

STUDY PROTOCOL

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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)

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Abstract

Background: Nutritional support is crucial to the management of patients receiving invasive mechanical ventilation (IMV) and the most commonly prescribed treatment in intensive care units (ICUs). International guidelines consistently indicate that enteral nutrition (EN) should be preferred over parenteral nutrition (PN) whenever possible and started as early as possible. However, no adequately designed study has evaluated whether a specific nutritional modality is associated with decreased mortality. The primary goal of this trial is to assess the hypothesis that early first-line EN, as compared to early first-line PN, decreases day 28 all-cause mortality in patients receiving IMV and vasoactive drugs for shock.

Methods/Design: The NUTRIREA-2 study is a multicenter, open-label, parallel-group, randomized controlled trial comparing early PN versus early EN in critically ill patients requiring IMV for an expected duration of at least 48 hours, combined with vasoactive drugs, for shock. Patients will be allocated at random to first-line PN for at least 72 hours or to first-line EN. In both groups, nutritional support will be started within 24 hours after IMV initiation. Calorie targets will be 20 to 25 kcal/kg/day during the first week, then 25 to 30 kcal/kg/day thereafter. Patients receiving PN may be switched to EN after at least 72 hours in the event of shock resolution (no vasoactive drugs for 24 consecutive hours and arterial lactic acid level below 2 mmol/L). On day 7, all patients receiving PN and having no contraindications to EN will be switched to EN. In both groups, supplemental PN may be added to EN after day 7 in patients with persistent intolerance to EN and inadequate calorie intake. We plan to recruit 2,854 patients at 44 participating ICUs.

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Discussion: The NUTRIREA-2 study is the first large randomized controlled trial designed to assess the hypothesis that early EN improves survival compared to early PN in ICU patients. Enrollment started on 22 March 2013 and is expected to end in November 2015.

Trial registration: ClinicalTrials.gov Identifier: NCT01802099 (registered 27 February 2013)

Keywords: Critical illness, Enteral nutrition, Mechanical ventilation, Mortality, Nosocomial infection, Parenteral nutrition, Shock, Vasoactive drugs

Background

Nutritional support is a key component of the life-sustaining strategies used on an everyday basis in intensive care units (ICUs) to combat the adverse effects of critical illnesses. The latest international guidelines recommend enteral nutrition (EN) as opposed to parenteral nutrition (PN) as the first-line route for nutritional support [1-4]. EN has documented beneficial effects on gastrointestinal mucosa integrity, wound healing, immune function and response to tissue damage [5-7]. EN may contribute to diminishing nosocomial infection rates, length of stay and health-care costs [8-11]. Early EN initiation (within 24 to 48 hours after ICU admission) may enhance these beneficial effects and decrease mortality rates [12-15]. EN initiation within 48 hours after invasive mechanical ventilation (IMV) has been reported to improve outcomes of patients with multiple organ failure [12,14]. Despite this evidence base, substantial gaps persist between everyday practice and clinical guidelines about nutritional support. EN is frequently delayed and PN used in patients who are eligible for EN [16-18]. At least two factors may explain the current underuse of EN—namely, legitimate or exaggerated concerns about complications related to EN and the absence of sound scientific evidence that one route is superior to the other [19].

The most common complication of early EN is upper gastrointestinal intolerance, which occurs in 30% to 70% of ICU patients [20]. Upper gastrointestinal intolerance manifests as gastric hypokinesia responsible for an increase in the residual gastric volume, which in turn is believed to increase the risk of gastroesophageal reflux, aspiration and nosocomial pneumonia [21-28]. The sequence of incomplete gastric emptying, gastroesophageal reflux, aspiration and nosocomial pneumonia is a constant source of concern for health-care workers. Ventilator-associated pneumonia (VAP) is a major complication of IMV; it is seen in 8% to 27% of patients and is responsible for longer ICU stays and increased mortality in some patients [29]. The measure most commonly used to prevent or decrease the risk of upper gastrointestinal intolerance is discontinuation or substantial reduction of the enteral feed flow rate. However, this measure decreases energy and nutrient intake below what is required to meet the needs of the patient. A

negative energy balance is associated with undernutrition, which in turn correlates with higher rates of infection and death in the most severely ill patients [30-35]. Concern about VAP and undernutrition related to EN intolerance is a major deterrent to the use of early EN [36-45]. EN has also been associated with an increased risk of gut ischemia in critically ill patients with shock [46-49]. Gut ischemia may result in necrotizing enterocolitis, which is fatal in 70% to 100% of cases [50,51]. Factors involved in gut ischemia include impaired splanchnic blood flow, vasoactive drug use, preexistent arterial disease and specific clinical conditions such as renal failure, heart surgery, multiple trauma, acute respiratory distress syndrome, septic shock, cardiogenic shock and fluid overload [49,52,53]. Whether EN contributes to the development of gut ischemia remains controversial. Experimental studies have demonstrated better preservation of gastrointestinal mucosal integrity with EN [54,55]. However, splanchnic blood flow has been found to increase by 50% with EN and decrease by over 60% with PN, suggesting a risk of inadequate splanchnic oxygen supply in the face of high demand in patients with shock who are receiving EN [46]. Guidelines recommend postponing EN in patients with shock until full resuscitation with achievement of hemodynamic stability [2,3]. This delay in EN delivery may be associated with calorie deficiencies and adverse outcomes in patients with severe critical illnesses [30,34]. These considerations explain why clinicians perceive PN as the safest means of delivering adequate energy and protein to patients at high risk for intolerance to EN or gut ischemia.

Another contributor to the current underuse of early EN in ICU patients may be the reliance of international guidelines on studies that have provided low-level evidence and on meta-analyses whose results are conflicting [1,13,15]. Most meta-analyses comparing EN and PN have shown no effect on mortality, but have indicated that EN, compared to PN, was associated with decreases in nosocomial infections, hospital and ICU lengths of stay and health-care costs [9,10,56-58]. A meta-analysis confined to trials involving an intention-to-treat analysis (9 of 465 trials) demonstrated higher mortality with EN than with PN [59]. However, all the available meta-analyses included highly heterogeneous studies that were

done in small numbers of patients and were focused on surgical patients and/or on patients who did not require ventilatory support or who had critical illnesses of limited severity. These characteristics preclude drawing definitive conclusions about the respective effects of EN and PN in critically ill patients. Many authors have emphasized the need for well-designed, adequately powered, randomized trials in uniform populations of ICU patients with severe critical illnesses associated with a high risk of death and/or complications, in whom optimal nutritional support raises the greatest challenges but is likely to have the greatest impact on patient outcomes [59-61].

Study rationale

Patients with shock requiring both IMV and vasoactive drugs are at high risk for complications and death. Given their vulnerability to EN intolerance and gut ischemia, guidelines indicate that EN should be postponed until hemodynamic stability is restored [2,3]. These patients consequently receive either delayed EN or initial PN, although they may have a high likelihood of survival benefits from early EN compared to PN, according to several observational [12,14,17]. No adequately designed study has compared early EN to early PN in this population. The primary goal of the present trial is to assess the hypothesis that early first-line EN decreases day 28 all-cause mortality in these patients compared to early first-line PN.

