CLINICAL TRIAL PROTOCOL

NUTRIREA-2

TRIAL IDENTIFIER **STRATEGY**	– Early nutritional support in mechanically ventilated patients: enteral vs. parenteral
FULL TITLE	Impact of Early Enteral vs. Parenteral Nutrition on Mortality in Patients Requiring Mechanical Ventilation and Catecholamines: Multicenter Randomized Controlled Trial (NUTRIREA-2)
TARGET POPULATION	Patients receiving endotracheal mechanical ventilation and one or more vasoactive agents
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VERSION OF THE PROTOCOL	Version 5.1
DATE OF THE PROTOCOL	December 12, 2014
ETHICS COMMITTEE (*Comité de Protection des Personnes*, *CPP*)	Poitiers - Ouest III (Approved on Dec. 21, 2014)
FRENCH HEALTHCARE PRODUCT SAFETY AGENCY (AFSSAPS)	Not applicable

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SIGNATURE OF THE CHIEF INVESTIGATOR

I have read all the pages of the clinical trial protocol. I confirm that this protocol contains all the information needed to conduct the trial. I undertake to conduct the trial in compliance with the protocol and with the terms and conditions defined in the protocol.

I also undertake that the investigators and other qualified members of my team will have access to copies of this protocol and to the documents relevant to the conduct of the trial, in order to ensure that they can work in compliance with the rules set forth in this protocol.

NAME: Dr Reignier

Signature: …….. Date: _____

SYNOPSIS

TITLE	Impact of Early Enteral vs. Parenteral Nutrition on Mortality in Patients Requiring Mechanical Ventilation and Catecholamines: Multicenter Randomized Controlled Trial (NUTRIREA-2)
KEYWORDS	Nutritional support. Intensive care. Intensive care units. Enteral nutrition. Parenteral nutrition. Shock.
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VERSION OF THE PROTOCOL	Version #3
METHODOLOGY / STUDY DESIGN	Multicenter randomized controlled trial without blinding
STUDY TYPE	Evaluation of standard care
RATIONALE / SETTING	Nutritional support is a mainstay of the management of patients receiving invasive mechanical ventilation and the most commonly prescribed treatment in intensive care units (ICUs). Malnutrition in critically ill patients is associated with an increased risk of infection, delayed wound healing, longer times on mechanical ventilation, longer ICU stays and, probably, a higher risk of death. Recommendations issued by international professional organizations consistently indicate that enteral nutrition should be preferred over parenteral nutrition whenever possible and that nutritional support should be started as early as possible after the initiation of mechanical ventilation. Numerous studies suggest that early enteral nutrition may be associated with lower nosocomial infection rates, a decreased risk of progression to multiorgan failure, shorter hospital stays, and decreased hospital costs, compared to parenteral nutrition. Furthermore, evidence from observational studies suggests lower mortality rates with the enteral route compared to the parenteral route. However, recent studies showed chronic suboptimal use of enteral nutrition, as well as considerable variability in nutritional management across ICUs and across patients in a given unit. Failure to initiate early nutritional support via any modality is common, the calorie targets are frequently inconsistent, and routine use of first-line enteral nutrition is far from being the rule. As a result, malnutrition remains common among ICU patients receiving invasive mechanical ventilation. This fact is ascribable both to the difficulty of initiating early enteral nutrition in mechanically ventilated patients and to the conflicting results of studies comparing the enteral and parenteral routes. Manifestations of gastrointestinal intolerance occur in about 50% of patients. More specifically, regurgitation affects 8% to 27% of patients and may be associated with an increased risk of ventilator-associated pneumonia.

