Nutrition in the ICU: sometimes route does matter

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The NUTRIREA-2 trial by Jean Reignier and colleagues[1] in *The Lancet* provides an important piece in the puzzle of intensive-care unit (ICU) nutrition management. This pragmatic multicentre study done at 44 French ICUs randomly assigned patients aged 18 years or older requiring invasive mechanical ventilation and vasopressors (median 0·5 μg/kg per min) to receive either enteral nutrition (n=1202) or parenteral nutrition (n=1208), both targeting normocaloric goals (20–25 kcal/kg per day), within 24 h after intubation or ICU admission. The primary endpoint of early survival (mortality on day 28 after randomisation) was comparable in both study groups. By day 28, 443 (37%) patients in the enteral group and 422 (35%) patients in the parenteral group had died (absolute difference estimate 2·0% [95% CI −1·9 to 5·8]; p=0·33).

For decades, nutritional management in critically ill patients was largely based on physiological observations, clinical associations, and expert opinion. During the past 10 years, however, several high-quality randomised controlled trials (RCTs) assessed different nutritional strategies in more than 10 000 patients and challenged long-standing dogmas. One RCT showed lower survival with early enhanced feeding after hypophosphataemia[2] and in some studies enhanced feeding compromised recovery,[3] but most often the dosing, timing, and route of nutrition did not seem to affect hard clinical endpoints.[4–6] Such negative trials might lead to the assumption that nutritional management in the ICU does not really matter or even worse should not be evaluated in large protocolised RCTs. The results of the NUTRIREA-2 trial[1] caution against such reasoning.

Although their supporting evidence is to some extent insufficient, the European Society of Intensive Care Medicine's clinical guidelines, published in March, 2017, recommend early enteral rather than parenteral nutrition in the ICU because it reduces the incidence of new infections.[7] In patients with stabilised haemodynamic shock, a gradual initiation of enteral nutrition is suggested on the basis of expert opinion.[7] Indeed, both a protective effect of enteral nutrition on intestinal integrity and a detrimental effect through non-occlusive bowel necrosis or intestinal ischaemia were at that point purely speculative.

The NUTRIREA-2[1] trial helps fill this evidence gap, showing an increase in severe gastrointestinal complications with early enteral nutrition, particularly a four-fold increase (from five patients [<1%] with parenteral nutrition to 19 [2%] patients with enteral) in bowel ischaemia. The similarly designed CALORIES trial[4] assessed a lower nutrition dose in less severely ill patients, perhaps explaining why no difference in bowel ischaemia was observed in that study.

Caution is thus warranted when starting enteral nutrition early in haemodynamically unstable patients, not only because of these rare complications but above all because enteral nutrition generated no benefit either in CALORIES[4] or in NUTRIREA-2.[1] Moreover, the 10% absolute increase in minor gastrointestinal complications such as vomiting and diarrhoea with enteral nutrition in NUTRIREA-2 could aggravate the physical and psychological burden for patients, proxies, and caregivers, which is difficult to quantify. Interestingly, as in CALORIES[4] and NUTIREA-1,[8] increased incidence of vomiting did not translate into additional airway infections, contradicting common clinical intuition.[8]

Adding to the controversy regarding the optimal route of nutrition, in NUTRIREA-2 nearly isocaloric doses of parenteral nutrition (19·6 kcal/kg per day [SD 5·3] compared with 17·8 kcal/kg per day [5·5] in the enteral group) did not provoke an increase in complications. Perhaps, complications attributed to parenteral nutrition are more related to dose than to route of administration,

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as suggested by a recent meta-analysis.[9] Indeed, enteral nutrition is often administered in lower doses due to intolerance. In previous studies, an increase in complications with a higher dose of artificial nutrition seemed to occur only when the energy gap with the lower intake group was sufficiently large to result in increased insulin needs.[2,3] In NUTRIREA-2, the early insulin needs in the parenteral group were substantially higher (IU/day –0·2 [95% CI –0·3 to –0·1]; p<0·0001), but only a non-significant 1 day increase in length of stay in the ICU (from 9 days [5–16] to 10 days [5–16]; p=0·08) and a 40% relative increase in bloodstream infections from 3·2% to 4·6% with parenteral nutrition (p=0·08) was observed, which might be due to lack of power or might be chance findings.