Methods/Design

Design and setting

NUTRIREA-2 is a multicenter, open-label, parallel-group randomized controlled trial in patients receiving IMV and vasoactive drugs for shock. They will be allocated to early first-line EN or early first-line PN in the acute phase of ICU management.

Ethical aspects

The study protocol and patient information documents were approved by the ethics committee of the French Society for Intensive Care Medicine (Société de Réanimation de Langue Française (SRLF) approval CE SRLF 11-340) and by the competent French authorities (Comité de Protection des Personnes de Poitiers registration 2011-A01483-38 (approved on 26 January 2012)). According to French law, as the strategies used in both study arms are classified as standard care, patient consent is not required; however, the patients or their next of kin must be informed about the study before enrollment. Before study enrollment, all patients or their next of kin will confirm in writing that they have received this information.

Participating units

Of the 44 French ICUs participating in the study, 28 are in university hospitals. All participating ICU staff members

have received training in the study procedures and protocols for providing nutritional support and managing EN intolerance.

Study population

Eligible patients are adults (≥ 18 years of age) admitted to the study ICUs who are expected to require IMV for longer than 48 hours, are being treated with a vasoactive drug (adrenaline, dobutamine or noradrenaline) via a central venous catheter and are eligible for nutritional support started within 24 hours after endotracheal intubation (or within 24 hours after ICU admission if intubation occurred before ICU admission).

Exclusion criteria are IMV started more than 24 hours after endotracheal intubation or ICU admission; surgery on the gastrointestinal tract within the past month; history of gastrectomy, esophagectomy, duodenopancreatectomy, bypass surgery, gastric banding or short bowel syndrome; gastrostomy or jejunostomy; specific nutritional needs, such as preexisting long-term home-based EN or PN; active gastrointestinal bleeding; treatment limitation decisions; adult under guardianship; pregnancy; breastfeeding; current inclusion in a randomized trial designed to compare EN and PN; and/or contraindication to PN (known hypersensitivity to egg or soybean proteins or to another component, inborn error in amino acid metabolism or severe familial dyslipidemia affecting triglyceride levels).

All patients receiving IMV and vasoactive drugs for shock within 24 hours after ICU admission are screened for eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days per week.

Randomization

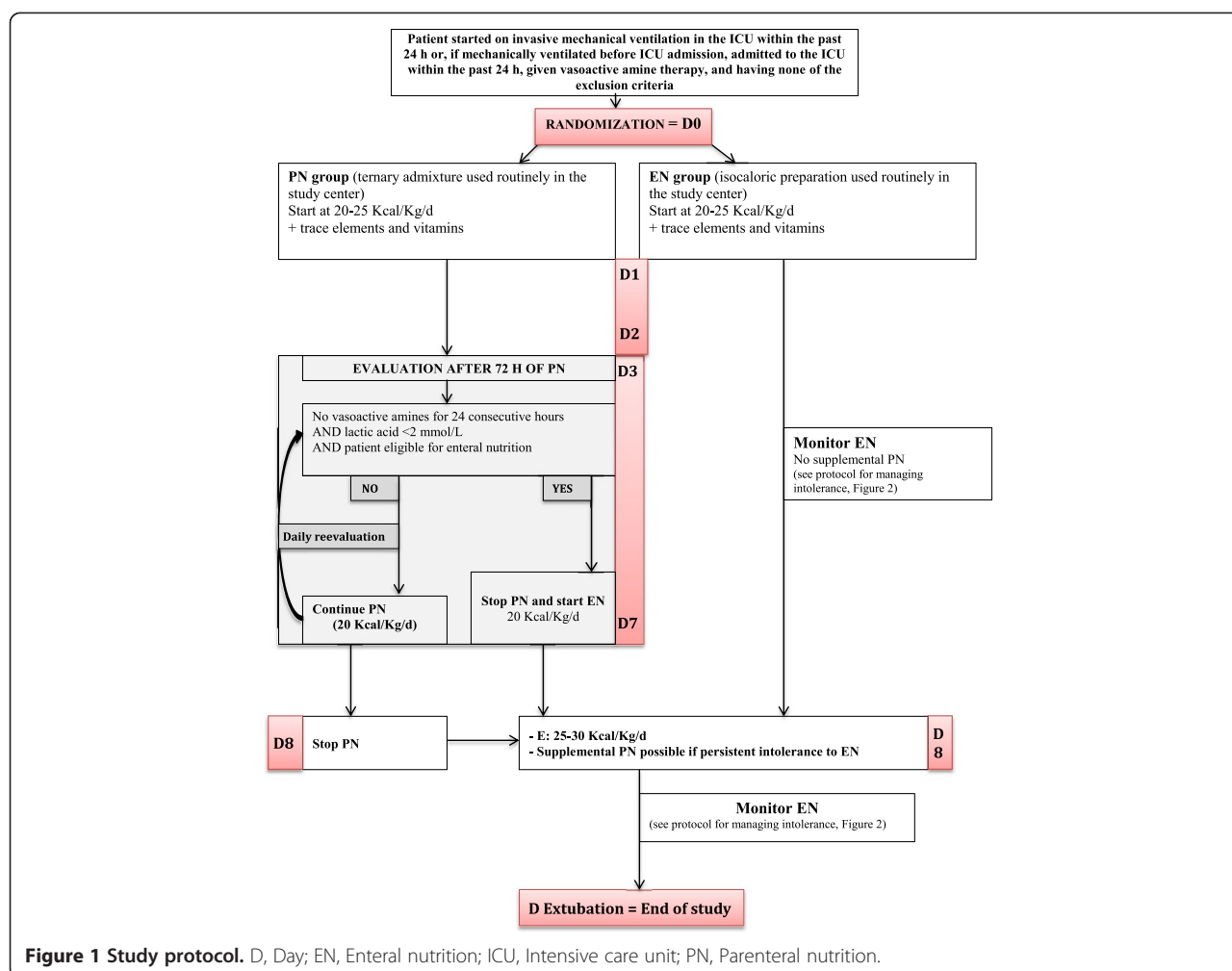
Consecutive eligible patients are randomly allocated in a 1:1 ratio to one of the two treatment groups: the EN group or the PN group. Randomization is stratified by centers. The patients are enrolled in each ICU by the local physicians and a clinical research nurse and/or clinical research assistant. Randomization and concealment are ensured by using a secure, computer-generated, interactive, response system available at each study center and managed by the biometrical unit of the Tours University Hospital, which has no role in recruitment.

Study interventions

The study protocol and randomization arms are detailed in Figure 1.

Parenteral nutrition group

In the PN group, the patients receive first-line PN for at least 72 hours. The route used subsequently depends on the results of the daily hemodynamic evaluations. If the



hemodynamic condition is stable (no vasoactive drugs for 24 consecutive hours and arterial lactic acid level below 2 mmol/L) and the enteral route can be used, PN is stopped and immediately replaced by EN at the flow rate needed to achieve the previously defined calorie target. If, on the contrary, the patient still requires vasoactive drugs and/or the arterial lactic acid level is equal to or greater than 2 mmol/L, PN is continued for a total of 7 days (168 hours). On day 8, in the absence of contraindications to EN, PN is stopped and EN started, regardless of hemodynamic status. Supplemental PN may be added in the event of persistent intolerance to EN precluding achievement of the predefined calorie target.