	In addition, the safety of enteral nutrition in patients with circulatory failure, particularly those with low splanchnic blood flow, remains in doubt. In healthy individuals, enteral nutrition increases blood flow in the superior mesenteric artery by over 50%. As a result, in patients with circulatory failure, enteral nutrition may induce nonocclusive mesenteric ischemia, a condition associated with mortality rates of 70% to 100%. Although these potential complications have not been convincingly linked to enteral nutrition, they lead many physicians to delay the initiation of nutritional support by several days or to prefer parenteral nutrition at the acute phase of the management of critically ill patients and/or of patients with shock. This attitude is strengthened by the absence of a vast multicenter randomized trial evaluating the impact of early enteral nutrition on outcomes of patients receiving mechanical ventilation. Current recommendations are based on observational or retrospective data and on studies that have inadequate statistical power. Thus, several recent editorials have emphasized the need for well-designed clinical trials capable of resolving current uncertainties about the nutritional management of mechanically ventilated patients. A recent randomized controlled trial found that parenteral nutrition added to inadequate enteral nutrition was associated with longer stays and higher infection rates while failing to affect mortality when started early instead of at the end of the first week in the ICU. An as yet unpublished study from Switzerland investigated the same topic and found contrary results. These studies fail to establish that the enteral route is superior over the parenteral route at the acute phase. Choosing between these two routes is among the crucial unresolved issues in the management of mechanically ventilated patients in the ICU. The working hypothesis for the present study is that, compared to early parenteral nutrition, early enteral nutrition is associated with lower mortality rates in patients receiving invasive mechanical ventilation and vasoactive agents for shock. **Ancillary studies:** The NUTRIREA2 trial provides the opportunity to answer two additional questions, via an ancillary study for each. – *Ancillary study 1. Is enteral nutrition associated with better preservation of gut mucosa integrity compared to parenteral nutrition?* Published data suggest that enteral nutrition may be associated with improved preservation of the gut lymphoid tissues and gut immune function, as well as with decreased gut mucosa permeability, thereby diminishing the risk of organ failure. Citrulline is an amino acid produced from glutamine by small-bowel enterocytes. Plasma citrulline levels reflect functional enterocyte mass. Intestinal fatty acid-binding protein (I-FABP, also known as FABP2) is a small protein found in the cytosol of small-bowel enterocytes. Plasma I-FABP is normally undetectable and, when elevated, constitutes a reliable marker for enterocyte damage. The hypothesis underlying this ancillary study is that first-line enteral nutrition is associated with improved gut mucosa integrity and function compared to parenteral nutrition. – *Ancillary study 2. Is enteral nutrition associated with a higher risk of gastric-content aspiration compared to parenteral nutrition?* As indicated above, a common obstacle to enteral nutrition is gastrointestinal intolerance, with regurgitations potentially responsible for gastric-content aspiration. Several studies involving technetium 99m (^{99m}Tc) labeling of gastric contents have established that gastric-

	fluid microaspiration is common in critically ill patients receiving both endotracheal ventilation and enteral nutrition. However, to our knowledge, no studies have specifically addressed the role for enteral nutrition in the occurrence of microaspiration. The objective of this ancillary study is to compare the frequency of gastric-content microaspiration in patients given enteral versus parenteral nutrition during the NUTRIREA2 trial. The new knowledge of risk factors for microaspiration provided by this study may help to improve strategies for preventing microaspiration and ventilator-associated pneumonia (VAP).
PRIMARY OBJECTIVE	To investigate whether a strategy involving early first-line enteral nutrition decreases day-28 all-cause mortality in patients receiving mechanical ventilation and vasoactive agents for shock, compared to a strategy of early first-line parenteral nutrition.
SECONDARY OBJECTIVES	The secondary objectives are to compare the following in the two groups: ▪ proportion of patients with at least one VAP episode ▪ VAP incidence density ▪ number of VAP episodes ▪ rates and incidence densities of other nosocomial infections: o bloodstream infections (BSI): proportion of patients with at least one BSI episode, BSI incidence density o central venous catheter (CVC)-related infections: proportion of patients with at least one CVC-related infection, incidence density of CVC-related infections o urinary tract infections: proportion of patients with at least one urinary tract infection, incidence density of urinary tract infections ▪ proportion of patients with at least one nosocomial infection ▪ descriptive bacteriological data (organisms recovered and antibiotic resistance profile for each nosocomial infection) ▪ proportion of patients with at least one episode of regurgitation or vomiting ▪ proportion of patients with diarrhea ▪ proportion of patients with constipation ▪ proportion of patients with a documented episode of bowel ischemia ▪ number of calories administered per day by the enteral and parenteral routes ▪ volume of enteral and parenteral feeds administered per day ▪ ratio of prescribed versus delivered calories ▪ ICU mortality, hospital mortality, and day-90 mortality ▪ time-course of nutritional markers during follow-up (measured at discontinuation of mechanical ventilation, on day 7 in patients receiving mechanical ventilation for more than 7 days, and at ICU discharge) ▪ proportion of patients with at least one episode of liver dysfunction (evaluated at discontinuation of mechanical ventilation, on day 7 in patients receiving mechanical ventilation for more than 7 days, and at ICU discharge) ▪ ICU stay length ▪ hospital stay length ▪ total time spent on mechanical ventilation ▪ change in body weight from admission to day 7 and to ICU