So should we choose parenteral nutrition for patients requiring vasopressors during the first week in the ICU? Unfortunately, NUTRIREA-2[1] cannot answer this question because it did not include a third group receiving no nutrition in the first week in the ICU, which might be an even better clinical option. Withholding early parenteral nutrition during 1 week enhanced recovery in a subgroup of 517 patients with absolute counterindication for enteral nutrition in the EPaNIC-RCT[3] and was not inferior to parenteral nutrition in 1372 patients with a relative counter-indication to enteral nutrition in the Early-PN trial.[10]

The NUTRIREA-2 trial not only provides new and crucial clinical guidance against early enhanced enteral nutrition in stable haemodynamic shock patients, it also contributes to further orienting nutrition research in the ICU, particularly in the choice of a primary endpoint.[6] The study confirms the aggregated conclusion of all recent RCTs that early nutrition interventions do not save lives in the ICU.[6] This contradicts the effect of closer-to-target feeding, predicted in observational studies, perhaps confounded by feeding being easier when patients recover.[11] Today, overall ICU mortality has reduced substantially from previous decades[12] and reducing the burden of long-term limitations in physical function might be a more appropriate endpoint for RCTs evaluating (early) nutrition interventions in the ICU.[6]

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

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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.

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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

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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 heterogeneous 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

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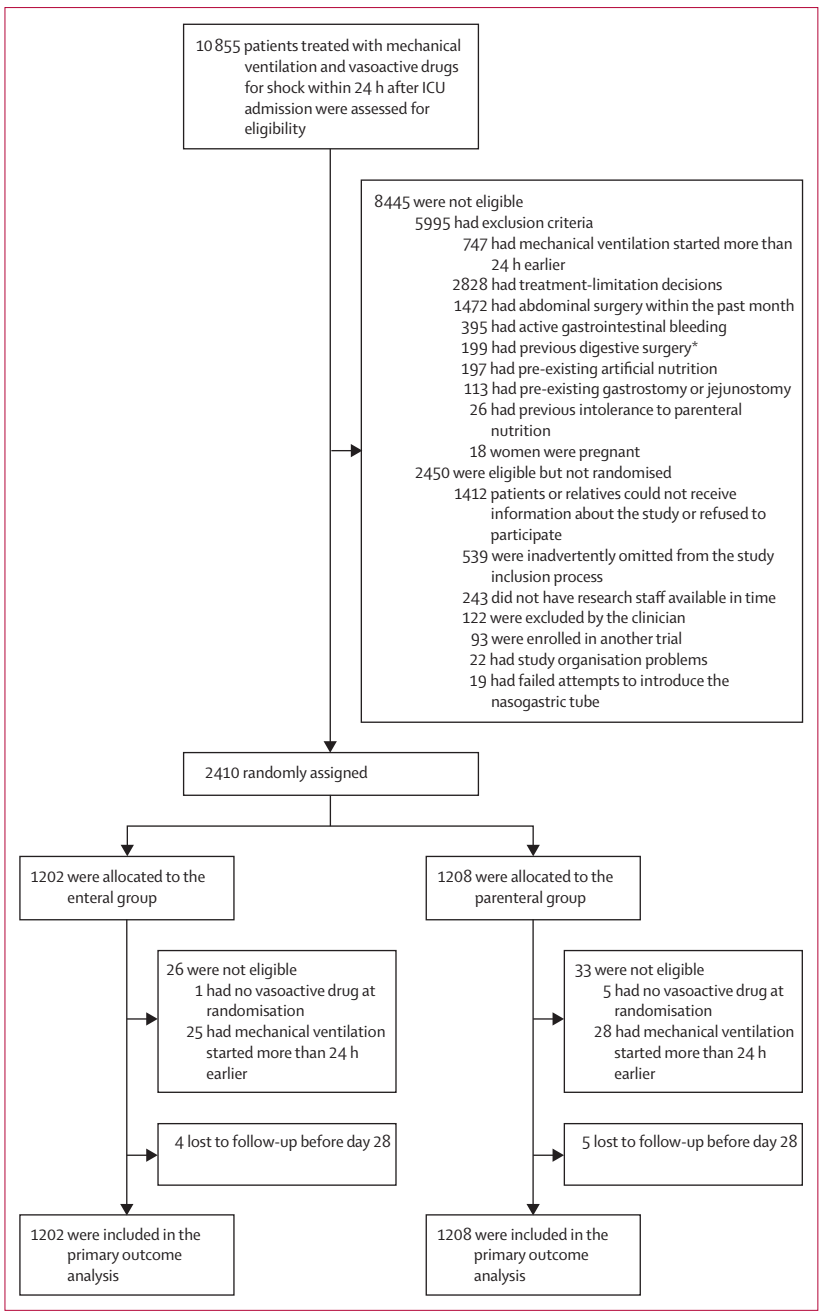