Enteral nutrition group

In the EN group, the patients receive first-line EN. In the event of persistent gastrointestinal intolerance precluding achievement of the predefined calorie targets, supplemental PN may be added starting on day 8 [3,62]. Isosmotic, isocaloric, normal protein polymeric preparations are used during the first week, after which the

choice of the preparation is at the discretion of the physician at the bedside. To minimize the risk of upper gastrointestinal intolerance and consequently of vomiting, the volume of supplemental water given via the gastric route is as small as possible during the first study week.

Nutritional support protocol

The nutritional support protocol, including measures designed to evaluate tolerance, is standardized as indicated below.

General principles of nutritional support in both study arms

Nutritional support is started as soon as possible after IMV initiation and no later than 24 hours after intubation or after ICU admission in patients intubated before ICU admission. The calorie target for each patient is estimated based on body weight as 20 to 25 kcal/kg/day during the acute phase (day 0 to day 7), then 25–30 kcal/kg/day from day 8 to extubation. The recommended calorie target is 20 kcal/kg/day during the acute phase (day 0 to day 7)

and 30 kcal/kg/day from day 8 to extubation. In obese patients (body mass index (BMI) greater than 30 kg/m²), the body weight yielding a BMI of 30 kg/m² is used to estimate the calorie target.

Nutritional support is prescribed as a flow rate (in milliliters per hour) and started at the flow rate required to achieve the calorie target on day 1 (as opposed to a gradual increase). The feed is delivered continuously over the 24-hour cycle without interruption. Actual feed delivery is monitored regularly by comparing delivered volumes to predefined daily calorie targets. In addition, special attention is directed to avoiding delays. Any interruption in feed delivery is reported to the ICU physician in charge. Usually, nutritional support is not interrupted while transporting the patient. However, when EN or PN must be interrupted (for example, for a specific gastrointestinal or radiological investigation), the flow rate is not increased to compensate for the interruption. All patients are kept in the semirecumbent supine position.

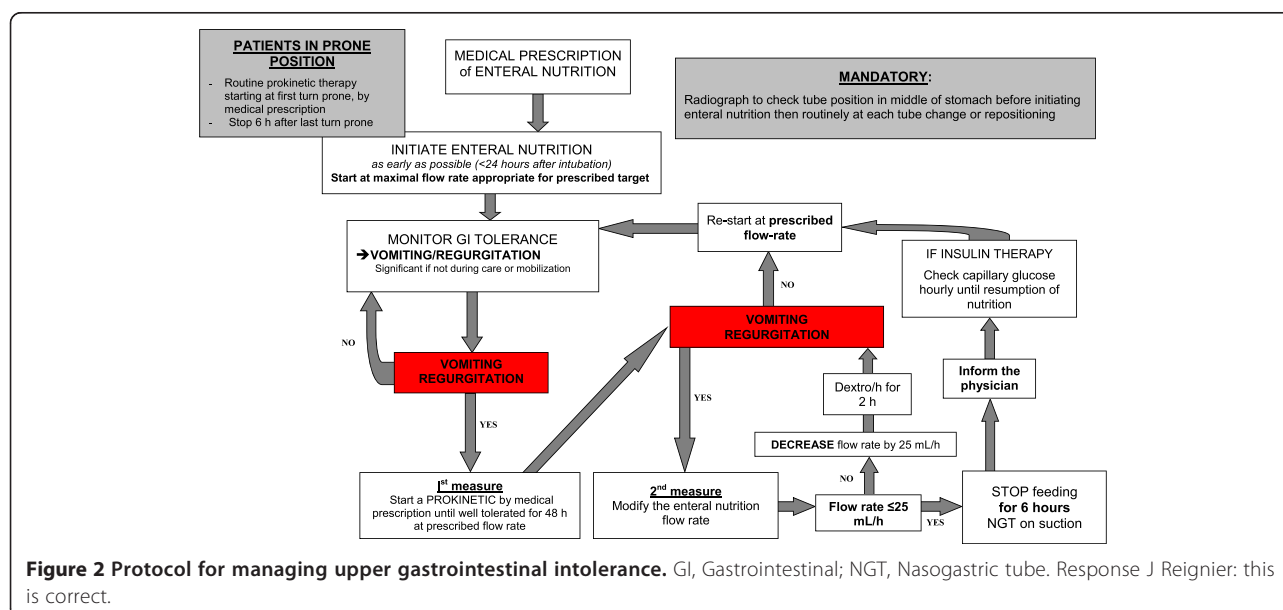
After extubation, regardless of time since randomization, decisions about the continued need for, and optimal route of, nutritional support are made by the physician in charge of the patient. Patients who are reintubated within 7 days after trial inclusion are managed until the end of the acute phase according to the arm to which they were randomized during the first period of intubation. Patients reintubated after the end of the acute phase (day 7) receive EN in the absence of contraindications.

Enteral nutrition

The feed is delivered continuously via a 14-French silicone gastric tube. The tube's position in the middle of the stomach is checked on a radiograph obtained at ICU

admission or immediately after tube placement, as well as when the tube is changed or repositioned. Special attention is directed to the risk of tube obstruction, particularly when administering medications. The tube is flushed regularly with 20 to 30 ml of water.

A predefined protocol is used to manage upper gastrointestinal intolerance to EN (Figure 2). Residual gastric volume is not monitored [63]. EN tolerance is assessed based only on episodes of significant vomiting or regurgitation (passage of feed into the mouth, outside the mouth or into the endotracheal tube in the absence of care procedures or mobilization). Minimal regurgitation or vomiting triggered by tracheal aspiration or oral cavity care is not taken to indicate intolerance. EN intolerance (that is, significant vomiting or regurgitation) leads to the following two measures. First, treatment with a prokinetic agent is to be administered after confirmation that there are no contraindications. The study ICUs use the prokinetic agent of their choice according to their standard practice. The prokinetic agent is continued until EN at the highest prescribed flow rate has been well tolerated for 48 hours. The prokinetic agent is then discontinued. Second, if gastric intolerance persists despite prokinetic therapy, the flow rate is decreased by 25 ml/hr every 6 hours until the signs of intolerance resolve. Therefore, EN is stopped (and the gastric tube placed under suction) only in patients with intolerance despite a flow rate ≤25 ml/hr. All interruptions in EN delivery must be reported to the physician in charge of the patient. EN is resumed at the prescribed flow rate (appropriate to the patient's needs) after 6 hours have elapsed without further signs of intolerance. Patients at high risk for gastric intolerance, such as those turned in



the prone position for acute respiratory distress syndrome, receive prophylactic prokinetic treatment starting at the first turn in the prone position [64,65].

Parenteral nutrition

Ternary admixtures packaged in bags and containing the three groups of macronutrients are used according to standard practice in each participating center. Supplemental electrolytes are provided in a solution separate from the parenteral feed, according to the needs of each patient. PN is delivered continuously via a central venous catheter (CVC). Special attention is directed to preventing infections by complying with the standard protocols for CVC insertion and maintenance followed in each of the participating centers. Proper CVC position is checked routinely on a radiograph.

