), protein intake (G), SOFA score (H), blood glucose level (I) and daily insulin intake (J) during the intervention period in the enteral and parenteral groups**

The top panels show calories administered daily during the intervention period (from day 0 to day 7), expressed in kcal/kg per day via the enteral route only (A) and the parenteral route only (B). Panels C and D show calories administered via nutritional solutions during the intervention period (from day 0 to day 7), expressed as kcal/kg per day (C: mean difference –3·1 [95% CI –3·6 to –2·7]; p<0·0001) and as the percentages of the calorie targets (D: mean difference –6·4 [–7·9 to –4·9]; p<0·0001). Panel E shows calories administered daily during the intervention period (from day 0 to day 7), expressed in kcal/kg per day via non-nutritional solutions (glucose and propofol). Panel F shows the total amount of calories administered daily. Panel G shows the differences between the enteral group and the parenteral group in daily protein intake expressed in g/kg per day during the intervention period; mean difference –2·4 [95% CI –2·6 to –2·2]; p<0·0001). Bodyweight measured on admission was used throughout the intensive-care unit (ICU) stay to calculate calorie and protein intakes. Panel H shows differences between the enteral and parenteral groups for the Sequential Organ Failure Assessment (SOFA) score during the intervention period (mean difference –0·01 [95% CI –0·2 to 0·2]; p=0·88). SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multi-organ failure). Panels I and J show differences between the enteral group and the parenteral group in daily blood glucose levels (mmol/L; mean difference –0·02 [95% CI –0·05 to 0·01]; p=0·11) and in daily insulin intake (IU/d; mean difference –0·2 [–0·3 to –0·1]; p<0·0001), respectively. Box height indicates IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line across and near the middle of the box is the median. The lower whisker represents the 25th percentile minus 1·5 times the IQR and the upper whisker the 75th percentile plus 1·5 times the IQR. If no horizontal line is present within the box, the median value is the same as the 75th percentile.

patients.[40] Our feeding protocol was designed to match the course of critical illness, which is usually divided into an acute (catabolic) phase and a recovery (anabolic) phase.[4] The acute phase is associated with variable inflammatory, metabolic, and immune responses to the critical illness, which in turn might promote organ failure, secondary infections, muscle wasting, higher mortality, and residual impairments.[1] Whether early nutrition might contribute to lessen the acute-phase abnormalities, thereby improving patient outcomes, is controversial and not supported by the most recent trials in the field.[1,3] Research on nutrition in ICU patients has focused almost exclusively on the acute phase, for which there is no clear definition. In most studies, including the CALORIES trial, the study treatments lasted 5–7 days. Strategies that match nutritional support to the course of the critical illness are recommended to ensure that patient needs are accurately met.[1,4] Thus, patients in our parenteral group were switched to enteral feeding when they achieved predefined criteria for entry into the recovery phase. To the best of our knowledge, the NUTRIREA-2 trial is the first multicentre trial in which the nutrition protocol involved adaptation to the course of the acute phase of critical illness.

In addition to the mortality data, two other findings from our study deserve special attention. First, the higher risk of bowel ischaemia and colonic pseudo-obstruction in the enteral compared with in the parenteral group contrasts with previous non-randomised studies in which early enteral nutrition was feasible and beneficial in patients with shock.[14,28–30] A non-significant trend toward an increased risk of gastrointestinal complications with enteral feeding was also observed in the CALORIES trial.[39] However, the NUTRIREA-2 randomised trial provides the first strong evidence that enteral feeding might promote gut ischaemia in patients with severe critical illness. These findings provide scientific support for recommendations to postpone full enteral nutrition until haemodynamic stability is restored and to prefer parenteral nutrition or no nutrition in patients at the worst end of the severity spectrum.[3,41] Clearly, the amount of calories might also have an effect on patient outcomes. In both CALORIES and NUTRIREA-2, the calorie targets were similar and the patients received nearly 20 kcal/kg per day during the acute phase, either via the enteral or via the parenteral route. These calorie doses are close to guidelines. Targeting hypocaloric feeding during the acute phase of critical illness might be beneficial and hypocaloric enteral feeding might be associated with a lower risk of gastrointestinal complications, in particular bowel ischaemia. However, our aim was to focus only on the debate regarding the route of feeding and not to address the issue of nutrition doses. Whether hypocaloric feeding might be beneficial at the acute phase of critical illness and whether the effect of the feeding route might differ with hypocaloric feeding deserve further investigation. Similarly, our trial does not provide answers to the issues