Figure 1: **Trial profile**
ICU=intensive-care unit. *Gastrectomy, oesophagectomy, duodeno-pancreatectomy, bypass surgery, gastric banding, or short bowel syndrome.

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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 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

	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)

(Continued from previous column)

	Enteral group (n=1202)	Parenteral group (n=1208)
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)
FiO_2	55 (23)	55 (23)
PEEP (cmH_2O)	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. FiO_2=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 χ^2 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.

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	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 X^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.

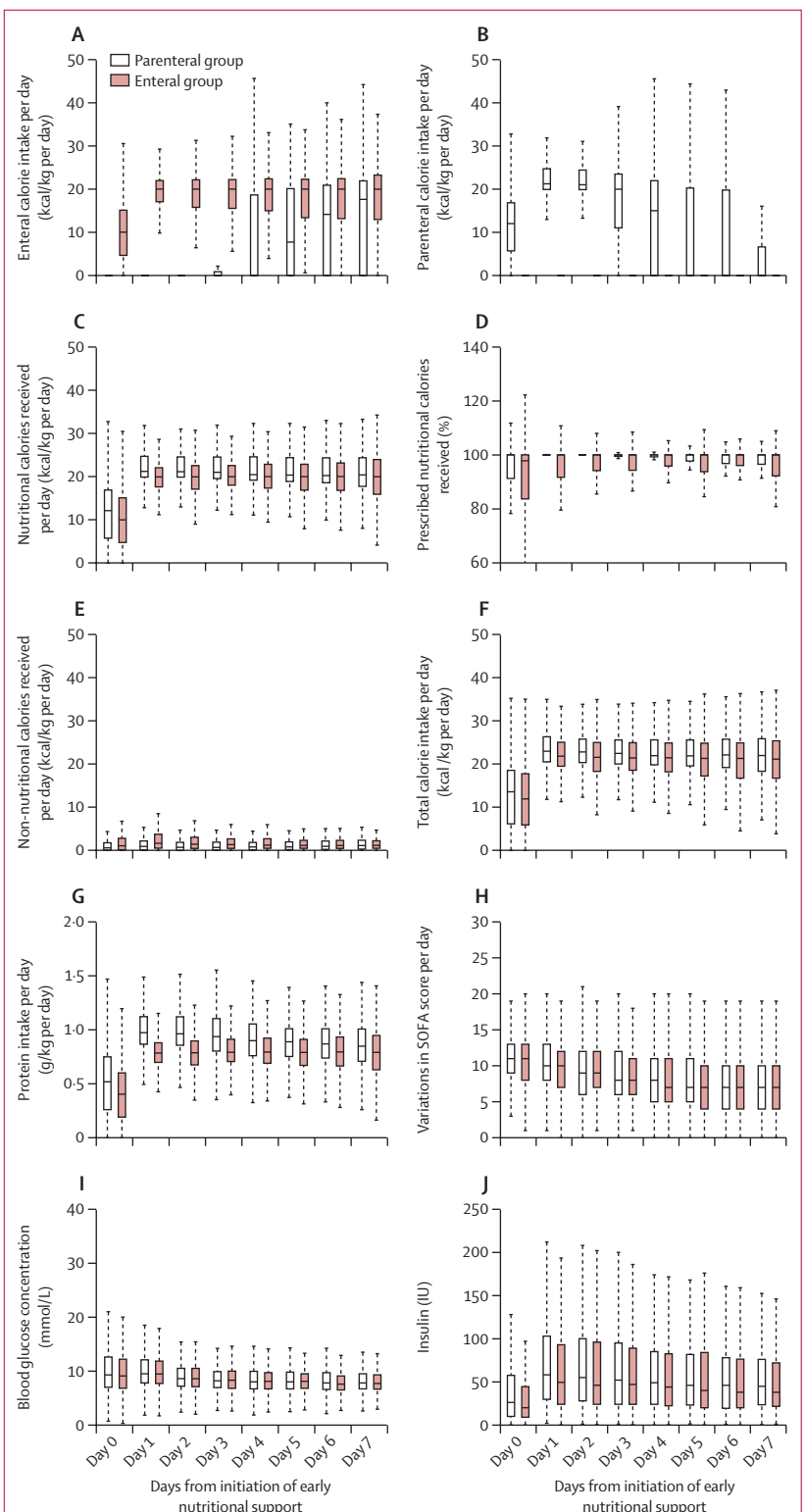

Figure 2: **Daily calorie intake (A–F), protein intake (G), SOFA score (H), blood glucose level (I) and daily insulin intake (J) during the intervention period in the enteral and parenteral groups**

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.

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

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 counter-balancing 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.

Contributors

JR, LB, J-BL, BG, and ALG designed the study. ALG and BG did the statistical analysis. JR, JB-H, LB, J-BL, AAH, NA, LA, KA, PA, FB, VB, AB, H-NB, EC, DDS, MD, VD, JD, MD, FG, MG-O, SG, OG, CG, BG, CG, J-EH, J-CL, PL, FM, VM, EM, J-PQ, JR, J-PR, RR, NR, CS, MS, FT, and DT approved the design of the study, coordinated individual sites, participated in the inclusion of study participants, and collected the data. JR wrote the first draft of the report with input from ALG. All authors revised the report and read and approved the final version before submission.

Declaration of interests

We declare no competing interests.

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similar numerous reports on the signs of declining male reproductive health.

A crucial, but simple question for societies with high economic activity is whether the trend toward decreased fertility rates is reversible. If economic growth and social factors, including altered family structures alone were responsible, then this effect is probably not worrisome because economic and social trends often change. However, fertility rates far below replacement levels have been the status quo for decades in high-income countries. For example, in Denmark, the average fertility rate in the past 40 years has been approximately 1·7 children per woman. Furthermore, there are absolutely no signs that rates will soon increase toward positive replacement (>2·1 children per woman), not even with the current high rate of assisted reproduction (>9% of all Danish children are born after assisted reproductive technology, including insemination).[9] Despite these interventions, more than 20% of Danish men born in the 1960s will never become fathers.[10]

Therefore, we are convinced that reduced fertility in young couples, not just rising economic activity and changed social structures, is a key contributor to the low fertility rates reported by the Collaborators. However, the causes for the low fertility rates can only be determined by solid research involving both demographers and researchers in reproductive biomedicine. Leading medical journals also have important roles to play in this endeavour by promoting this unprecedented type of collaborative research. As Nicholas Kristof wrote[11] in *The New York Times*, "our human future will only be as healthy as our sperm".