Additional intakes

Additional water and electrolytes are given intravenously according to the needs of each patient as assessed by the physician in charge and in compliance with standard practice in each study ICU. Intravenous vitamins and trace elements are given according to the needs of each individual patient using the standard preparations and protocols available in each study ICU. These components are not added to the PN bags. Instead, they are given continuously over the 24-hour cycle using a separate intravenous bag and line; if needed, this separate preparation is shielded from light using aluminum foil.

Intestinal transit monitoring

Stool volume and appearance are monitored daily. Constipation (no stool for more than 6 days) or diarrhea (more than 300 ml of liquid stool or more than four loose stools per day) must be reported. Episodes of diarrhea are managed

according to a specific diagnostic and therapeutic protocol (Figure 3) [66].

Diagnosis of ventilator-associated pneumonia

VAP is suspected in patients with new and persistent or progressive lung infiltrates on the chest radiograph, combined with at least two of the following criteria: body temperature $\geq 38.5^{\circ}\text{C}$ or $\leq 35.5^{\circ}\text{C}$, peripheral leukocytosis ($>10,000/\text{mm}^3$) or leukopenia ($<4,000/\text{mm}^3$), and purulent tracheal aspirates. The diagnosis must be confirmed in each participating ICU on the basis of a positive semi-quantitative bacteriological result from a distal respiratory specimen: bronchoalveolar lavage fluid (positive if there are $\geq 10^4$ colony-forming units (cfu)/ml), protected specimen brush (positive if there are $\geq 10^3$ cfu/ml) or tracheo-bronchial aspirate (positive if there are $\geq 10^5$ cfu/ml) [29,67]. VAP episodes are recorded from 48 hours after intubation until day 2 after extubation.

Diagnosis of bowel ischemia

Bowel ischemia is defined in this trial as absent blood flow in one of the main arteries supplying the bowel (superior mesenteric artery, inferior mesenteric artery or celiac artery) with evidence of bowel wall compromise on an imaging study (computed tomography angiography, angiography or magnetic resonance angiography) or the presence of rectosigmoidoscopy- or colonoscopy-based criteria for colonic ischemia according to the Favier classification system (stage I, petechiae; stage II, petechiae and superficial ulcers; and stage III, necrotic ulcers and polypoid lesions) [68].

Data collection and follow-up

At the time of inclusion, the following baseline characteristics are recorded: age, sex, date of ICU admission,

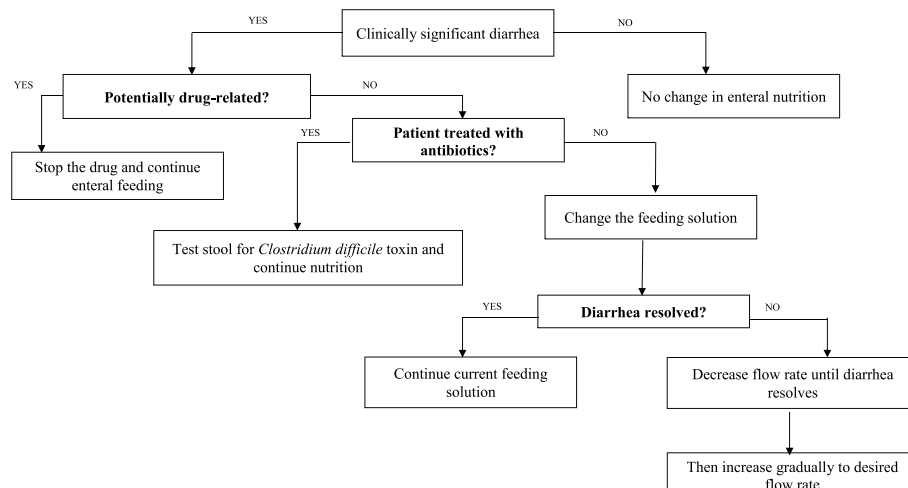


Figure 3 Protocol for diarrhea management.

height, body weight, BMI, primary diagnosis, McCabe score, Knaus score and preexisting comorbidities (including chronic renal failure, liver failure, pulmonary disease and heart failure; malignant disease; and immunosuppression). Use of sedatives, insulin, proton pump inhibitors, dialysis, neuromuscular blockers and gastric prokinetic agents before inclusion are also recorded. The Simplified Acute Physiology Score II is computed 24 hours after ICU admission [69].

The information listed below is recorded daily until extubation or until day 28 during intubation, whichever occurs first.

1. **Nutritional data:** name of the enteral or parenteral preparation, target volume and number of calories, volume and calories delivered per day, vomiting (yes/no, daily), decrease or discontinuation of nutritional support (yes/no), reason for decreasing or discontinuing nutritional support (vomiting, diarrhea, acute colonic pseudo-obstruction, other acute abdominal symptoms, abdominal complication, imaging study, other), stools (yes/no, daily) and diarrhea with its presumed cause (intolerance to nutritional support, medication, *Clostridium difficile*, other).
2. **Treatments:** prokinetic agent, sedation, neuromuscular blockers, catecholamines (dobutamine, noradrenaline or adrenaline), renal replacement therapy, antibiotics, insulin (total dose/24 hr), volume of intravenous fluids (total/24 hr) and gastric antiseptory agents (sucralfate, proton pump inhibitors, histamine receptor antagonists, other).
3. **Laboratory data:** (a) at baseline—hemoglobin, leukocytes, platelets, Na^+ , K^+ , Ca^{2+} , pH, triglycerides, partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood, pH, arterial lactic acid, bicarbonate, urea, creatinine, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase, alkaline phosphatase and total protein; (b) daily from day 1 to day 7 or until extubation— PaO_2 , arterial lactic acid, bilirubin, AST, ALT, γ -glutamyl transpeptidase, alkaline phosphatase, glucose, protein, Na^+ , K^+ , Ca^{2+} , pH, triglycerides and creatinine; (c) on day 1 and on day 7 or the day of extubation—albumin, prealbumin and C-reactive protein levels; daily from day 1 to day 7—Sepsis-related Organ Failure Assessment (SOFA) score [70].
4. **Nosocomial infections** (one data collection form per infection): VAP (date of diagnosis, organism, resistance profile), bacteremia (date of diagnosis, organism, resistance profile), intravascular catheter-related infection (date of diagnosis, organism, resistance profile), urinary tract infection (date of diagnosis,

organism, resistance profile), soft tissue infection (date of diagnosis, organism, resistance profile) and other (type, date of diagnosis, organism, resistance profile).

5. **Invasive devices:** endotracheal tube, intravascular catheters and urinary catheters, with the dates of insertion and removal for each.
6. Each patient is followed until hospital discharge or day 90, whichever occurs first. Vital status is recorded at ICU discharge, at hospital discharge, on day 28 and on day 90. Table 1 is the study flowchart.

Organization of the trial

Funding/support

NUTRIREA-2 is sponsored by the La Roche sur Yon Hospital (Centre Hospitalier de la Vendée, La Roche sur Yon, France) and supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2012, PHRC-12-0184).