	discharge
OBJECTIVES OF THE ANCILLARY STUDIES	– *Ancillary study 1*. To demonstrate that a strategy involving early first-line enteral nutrition is associated with improved preservation of gut mucosa integrity, as assessed based on the plasma citrulline level at H72, compared to a strategy involving early first-line parenteral nutrition – *Ancillary study 2.* To evaluate the impact of enteral nutrition on microaspiration of gastric content and pharyngeal secretions
PRIMARY OUTCOME MEASURE	All cause day-28 mortality
SECONDARY OUTCOME MEASURES	▪ proportion of patients with at least one episode of ventilator-associated pneumonia (VAP) ▪ VAP incidence density per 1000 days of mechanical ventilation ▪ number of VAP episodes per patient ▪ proportion of patients with at least one bloodstream infection (BSI) and incidence density per 1000 ICU days ▪ proportion of patients with at least one central venous catheter (CVC)-related infection and incidence density per 1000 CVC days ▪ proportion of patients with at least one urinary tract infection and incidence density per 1000 urinary-catheter days ▪ proportion of patients with at least one soft tissue infection and incidence density per 1000 ICU days ▪ proportion of patients with at least one nosocomial infection ▪ descriptive bacteriological data (organisms recovered and antibiotic resistance profile for each nosocomial infection) ▪ proportion of patients with at least one episode of vomiting ▪ proportion of patients with at least one episode of diarrhea ▪ proportion of patients with an episode of acute colonic pseudoobstruction ▪ proportion of patients with a documented episode of bowel ischemia ▪ number of calories (in Kcal) given enterally and parenterally: o time-course of mean daily values over the first week o time-course of mean daily values throughout the time spent on mechanical ventilation ▪ ratio of prescribed calories over calories delivered enterally and parenterally (as percentages): o time-course of mean daily values over the first week o time-course of mean daily values throughout the time spent on mechanical ventilation o proportion of patients in whom the calorie target was achieved on each day ▪ volume of feed (in mL) administered: o time-course of mean daily values over the first week o time-course of mean daily values throughout the time spent on mechanical ventilation ▪ ICU mortality, hospital mortality, 90-day mortality ▪ mean changes in serum albumin, prealbumin, transthyretin, and C-reactive protein between study inclusion and mechanical ventilation discontinuation, day 7 (in patients on mechanical ventilation for more than 7 days), and ICU discharge ▪ proportion of patients with at least one episode of liver dysfunction at mechanical ventilation discontinuation, on day 7 (in patients on mechanical ventilation for more than 7 days), and at ICU discharge

	▪ ICU stay length ▪ hospital stay length ▪ total time spent on mechanical ventilation ▪ mean change in body weight from admission to day 7 and to ICU discharge
OUTCOME MEASURES FOR THE ANCILLARY STUDIES	▪ <u>Ancillary study 1</u> *Primary outcome measure:* Plasma citrulline level at H72 *Secondary outcome measures*: SOFA score; plasma levels of citrulline and I-FABP on D0, D3, and D8; proportion of patients whose plasma I-FABP is ≥100 pg/mL on D0, D3, and D8; proportion of patients whose plasma citrulline is ≤10 µL/L on D0, D3, and D8; mean plasma I-FABP; mean plasma citrulline; proportion of patients with at least one episode of bacteremia; proportion of patients with at least one episode of gastrointestinal intolerance; proportion of patients with at least one episode of diarrhea; in the enteral-nutrition group, cumulative calorie intake over the first 3 days and on D7; impossibility of administering enteral nutrition. ▪ <u>Ancillary study 2</u> *Primary outcome measure:* proportion of patients with abundant microaspiration (defined as a pepsin level >200 ng/mL in at least 30% of tracheal aspirates). *Secondary outcome measures*: Salivary amylase levels in tracheal aspirates.
INCLUSION CRITERIA FOR STUDY PARTICIPANTS	▪ invasive mechanical ventilation for an expected duration of at least 48 hours ▪ nutritional support started within 24 hours after intubation, or after ICU admission in patients intubated before ICU admission ▪ administration of a vasoactive agent (adrenaline, dobutamine, or noradrenaline) via a central venous catheter ▪ age older than 18 years ▪ informed consent to study participation ▪ coverage by one of the French statutory health insurance agencies
NONINCLUSION CRITERIA FOR STUDY PARTICIPANTS	▪ invasive mechanical ventilation started more than 24 hours earlier ▪ surgery on the gastrointestinal tract within the past month ▪ history of gastrectomy, esophagectomy, duodenopancreatectomy, gastric bypass or banding, or short bowel syndrome ▪ gastrostomy or jejunostomy ▪ specific diet ▪ active bleeding from the gastrointestinal tract ▪ dying patient – not-to-be-resuscitated order or other treatment limitation decision at ICU admission ▪ adult under guardianship ▪ pregnancy, recent delivery, or lactation ▪ patient admitted without his or her consent ▪ department of corrections inmate ▪ institutionalized patient ▪ prior inclusion in a randomized trial comparing early enteral nutrition to early parenteral nutrition and having mortality as the primary outcome measure ▪ contraindication to parenteral nutrition: known hypersensitivity to egg protein, soybean protein, or another component; inborn error in