We declare no competing interests.

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The NUTRIREA-2 study

We read with interest the results of the NUTRIREA-2 study by Jean Reignier and colleagues (Jan 13, 2018, p 133).[1] In this well designed, open-label, randomised controlled trial, enteral nutrition did not improve mortality at day 28 compared with parenteral nutrition with a normocaloric target in mechanically ventilated patients with shock. A major finding of this study was the significantly higher rate of bowel ischaemia in the enteral group (19 [2%] patients *vs* five [<1%] patients; p=0·007), leading the authors to conclude that enteral nutrition might promote gut ischaemia in critically ill patients. This finding is important and warrants further discussion, as intensive care unit-acquired bowel ischaemia is a challenging diagnosis associated with a dismal prognosis.[2,3] Importantly, previous trials on enteral nutrition in patients in intensive care units did not report such a high rate of bowel ischaemia. For example, in the CALORIES trial,[4] 11 (0·9%) of 1197 patients in the enteral group were suspected to have mesenteric ischaemia.

First, regarding the proposed definition of bowel ischaemia, it might be interesting to detail mechanisms and locations of bowel ischaemia in these patients. Indeed, non-occlusive mesenteric ischaemia is by far the main mechanism of intensive care unit-acquired mesenteric ischaemia, and enteral nutrition is unlikely to induce mesenteric vascular occlusion. Additionally, CT scan performance for the diagnosis of non-occlusive mesenteric ischaemia is poor. In a case-control study including 114 patients,[3] classic signs of bowel ischaemia such as gas in the portal or mesenteric veins, pneumatosis intestinalis, and abnormal contrast enhancement of the bowel wall had low diagnostic sensitivity, as they were missing in 25% of patients with proven mesenteric ischaemia. Symptoms of enteral feeding intolerance might also have prompted bowel ischaemia suspicion, and the study's open-label design might have introduced a detection bias. The number of patients with stage I ischaemia (petechiae) at endoscopy should also be reported, as this finding might be associated with causes

other than bowel ischaemia. Finally, it would be of interest to analyse if the occurrence of bowel ischaemia was related to the amount of enteral nutrition.

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In the NUTRIREA-2 trial,[1] patients who received mechanical ventilation and vasopressor support showed no statistically significant differences in mortality and infection rates when given either enteral nutrition or parenteral nutrition. Enteral nutrition was more frequently associated with adverse gastrointestinal events. Full doses of macronutrients corresponding to about 60–70% of daily requirements were provided throughout the intervention period.[1,2] Such a calorie target might attenuate the potential benefit of enteral nutrition and increase the risk of complications related to enteral nutrition. The current guidelines[3] show concerns about enteral nutrition for unstable patients who need high doses of vasopressor, because the gut is susceptible to ischaemia in such patients.

In a randomised controlled trial,[4] which enrolled 200 patients on mechanical ventilation, no differences were observed in mortality between individuals assigned to full-energy enteral nutrition (average delivery of 74·8% of calorie requirements) and individuals assigned to trophic enteral nutrition (average delivery of 15·8% of calorie requirements) for 6 days. Trophic enteral nutrition had a trend towards less adverse gastrointestinal events.[4] Also, in a larger randomised controlled trial,[5] which recruited mechanically ventilated patients, initial trophic enteral nutrition (400 kcal per day) resulted in a significant reduction in gastrointestinal intolerance with similar mortality and infection rates compared with full-energy enteral nutrition (1300 kcal per day). A non-significant risk difference in mortality at day 28 (2·0%, 95% CI −1·9 to 5·8) in favour of parenteral nutrition appears to have occurred at the end of the intervention on day 7.[1] These findings would suggest the need for refinements in calorie targets for early enteral nutrition in severe, critical illness with a potentially ischaemic gut.