Coordination and conduct of the trial

Before the start of patient recruitment procedures, all physicians and other health-care workers in the 44 participating ICUs attended formal training sessions on the study protocol and data collection in the electronic case report form (eCRF). All documents required for the study are available in each ICU. The eCRF is a secure, interactive, web response system available at each study center, provided and managed by the biometrical unit of the Tours University Hospital (CIC INSERM 1415, Tours, France). In each participating ICU, the physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data in the eCRFs. The Clinical Research Unit of the La Roche-sur-Yon Hospital will review the screening forms and clinical data at regular intervals. The principal investigators will meet with the ICU teams to discuss any problems with data collection and protocol compliance and to evaluate study progress. According to French law, the eCRF and database organization have been approved by the appropriate committees (CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé; and CNIL: Commission Nationale de l'Informatique et des Libertés).

Interim analyses

Given the need for a large sample size, two interim analyses are scheduled, one after enrollment of 1,000 patients and the other after enrollment of 2,000 patients. The independent Data Safety Monitoring Board (DSMB) is composed of two physicians and one biostatistician not otherwise involved in the trial. For both interim analyses, the DSMB will have access to unblinded results on

Table 1 Study flowchart

	Inclusion	Day 0 ^a	Day 1 to Day <i>n</i>	End of study	Day 28	Day 90
Eligibility: check inclusion and exclusion criteria	X					
Patient information and consent	X					
Randomization	X					
Demographics	X					
Characteristics		X				
Ventilation		X				
Laboratory tests		X	X			
SOFA score ^b		X	X			
Nutritional evaluation		X	X			
Treatments used		X	X			
Daily calorie intake			X			
Nosocomial infections			X			
Final extubation				X		
Final discontinuation of nutritional support				X		
Survived/died				X	X	X

^aFrom time at inclusion to 11:59 PM. ^bSOFA, Sepsis-related Organ Failure Assessment.

day 28 mortality, variations in SOFA scores from day 1 to day 7, blood bilirubin values and nosocomial infections. The results of the interim analyses will not be disclosed unless they lead the DSMB to request premature trial discontinuation.

Blinding

Blinding of the physicians, nurses and patients to the use of EN and/or PN is not feasible. The absence of blinding cannot have an impact, however, because the primary outcome is objective (day 28 mortality) [71]. Moreover, all VAP diagnoses are adjudicated by an independent blinded committee on the basis of all available clinical, radiological and bacteriological data.

Study outcomes

Primary endpoint

The primary endpoint is all-cause mortality by day 28. Information on this endpoint is collected on the 28th day after patient inclusion in the study. For discharged patients, information on the primary endpoint is collected by a telephone call to the patient at home.

Secondary endpoints

The following are the secondary endpoints of the study:

1. The proportion of patients with at least one VAP episode
2. VAP incidence density per 1,000 days of IMV (that is, ratio of the number of patients with at least one VAP episode during IMV or within 2 days after extubation over the period at risk, defined as

follows: total number of IMV days in patients without VAP or number of IMV days before the first VAP episode in patients with VAP)

3. Number of VAP episodes per patient
4. Proportion of patients with at least one episode of bacteremia and incidence density of bacteremia per 1,000 ICU days
5. Proportion of patients with at least one CVC-related infection and incidence density of CVC-related infections per 1,000 CVC days
6. Proportion of patients with at least one episode of urinary tract infection and incidence density of urinary tract infections per 1,000 urinary catheter days
7. Proportion of patients with at least one soft tissue infection and incidence density of soft tissue infections per 1,000 ICU days
8. Proportion of patients with other nosocomial infections and incidence density of other nosocomial infections per 1,000 ICU days
9. Proportion of patients with at least one nosocomial infection
10. Descriptive bacteriological data (organisms recovered in the overall population of nosocomial infections and antimicrobial resistance profiles)
11. Proportion of patients with at least one episode of vomiting or regurgitation during IMV
12. Proportion of patients with at least one episode of diarrhea
13. Proportion of patients with at least one documented episode of bowel ischemia
14. Number of calories (in kilocalories) delivered enterally and parenterally (daily mean during the

- first week and daily mean throughout the time on IMV)
15. Ratio (as a percentage) of prescribed over delivered calories via the enteral and parenteral routes (daily mean during the first week, daily mean throughout the time on IMV and proportion of patients who achieved their calorie target on each follow-up day)
 16. Volume of liquid feed (in milliliters) delivered (daily mean during the first week and daily mean throughout the time on IMV)
 17. Variations in SOFA scores from day 1 to day 7
 18. ICU mortality, 90-day mortality and hospital mortality
 19. Mean changes in serum albumin, prealbumin and C-reactive protein measured at baseline, at the end of IMV, on day 7 (in patients on IMV for more than 7 days) and at ICU discharge
 20. Proportion of patients with at least one liver dysfunction episode (defined as serum bilirubin >50 µmol/L and/or γ-glutamyl transferase, alkaline phosphatase and/or AST or ALT >3 N) evaluated at the end of IMV, on day 7 (in patients on IMV for more than 7 days) and at ICU discharge
 21. ICU length of stay
 22. Hospital length of stay
 23. Time on IMV
 24. Changes in mean body weight determined at baseline, on day 7 and at ICU discharge

Sample size

The working hypothesis of this randomized controlled trial is that day 28 all-cause mortality in patients admitted to the ICU and treated with IMV and vasoactive drugs will be lower when early nutritional support is provided enterally rather than parenterally. We have determined that 1,427 patients are needed in each group (2,854 patients in all), assuming a 37% day 28 mortality rate in the PN group and a 5% decrease in mortality with early EN (that is, a 32% day 28 mortality rate), with a 4.9% two-sided type I error rate and 80% power, given that two interim analyses will be performed, and given that the statistical tests will be performed using significance thresholds of 0.001 for the two interim analyses and 0.049 for the final analysis according to the Peto's method [72]. The mortality rates used for the sample size estimation are those obtained in the NUTRIREA-1 randomized controlled trial performed in nine centers using similar inclusion criteria [63].

Statistical analysis

The statistical analysis will follow the intention-to-treat approach; that is, each patient will remain in the group assigned by randomization, regardless of subsequent events. A statistical analysis report will be written to describe all the