of timing of supplemental parenteral feeding in patients intolerant to enteral feeding or of timing of enteral feeding initiation in patients who tolerate this route. Second, the frequency of ICU-acquired infections did not differ significantly between the two groups. That the larger proportion of patients with bacteraemia in the parenteral group versus the enteral group did not reach statistical significance might be ascribable to inadequate statistical power. However, this finding is consistent with CALORIES trial results.[39] Meta-analyses consistently showed higher frequencies of infections with parenteral compared with enteral nutrition but chiefly included studies done more than 20 years ago.[6,26,27] Our results thus suggest that progress might have occurred in the management of parenteral nutrition and prevention of nosocomial infections in the ICU, or that infections related to parenteral nutrition in older randomised trials were related to the dose rather than the route. Together with those from previous randomised trials, our data indicate a need for caution when interpreting treatment effect sizes suggested by observational studies, particularly in the field of nutrition in the ICU, where the clinical course could affect nutritional intake to a larger extent than nutrition affects clinical outcomes.

A limitation of our trial is the premature discontinuation of patient recruitment after the second interim analysis. However, 2410 (84%) of the 2854 patients required according to the sample size estimation were included, and the results were similar to those of the interim analyses with 1000 and 2000 patients, respectively. Thus, it is unlikely that including the remaining 444 patients would have changed the study results. A second limitation of the trial is that neither the patients nor the ICU staff were masked to treatment allocation. However, the nature of the treatments precluded blinding. Moreover, the primary endpoint—ie, day 28 mortality—is objective and cannot be significantly affected by the absence of masking. We used pre-established definitions or adjudication for the secondary endpoints when required. The multicentre patient recruitment supports the external validity of our trial. The observed mortality rates were similar to those used in the sample size estimation and to those reported in studies that included patients with severe critical illness. Last, the nutrition protocols were scrupulously followed in all participating ICUs. A third limitation is that we cannot exclude bias in the detection of gastrointestinal complications. Indeed, gut function might have been assessed more actively in patients receiving enteral nutrition than in those receiving parenteral feeding. However, predetermined definitions of gastrointestinal complications were provided to investigators, thus limiting the risk of bias. A last limitation of the trial might be the absence of functional or long-term outcome assessments. However, no previously published data suggest that feeding route might affect long-term outcomes of critically ill patients. Moreover, the absence of differences in

infectious complications, organ failure, duration of mechanical ventilation, hospital and ICU stay lengths, and day 90 mortality between our two groups argues strongly against a long-term effect of feeding route at the acute phase of critical illness. A major strength of the study is the good external validity provided by the multicentre and pragmatic study design. Internal validity is supported by the randomised design, predefined sample size estimated from reliable data, and counterbalancing of the non-blinded design by the primary outcome of all-cause mortality, whose evaluation is not susceptible to bias.

In conclusion, our trial shows that the enteral route is not clinically superior over the parenteral route for early nutritional support with a normocaloric target in critically ill patients treated with mechanical ventilation and vasopressor support for shock. Our data indicate an increased risk of gastrointestinal complications with early isocaloric enteral nutrition compared to parenteral nutrition in these patients.