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In the NUTRIREA-2 trial,[1] enteral nutrition was compared with parenteral early nutrition in ventilated adults with shock. In particular, the authors aimed at ascertaining whether early first-line enteral nutrition showed positive clinical effects compared with parenteral nutrition. Both arms of the study targeted normocaloric supplementation in patients needing invasive mechanical ventilation and vasopressor support for shock.[1] The results show that early isocaloric enteral and parenteral nutrition did not differ in mortality or risk of secondary infections. However, enteral nutrition was associated with a greater risk of gastrointestinal complications.[1]

The European Society for Clinical Nutrition and Metabolism guidelines[2] recommend the use of parenteral nutrition when enteral feeding is not tolerated or is contraindicated (grade B recommendation) within 3–7 days following intensive care admission but recommend careful consideration of the optimal timepoint for supplemental parenteral nutrition for those patients not tolerating exclusive enteral nutrition (grade good practice point recommendation).

In the NUTRIREA-2 study,[1] consecutive patients were randomly assigned (1:1) to one of the two treatment groups, independently of clinical indication. Therefore, it is possible that some patients were assigned to enteral nutrition when this treatment was not clinically indicated (ie, absence of gastrointestinal integrity or function, or both), possibly affecting the results. Patients in the enteral group had significantly more episodes of vomiting and diarrhoea and major events, such as bowel ischaemia and acute colonic pseudo-obstruction,[1] possibly affecting mortality and secondary infections.

Enteral nutrition has been indicated to stimulate intestinal function either directly by supplying substrates for enterocyte oxidation, or indirectly, by promoting hormone secretion and limiting bacterial translocation.[3]

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The European Society for Clinical Nutrition and Metabolism guidelines[2] recommend the use of parenteral nutrition when enteral feeding is not tolerated or is contraindicated (grade B recommendation) within 3–7 days following intensive care admission but recommend careful consideration of the optimal timepoint for supplemental parenteral nutrition for those patients not tolerating exclusive enteral nutrition (grade good practice point recommendation).

In the NUTRIREA-2 study,[1] consecutive patients were randomly assigned (1:1) to one of the two treatment groups, independently of clinical indication. Therefore, it is possible that some patients were assigned to enteral nutrition when this treatment was not clinically indicated (ie, absence of gastrointestinal integrity or function, or both), possibly affecting the results. Patients in the enteral group had significantly more episodes of vomiting and diarrhoea and major events, such as bowel ischaemia and acute colonic pseudo-obstruction,[1] possibly affecting mortality and secondary infections.

Enteral nutrition has been indicated to stimulate intestinal function either directly by supplying substrates for enterocyte oxidation, or indirectly, by promoting hormone secretion and limiting bacterial translocation.[3]

other than bowel ischaemia. Finally, it would be of interest to analyse if the occurrence of bowel ischaemia was related to the amount of enteral nutrition.

We declare no competing interests.

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In the NUTRIREA-2 trial,[1] patients who received mechanical ventilation and vasopressor support showed no statistically significant differences in mortality and infection rates when given either enteral nutrition or parenteral nutrition. Enteral nutrition was more frequently associated with adverse gastrointestinal events. Full doses of macronutrients corresponding to about 60–70% of daily requirements were provided throughout the intervention period.[1,2] Such a calorie target might attenuate the potential benefit of enteral nutrition and increase the risk of complications related to enteral nutrition. The current guidelines[3] show concerns about enteral nutrition for unstable patients who need high doses of vasopressor, because the gut is susceptible to ischaemia in such patients.