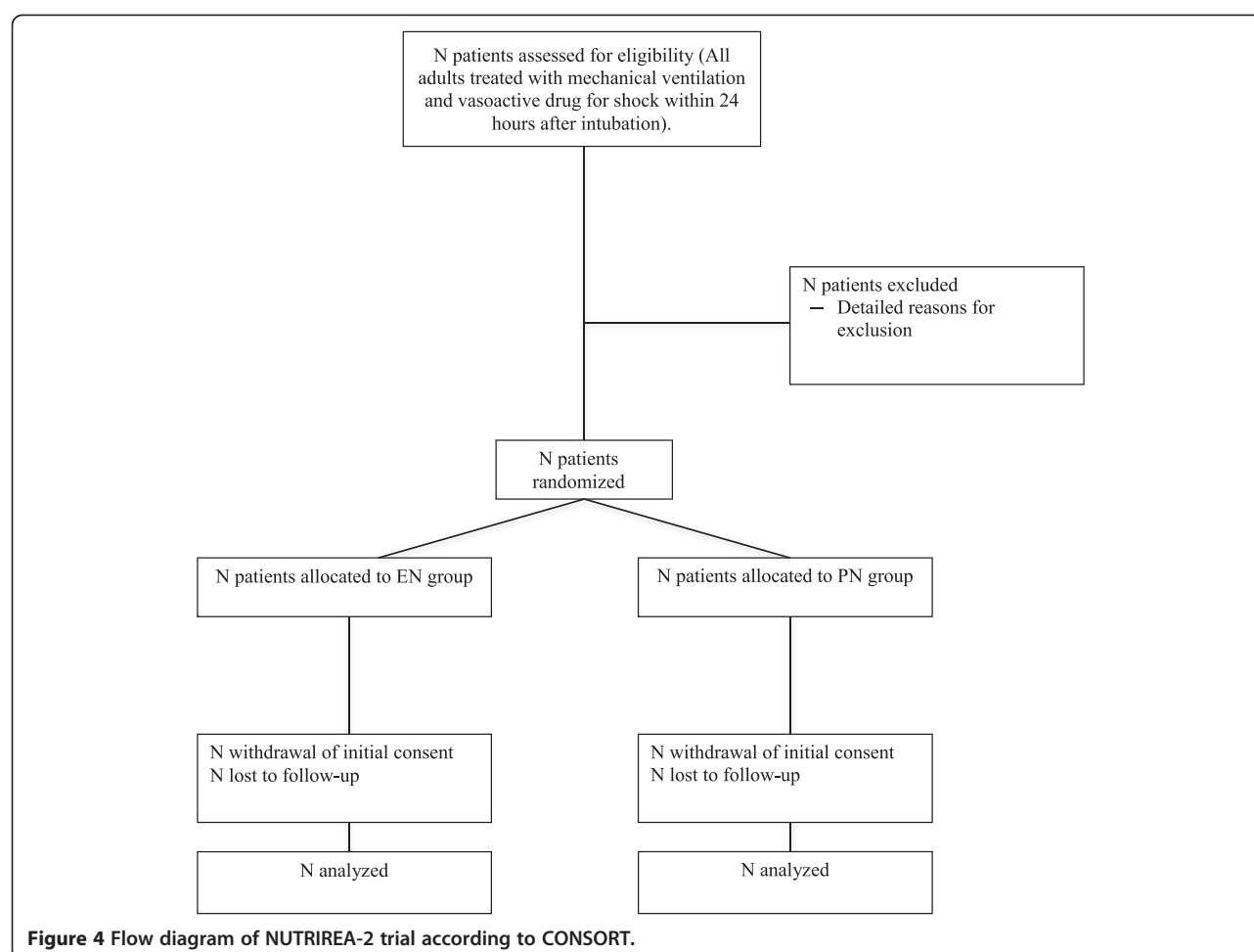
findings according to CONSORT statement recommendations, taking into account the specific features of the trial, most notably the nonpharmacological nature of the intervention (Figure 4). The baseline features of the groups established by randomization will be compared using descriptive statistics. No statistical tests will be performed.

Primary endpoint

Day 28 mortality will be reported as the point estimates with the 95% confidence intervals in each group and compared between the two groups using the χ^2 test.

Secondary endpoints

The analysis of patients with at least one nosocomial infection will rely on the competing-risk concept with death as the competing risk, because patients who have died cannot experience nosocomial infections. For the proportion of patients with at least one VAP episode, the method used will be the same as that used for nosocomial infections, with not only death as a competing risk but also time to extubation +2 days, because, after this point, any episode of pneumonia would not be classified as a VAP episode. The number of VAP episodes per patient will be analyzed using a negative binomial regression model with no offset variable. Bacteremia, CVC-related infections, urinary tract infections and soft tissue infections will be analyzed using the same method as that used for the pooled nosocomial infections. For descriptive bacteriological data (organisms recovered with their resistance profiles for each nosocomial infection), only descriptive analyses will be performed. For the proportion of patients with at least one episode of vomiting or regurgitation, diarrhea, constipation, documented acute colonic pseudo-obstruction (Ogilvie syndrome), documented bowel ischemia, mechanical complication of CVC insertion and liver dysfunction, the method used will be the same as that employed for the nosocomial infections. Changes over time in calories delivered daily by the enteral and parenteral routes and changes over time in enteral and parenteral feed volumes delivered daily will be compared between the two groups using a mixed linear model, after data transformation if necessary. The proportions of patients who achieved their daily calorie target will be compared between the two groups using a logistic random-effects model. Day 90 mortality will be analyzed in the same way as day 28 mortality. For ICU and hospital mortality rates, competing-risk models will be used, as ICU discharge and hospital discharge compete with death during the stay. Changes over time in nutritional markers and body weight will be analyzed using the method described above for the number of calories delivered. ICU length of stay, hospital length of stay and IMV duration will be compared between the two groups using nonparametric Wilcoxon tests.



Discussion

Nutritional support, whether delivered enterally or parenterally, is among the first-line treatments used routinely in the ICU. Guidelines state that the enteral route should be preferred to the parenteral route and should be used early in the course of the critical illness. However, guidelines are poorly followed and are not supported by adequately designed clinical studies. To date, no study has produced definitive information on the risks and benefits of EN versus PN in critical care. NUTRIREA-2 is the first large randomized controlled trial designed to evaluate the hypothesis that early EN decreases mortality compared to PN in ICU patients. The NUTRIREA-2 sample size provides sufficient statistical power to detect a significant mortality rate decrease on day 28. The study focuses on patients receiving IMV and vasoactive drugs for shock, because such very severely ill ICU patients with multiple organ failure may be most likely to benefit from early EN compared to early PN. Furthermore, at present, many of these patients do not receive early nutritional support or early PN, despite being eligible for EN. However, these

patients are considered at high risk for complications of EN, such as upper gastrointestinal intolerance, VAP or bowel ischemia. If the study hypothesis is confirmed, early EN will become the reference standard for initial nutritional support in patients with shock who are receiving IMV, and this change will decrease morbidity and mortality rates and improve patient outcomes.

Trial status

Enrollment is ongoing. Inclusion started in March 2013. By 10 March 2014, 1,000 patients had been included. The first interim analysis was performed on these 1,000 patients and led the DSMB to recommend continuation of the study. By 15 December 2014, 1,795 patients had been included. Recruitment is expected to be complete by November 2015.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (French Advisory Committee on Healthcare Research Data Handling); CépIdC: Centre

d'épidémiologie sur les causes médicales de décès (Epidemiology Center for Causes of Death); CNIL: Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority); CVC: Central venous catheter; DSMB: Data Safety Monitoring Board; eCRF: Electronic case report form; EN: Enteral nutrition; ICU: intensive care unit; PN: Parenteral nutrition; SOFA: Sepsis-related Organ Failure Assessment; SRLF: Société de Réanimation de Langue Française (French-Speaking Society for Critical Care); VAP: Ventilator-associated pneumonia.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LB and JeR prepared the first draft of the manuscript. LB, JeR, JBL, EG, SM, ALG and BG wrote the manuscript. LB, JeR, EG, ALG and BG participated in designing the NUTRIREA-2 study. ALG and BG wrote the statistical analysis plan and performed the sample size estimation. JeR, EG and SM obtained funding for the study. LB, JBL, HD, PA, MS, GP, HNB, OG, AAH, SG, JPR, JPO, VM, CS, DT, SN, EP, AEK, MJ, VL, NR, FB, VD, FG, CG, KA, AB, NA, JPM, EC, BG, MD, BM, RR, FM, PL, DS, MD, VB, JEH, FM, JD, EM, JaR and JeR contributed to acquisition of the study data. All authors revised the manuscript for important intellectual content, and all authors read and approved the final manuscript.