References
1 Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. *N Engl J Med* 2014; **370:** 2450–51.
2 Kreymann KG, Berger MM, Deutz NE, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr* 2006; **25:** 210–23.
3 Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *Crit Care Med* 2016; **44:** 390–438.
4 Preiser JC, van Zanten AR, Berger MM, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care* 2015; **19:** 35.
5 Gianotti L, Alexander JW, Nelson JL, Fukushima R, Pyles T, Chalk CL. Role of early enteral feeding and acute starvation on post-burn bacterial translocation and host defense: prospective, randomized trials. *Crit Care Med* 1994; **22:** 265–72.
6 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:** 843–48.
7 Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ* 2004; **328:** 1407.
8 Kang W, Kudsk KA. Is there evidence that the gut contributes to mucosal immunity in humans? *JPEN J Parenter Enteral Nutr* 2007; **31:** 246–58.
9 Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. *Am J Surg* 2002; **183:** 390–98.
10 Windsor AC, Kanwar S, Li AG, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998; **42:** 431–35.
11 Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med* 2001; **29:** 242–48.
12 Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest* 2006; **129:** 960–67.
13 Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Med* 2009; **35:** 2018–27.
14 Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care* 2010; **19:** 261–68.
15 Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001; **29:** 2264–70.
16 Blaser AR, Starkopf J, Kirsimagi U, Deane AM. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. *Acta Anaesthesiol Scand* 2014; **58:** 914–22.
17 Binnekade JM, Tepaske R, Bruynzeel P, Mathus-Vliegen EM, de Hann RJ. Daily enteral feeding practice on the ICU: attainment of goals and interfering factors. *Crit Care* 2005; **9:** R218–25.
18 Heyland D, Cook DJ, Winder B, Brylowski L, Van deMark H, Guyatt G. Enteral nutrition in the critically ill patient: a prospective survey. *Crit Care Med* 1995; **23:** 1055–60.
19 McClave SA, Sexton LK, Spain DA, et al. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. *Crit Care Med* 1999; **27:** 1252–56.
20 Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med* 2001; **29:** 1955–61.
21 Gatt M, MacFie J, Anderson AD, et al. Changes in superior mesenteric artery blood flow after oral, enteral, and parenteral feeding in humans. *Crit Care Med* 2009; **37:** 171–76.
22 Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. *Arch Intern Med* 2004; **164:** 1054–62.
23 Rokyta R Jr, Matejovic M, Krouzecky A, Novak I. Enteral nutrition and hepatosplanchnic region in critically ill patients—friends or foes? *Physiol Res* 2003; **52:** 31–37.
24 Thibault R, Pichard C, Wernerman J, Bendjelid K. Cardiogenic shock and nutrition: safe? *Intensive Care Med* 2011; **37:** 35–45.
25 Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am J Respir Crit Care Med* 1995; **152:** 1545–48.
26 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.
27 Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2016; **20:** 117.
28 Elke G, Schadler D, Engel C, et al. Current practice in nutritional support and its association with mortality in septic patients—results from a national, prospective, multicenter study. *Crit Care Med* 2008; **36:** 1762–67.
29 Berger MM, Revelly JP, Cayeux MC, Chiolero RL. Enteral nutrition in critically ill patients with severe hemodynamic failure after cardiopulmonary bypass. *Clin Nutr* 2005; **24:** 124–32.
30 Mancl EE, Muzevich KM. Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. *JPEN J Parenter Enteral Nutr* 2013; **37:** 641–51.

31   McClave SA, Chang WK. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? *Nutr Clin Pract* 2003; **18:** 279–84.

32   Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; **43:** 304–77.

33   Brisard L, Le Gouge A, Lascarrou J, et al. Impact of early enteral versus parenteral nutrition on mortality in patients requiring mechanical ventilation and catecholamines: study protocol for a randomized controlled trial (NUTRIREA-2). *Trials* 2014; **15:** 507.

34   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.

35   Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22:** 707–10.

36   Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270:** 2957–63.

37   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.

38   Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; **34:** 585–612.

39   Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014; **371:** 1673–84.

40   Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med* 2015; **372:** 2398–408.

41   Reintam Blaser A, Starkopf J, Alhazzani W, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med* 2017; **43:** 380–98.