In a randomised controlled trial,[4] which enrolled 200 patients on mechanical ventilation, no differences were observed in mortality between individuals assigned to full-energy enteral nutrition (average delivery of 74·8% of calorie requirements) and individuals assigned to trophic enteral nutrition (average delivery of 15·8% of calorie requirements) for 6 days. Trophic enteral nutrition had a trend towards less adverse gastrointestinal events.[4] Also, in a larger randomised controlled trial,[5] which recruited mechanically ventilated patients, initial trophic enteral nutrition (400 kcal per day) resulted in a significant reduction in gastrointestinal intolerance with similar mortality and infection rates compared with full-energy enteral nutrition (1300 kcal per day). A non-significant risk difference in mortality at day 28 (2·0%, 95% CI −1·9 to 5·8) in favour of parenteral nutrition appears to have occurred at the end of the intervention on day 7.[1] These findings would suggest the need for refinements in calorie targets for early enteral nutrition in severe, critical illness with a potentially ischaemic gut.

I declare no competing interests.

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Data for enteral feeding highlight benefits in comparison with parenteral nutrition, such as lower infectious and non-infectious complications and associated costs.[4,5] Therefore, when deciding the most appropriate route of nutrient delivery, continuous clinical judgment rather than strict adherence to protocols should inform therapy in ventilated adults with shock.

We declare no competing interests.

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Authors' reply

We thank correspondents for their comments on the NUTRIREA-2 trial.[1] We agree with Simon Bourcier and Alain Combes that bowel ischaemia is challenging to diagnose and can be caused by different mechanisms, including non-occlusive mesenteric ischaemia and vessel obstruction. Moreover, we agree that the unblinded study design could have caused detection bias. These points were clearly acknowledged in the discussion. However, predefined criteria were used in the NUTRIREA-2 trial to diagnose bowel ischaemia. Importantly, the use of diagnostic tools, including CT scanning, CT angiography, angiography, magnetic resonance angiography, endoscopy, and surgery strongly limited the risk of detection bias. In the CALORIES trial,[2] which used similar predefined criteria of bowel ischaemia, 11 (0·9%) of 1195 patients in the enteral nutrition group had bowel ischaemia, compared with eight (0·7%) of 1188 patients in the parenteral nutrition group. The proportion of patients with bowel ischaemia in the parenteral nutrition CALORIES group was similar to that in the corresponding NUTRIREA-2 group. The higher frequency in our enteral nutrition group could be related to the greater illness severity, as only mechanically ventilated patients with shock were included, compared with unselected critically ill patients in the CALORIES trial.

As stated by Tetsuji Fujita, the amount of enteral nutrition delivered during the acute phase of critical illness could have an impact on gastrointestinal complications. When the NUTRIREA-2 trial was designed, data for this point were very scarce. To the best of our knowledge, the only large trial comparing hypocaloric to normocaloric enteral nutrition is the EDEN trial[3] with patients receiving invasive mechanical ventilation for acute lung injury. There was no between-group difference in ventilator-free days or mortality at day 60. Patients with hypocaloric feeding had fewer days with regurgitation, vomiting, and constipation, compared with those with full enteral feeding. There were no differences in other gastrointestinal complications between groups. Whether the enteral feeding route and the enteral-nutrition calorie target could have beneficial or deleterious effects on the gut mucosa of critically ill patients with shock is unclear.[4,5] Current guidelines recommend prokinetic drug therapy of gastroparesis before lowering the calorie target in patients intolerant to early enteral nutrition.[6]