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References

- Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P: **Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients.** *JPEN J Parenter Enteral Nutr* 2003, **27**:355–373.
- Kreymann KG, Berger MM, Deutz NEP, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, DGEM (German Society for Nutritional Medicine), Ebner C, Hartl W, Heymann C, Spies C: **ESPEN Guidelines on Enteral Nutrition: intensive care.** *Clin Nutr* 2006, **25**:210–223.
- McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G, the A.S.P.E.N. Board of Directors, the American College of Critical Care Medicine: **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.).** *JPEN J Parenter Enteral Nutr* 2009, **33**:277–316.
- Thuong M, Leterre S: **[Experts recommendations of the Société de Réanimation de Langue Française: enteral nutrition in critical care] [Article in French].** *Reanimation* 2003, **12**:350–354.
- Beier-Holgersen R, Boesby S: **Influence of postoperative enteral nutrition on postsurgical infections.** *Gut* 1996, **39**:833–835.
- Bortenschlager L, Roberts PR, Black KW, Zaloga GP: **Enteral feeding minimizes liver injury during hemorrhagic shock.** *Shock* 1994, **2**:351–354.
- Gianotti L, Alexander JW, Nelson JL, Fukushima R, Pyles T, Chalk CL: **Role of early enteral feeding and acute starvation on postburn bacterial translocation and host defense: prospective, randomized trials.** *Crit Care Med* 1994, **22**:265–272.
- Binnekade JM: **Review: enteral nutrition reduces infections, need for surgical intervention, and length of hospital stay more than parenteral nutrition in acute pancreatitis.** *Evid Based Nurs* 2005, **8**:19.
- Braunschweig CL, Levy P, Sheean PM, Wang X: **Enteral compared with parenteral nutrition: a meta-analysis.** *Am J Clin Nutr* 2001, **74**:534–542.
- 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**:843–848.
- Pettignano R, Heard M, Davis R, Labuz M, Hart M: **Total enteral nutrition versus total parenteral nutrition during pediatric extracorporeal membrane oxygenation.** *Crit Care Med* 1998, **26**:358–363.

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**:960–967.
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**:2018–2027.
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**:261–268. A published erratum appears in *Am J Crit Care* 2010, 19:488.
15. Marik PE, Zaloga GP: **Early enteral nutrition in acutely ill patients: a systematic review.** *Crit Care Med* 2001, **29**:2264–2270. A published erratum appears in *Crit Care Med* 2002, 30:725.
16. Cahill NE, Murch L, Jeejeebhoy K, McClave SA, Day AG, Wang M, Heyland DK: **When early enteral feeding is not possible in critically ill patients: results of a multicenter observational study.** *JPEN J Parenter Enteral Nutr* 2011, **35**:160–168.
17. Elke G, Schädler D, Engel C, Bogatsch H, Frerichs I, Ragaller M, Scholz J, Brunkhorst FM, Löffler M, Reinhart K, Weiler N, the German Competence Network Sepsis (SepNet): **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**:1762–1767.
18. Quenot JP, Plantevefe G, Baudel JL, Camilatto I, Bertholet E, Cailliod R, Reignier J, Rigaud JP: **Bedside adherence to clinical practice guidelines for enteral nutrition in critically ill patients receiving mechanical ventilation: a prospective, multi-centre, observational study.** *Crit Care* 2010, **14**:R37.
19. Desai SV, McClave SA, Rice TW: **Nutrition in the ICU: an evidence-based approach.** *Chest* 2014, **145**:1148–1157.
20. Blaser AR, Starkopf J, Kirsimägi Ü, Deane AM: **Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis.** *Acta Anaesthesiol Scand* 2014, **58**:914–922.
21. Bosscha K, Nieuwenhuijs VB, Vos A, Samsom M, Roelofs JM, Akkermans LM: **Gastrointestinal motility and gastric tube feeding in mechanically ventilated patients.** *Crit Care Med* 1998, **26**:1510–1517.
22. Chapman MJ, Fraser RJ, Bryant LK, Vozzo R, Nguyen NQ, Tam W, Zacharakis B, Davidson G, Butler R, Horowitz M: **Gastric emptying and the organization of antro-duodenal pressures in the critically ill.** *Neurogastroenterol Motil* 2008, **20**:27–35.
23. Dive A, Moulart M, Jonard P, Jamart J, Mahieu P: **Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study.** *Crit Care Med* 1994, **22**:441–447.
24. Kölbel CB, Rippel K, Klar H, Singer MV, van Ackern K, Fiedler F: **Esophageal motility disorders in critically ill patients: a 24-hour manometric study.** *Intensive Care Med* 2000, **26**:1421–1427.
25. Landzinski J, Kiser TH, Fish DN, Wischmeyer PE, McLaren R: **Gastric motility function in critically ill patients tolerant vs intolerant to gastric nutrition.** *JPEN J Parenter Enteral Nutr* 2008, **32**:45–50.
26. McClave SA, DeMeo MT, DeLegge MH, DiSario JA, Heyland DK, Maloney JP, Metheny NA, Moore FA, Scolapio JS, Spain DA, Zaloga GP: **North American Summit on Aspiration in the Critically Ill Patient: Consensus Statement.** *JPEN J Parenter Enteral Nutr* 2002, **26**(6 Suppl):S80–S85.
27. Ritz MA, Fraser R, Tam W, Dent J: **Impacts and patterns of disturbed gastrointestinal function in critically ill patients.** *Am J Gastroenterol* 2000, **95**:3044–3052.
28. Schuster-Bruce M: **Gastric emptying in the critically ill.** *Crit Care Med* 2001, **29**:1293–1294.
29. Chastre J, Fagon JY: **Ventilator-associated pneumonia.** *Am J Respir Crit Care Med* 2002, **165**:867–903.
30. Villet S, Chiolerio RL, Bollmann MD, Revelly JP, Cayeux MC, Delarue J, Berger MM: **Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients.** *Clin Nutr* 2005, **24**:502–509.
31. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK: **The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study.** *Intensive Care Med* 2009, **35**:1728–1737. A published erratum appears in *Intensive Care Med* 2009, 35:1821.
32. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C: **Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial.** *Lancet* 2013, **381**:385–393.
33. van Schijndel RJM, Weijs PJM, Koopmans RH, Sauerwein HP, Beishuizen A, Girbes ARJ: **Optimal nutrition during the period of mechanical ventilation decreases mortality in critically ill, long-term acute female patients: a prospective observational cohort study.** *Crit Care* 2009, **13**:R132.
34. Tsai JR, Chang WT, Sheu CC, Wu YJ, Sheu YH, Liu PL, Ker CG, Huang MC: **Inadequate energy delivery during early critical illness correlates with increased risk of mortality in patients who survive at least seven days: a retrospective study.** *Clin Nutr* 2011, **30**:209–214.
35. Weijs PJM, Stapel SN, de Groot SD, Driessen RH, de Jong E, Girbes ARJ, Strack van Schijndel RJM, Beishuizen A: **Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study.** *JPEN J Parenter Enteral Nutr* 2012, **36**:60–68.
36. Adam S, Batson S: **A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK.** *Intensive Care Med* 1997, **23**:261–266.
37. 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–R225.
38. de Beaux I, Chapman M, Fraser R, Finnis M, De Keulenaer B, Liberalli D, Satanek M: **Enteral nutrition in the critically ill: a prospective survey in an Australian intensive care unit.** *Anaesth Intensive Care* 2001, **29**:619–622.
39. De Jonghe B, Appere-De-Vechi C, Fournier M, Tran B, Merrer J, Melchior JC, Outin H: **A prospective survey of nutritional support practices in intensive care unit patients: What is prescribed? What is delivered?** *Crit Care Med* 2001, **29**:8–12.
40. Heyland D, Cook DJ, Winder B, Brylowski L, Van de Mark H, Guyatt G: **Enteral nutrition in the critically ill patient: a prospective survey.** *Crit Care Med* 1995, **23**:1055–1060.
41. Heyland DK, Tougas G, King D, Cook DJ: **Impaired gastric emptying in mechanically ventilated, critically ill patients.** *Intensive Care Med* 1996, **22**:1339–1344.
42. McClave SA, Sexton LK, Spain DA, Adams JL, Owens NA, Sullins MB, Blandford BS, Snider HL: **Enteral tube feeding in the intensive care unit: factors impeding adequate delivery.** *Crit Care Med* 1999, **27**:1252–1256.
43. 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**:1955–1961.
44. Montejó JC: **Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study.** *Crit Care Med* 1999, **27**:1447–1453.
45. Röhm KD, Schöllhorn T, Boldt J, Wolf M, Papsdorf M, Piper SN: **Nutrition support and treatment of motility disorders in critically ill patients – results of a survey on German intensive care units.** *Eur J Anaesthesiol* 2008, **25**:58–66.
46. Gatt M, MacFie J, Anderson AD, Howell G, Reddy BS, Suppiah A, Renwick I, Mitchell CJ: **Changes in superior mesenteric artery blood flow after oral, enteral, and parenteral feeding in humans.** *Crit Care Med* 2009, **37**:171–176.
47. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD: **Acute mesenteric ischemia: a clinical review.** *Arch Intern Med* 2004, **164**:1054–1062.
48. Rokyta R Jr, Matějovič M, Kroužeký A, Novák I: **Enteral nutrition and hepatopulmonary region in critically ill patients - friends or foes?** *Physiol Res* 2003, **52**:31–37.
49. Thibault R, Pichard C, Wernerman J, Bendjelid K: **Cardiogenic shock and nutrition: safe?** *Intensive Care Med* 2011, **37**:35–45.
50. Stöckmann H, Roblick UJ, Kluge N, Kunze U, Schimmelpenninck H, Kujath P, Müller G, Bruch HP: **[Diagnosis and therapy of non-occlusive mesenteric ischemia (NOMI)] [Article in German].** *Zentralbl Chir* 2000, **125**:144–151.
51. Yasuhara H: **Acute mesenteric ischemia: the challenge of gastroenterology.** *Surg Today* 2005, **35**:185–195.
52. Bradbury AW, Britten J, McBride K, Ruckley CV: **Mesenteric ischaemia: a multidisciplinary approach.** *Br J Surg* 1995, **82**:1446–1459.
53. Schoots IG, Koffeman GI, Legemate DA, Levi M, van Gulik TM: **Systematic review of survival after acute mesenteric ischaemia according to disease aetiology.** *Br J Surg* 2004, **91**:17–27.
54. Braga M, Gianotti L, Costantini E, Di Francesco A, Succi C, Paganelli G, Ossi C, Di Carlo V: **Impact of enteral nutrition on intestinal bacterial translocation and mortality in burned mice.** *Clin Nutr* 1994, **13**:256–261.
55. 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**:1545–1548.
56. Marik PE, Zaloga GP: **Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis.** *BMJ* 2004, **328**:1407.

57. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, Kellum JM Jr, Welling RE, Moore EE: **Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis.** *Ann Surg* 1992, **216**:172–183.
58. Peter JV, Moran JL, Phillips-Hughes J: **A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients.** *Crit Care Med* 2005, **33**:213–220.
59. 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.
60. Casaer MP, Van den Berghe G: **Nutrition in the acute phase of critical illness [author reply].** *N Engl J Med* 2014, **370**:2450–2451.
61. Ziegler TR: **Nutrition support in critical illness—bridging the evidence gap.** *N Engl J Med* 2011, **365**:562–564.
62. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G: **Early versus late parenteral nutrition in critically ill adults.** *N Engl J Med* 2011, **365**:506–517.
63. Reignier J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, Clavel M, Frat JP, Plantefeve G, Quenot JP, Lascarrou JB, the Clinical Research in Intensive Care and Sepsis (CRICS) Group: **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**:249–256.
64. Reignier J, Dimet J, Martin-Lefevre L, Bontemps F, Fiancette M, Clementi E, Lebert C, Renard B: **Before-after study of a standardized ICU protocol for early enteral feeding in patients turned in the prone position.** *Clin Nutr* 2010, **29**:210–216.
65. Reignier J, Thenoz-Jost N, Fiancette M, Legendre E, Lebert C, Bontemps F, Clementi E, Martin-Lefevre L: **Early enteral nutrition in mechanically ventilated patients in the prone position.** *Crit Care Med* 2004, **32**:94–99.
66. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, the Nutrition Guidelines Investigators of the ANZICS Clinical Trials Group, Dobb G: **Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial.** *JAMA* 2008, **300**:2731–2741.
67. Hubmayr RD, Burchardi H, Elliot M, Fessler H, Georgopoulos D, Jubran A, Limper A, Pesenti A, Rubinfeld G, Stewart T, Villar J: **Statement of the 4th International Consensus Conference in Critical Care on ICU-Acquired Pneumonia—Chicago, Illinois, May 2002.** *Intensive Care Med* 2002, **28**:1521–1536.
68. Favier C, Bonneau HP, Tran Minh V, Devic J: **[Endoscopic diagnosis of regressive ischemic colitis: endoscopic, histologic and arteriographic correlations] [Article in French].** *Nouv Presse Med* 1976, **5**:77–79.
69. 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**:2957–2963. A published erratum appears in *JAMA* 1994, **271**:1321.
70. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG: **The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure.** *Intensive Care Med* 1996, **22**:707–710.
71. Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, Als-Nielsen B, Balk EM, Gluud C, Gluud LL, Ioannidis JP, Schulz KF, Beynon R, Welton NJ, Wood L, Moher D, Deeks JJ, Sterne JA: **Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials.** *Ann Intern Med* 2012, **157**:429–438.
72. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG: **Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design.** *Br J Cancer* 1976, **34**:585–612.

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