Lastly, we disagree with Alessio Molfino and Alessandro Laviano's suggestion that some patients in the enteral nutrition group could have had contraindications to enteral feeding, thus explaining the higher frequency of bowel ischaemia in this group compared with the parenteral nutrition group. Non-inclusion criteria in the NUTRIREA-2 protocol consisted of active gastrointestinal bleeding; gastrointestinal tract surgery within the past month; and a history of gastrectomy, oesophagectomy, duodenopancreatectomy, bypass surgery, gastric banding, or short bowel syndrome. The European Society for Clinical Nutrition and Metabolism guidelines[6] on supplemental parenteral nutrition were supported only by low-level evidence and have been contradicted by the EPaNIC trial results.[7] The possibility that enteral nutrition might decrease the risk of infectious and non-infectious complications compared with parenteral nutrition is not supported by the results of the NUTRIREA-2 and CALORIES trials. The NUTRIREA-2 trial provides the first evidence that early enteral nutrition could promote gut ischaemia in patients with severe, critical illness, including shock. We are confident that this evidence is reliable and constitutes valid grounds for concern about adverse effects of enteral nutrition in patients with shock who are receiving mechanical ventilation. Whether the route or dose of feeding plays the main role in these adverse effects requires further investigation. The NUTRIREA-3 trial (NCT03573739), comparing hypocaloric and standard feeding, is ongoing and will provide additional data for this issue.

We declare no competing interests.

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Science's place in shaping gender-based policies in athletics

Christian Petersen/Getty Images

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In 2009, South African runner Caster Semenya, aged 18 years, won the 800 m at the World Championships in Athletics in Berlin, only to be rapidly declared "a woman, but maybe not 100%" by the general secretary of the International Association of Athletics Federations (IAAF), and barred from competing. After being reinstated, she won Olympic Gold in 2012 and 2016 and became the 800 m World Champion in London in 2017. However, by the time the World Championships in Athletics take place between Sept 28 and Oct 6, 2019, new eligibility regulations for female classification from the IAAF,[1] based on the interpretation of data[2] from studies of androgen concentrations in elite athletes, might have prevented Semenya from competing again.

We have been deeply involved in shaping the rules of eligibility for female athletes throughout years of regulatory changes.[3,4] We have now become unlikely partners: an athlete wronged by misuse of genetic data[4] and a geneticist listening to an athlete's perspective—a rapprochement of sorts that has led to this common critique of the new regulations.

The IAAF published new eligibility regulations for female classification[1] that will, starting in 2019, prevent athletes with testosterone concentrations of more than 5 nmol/L from competing in the female category for so-called restricted events: 400 m, 400 m hurdles, 800 m, 1500 m, and 1 mile.[1] These regulations lower the 2012 threshold of testosterone from 10 nmol/L to 5 nmol/L, but its application is limited to a smaller number of events. The new eligibility rule is considerably more restrictive than before, and no convincing scientific argument exists for either the new testosterone threshold or the selection of restricted events.

First, the choice of 5 nmol/L is arbitrary, with little evidence that testosterone concentrations at or above this threshold affect actual athletic performance (beyond muscle mass). The IAAF based its decision on a supporting review[5] describing the new criterion of 5 nmol/L as generous to intersex females or females with disorders of sex development. There is nothing generous about it. Women certainly did not choose to have either of these conditions, and the underlying rationale perpetuates the notion that women with an intersex condition are not 100% women.

Second, the performance of athletes with high and normal testosterone has not been shown to be significantly different in some restricted events (eg, 1500 m), but it has in some that are not on the list (eg, hammer throw and pole vault),[2] raising questions about the neutrality of policy making. If the policy is enacted, the same athlete could be eligible for one event as a woman but not for another, creating an absurd sex-shifting situation (competing in the female category for one event and, with no other option, as a man for another).

History warns us about the dangers of using science to justify discriminatory policies. Semenya went from competing to being excluded to becoming eligible for competition again and winning, yet she was the same human throughout the vagaries of sports policies. As she risks becoming ineligible again, sport authorities need to understand the limitations of data interpretation and ensure that new policies are humane and based on irreproachable science.

We have been advising the International Olympic Committee on issues of hyperandrogenism in female athletes since 2010.

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Department of Error

Hamada H, Suzuki H, Onouchi Y, et al. Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. Lancet *2019;* **393:** *1128–37*—In table 1 of this Article, some data in the second column of the row entitled "C-reactive protein, mg/dL" was incorrect and should have read "9·46 (5·73–12·6)". This correction has been made as of April 3, 2019.