	amino acid metabolism; severe familial dyslipidemia manifesting as hypertriglyceridemia
STRATEGIES / PROCEDURES	In both groups, nutritional support will be started within 24 hours after the initiation of mechanical ventilation. Calorie targets will be 20-25 Kcal/Kg/day during the first week then 25-30 Kcal/Kg/day starting on day 8. In the parenteral nutrition group, a switch to the enteral route will be possible after at least 72 hours of parenteral nutrition, provided the vasoactive agent(s) were stopped at least 24 hours earlier and the arterial lactic acid level is lower than 2 mmol/L; on day 7, all patients will be switched to enteral nutrition in the absence of an absolute contraindication to use of the enteral route. In the enteral nutrition group, supplemental parenteral nutrition may be added, starting on day 8, in patients with intolerance to enteral nutrition and inadequate calorie intakes. A written protocol for prescribing and delivering nutritional support will be available to ensure standardization across study centers.
STRATEGIES / PROCEDURES SPECIFIC OF THE ANCILLARY STUDIES	– Ancillary study 1 The assays on D0, D3, and D8 will be performed on part of the blood samples drawn for the standard care of these critically ill patients. – Ancillary study 2 All tracheal aspirates (obtained routinely in patients receiving invasive mechanical ventilation) will be collected over the first 48 hours following randomization and stored at -20°. The aspirates will then be centralized at the Biology and Pathology Center of the Lille Teaching Hospital (Lille, France), where they will be used for quantitative assays of pepsin and salivary amylase.
NUMBER OF PATIENTS	1427 in each group, i.e., 2854 patients in all
NUMBER OF PATIENTS IN THE ANCILLARY STUDIES	– Ancillary study 1 85 patients per group, i.e., 170 patients in all – Ancillary study 2 94 patients per group, i.e., 188 patients in all
DURATION OF THE STUDY	Inclusion period duration: 30 months Duration of participation for each patient: duration of mechanical ventilation (final extubation), follow-up until hospital discharge Total study duration: 36 months (30 months for inclusion plus 6 months for follow-up and data checking).
PLANNED TRIAL START DATE	September 3, 2012
EXPECTED IMPACT	If the study hypothesis is confirmed, early enteral nutrition will become the reference standard for initial nutritional support in mechanically ventilated patients with shock, and the result will be decreased morbidity and mortality rates and improved overall patient outcomes.

LIST OF ABBREVIATIONS

AFSSaPS	*Agence Française de Sécurité Sanitaire des Produits de Santé* (French Healthcare Product Safety Agency)
APACHE	Acute Physiology And Chronic Health Evaluation
BMI	Body mass index
CCTIRS	*Comité Consultatif sur le Traitement de l'Information en matière de Recherche* (French Advisory Committee on Data Handling in Healthcare Research)
CepiDc	*Centre d'épidémiologie sur les causes médicales de décès* (Epidemiology center for medical causes of death)
CFU	Colony-forming unit
CIRCI	Critical illness-related colonic ileus
CNIL	*Commission Nationale de l'Informatique et des Libertés* (French Data Protection Authority)
CRA	Clinical research assistant
CRF	Case-report form
CRN	Clinical research nurse
CRP	C-reactive protein
CRT	Clinical research technician
CT	Computed tomography
CTA	Computed tomography angiography
CVC	Central venous catheter
D	Day
GCP	Good clinical practice
H	Hour
ICH	International Conference on Harmonization
ICU	Intensive care unit
I-FABP	Intestinal Fatty Acid-Binding Protein
INSERM	*Institut National de la Santé et de la Recherche Médicale*, (French National Institute for Health and Medical Research)
ITT	Intention to treat
IV	Intravenous
MPM-0	Mortality Prediction Model at admission
MRA	Magnetic resonance angiography
NOMI	Nonocclusive mesenteric ischemia
NRS	Nutritional Risk Screening
NTBR	Not to be resuscitated
REE	Resting energy expenditure
RN	Registered nurse
RRT	Renal replacement therapy
SAE	Serious adverse event
SAPSII	Simplified Acute Physiology Score version II
SOFA	Sequential Organ Failure Assessment
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TEI	Total energy intake
USAE	Unexpected serious adverse event
VAP	Ventilator-associated pneumonia

1) BACKGROUND

5.1 Title

Impact of Early Enteral vs. Parenteral Nutrition on Mortality in Patients Requiring Mechanical Ventilation and Catecholamines: Multicenter Randomized Controlled Trial (NUTRIREA-2)

5.2 Coordination and monitoring of the study

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2) SCIENTIFIC RATIONALE FOR THE STUDY

5.5 Overview of the research project

In everyday ICU practice, nutritional support is an integral part of the life-sustaining strategies used to combat the impact of critical insults (1). The enteral route, as opposed to the parenteral route, is the recommended first-line route of administration in the most recent French and international guidelines (2-7). Enteral nutrition has well-documented beneficial effects on gastrointestinal mucosa integrity, wound healing, immune function, and responses to tissue damage; these benefits may preserve the physical and functional integrity of the gastrointestinal tract (8-11). Enteral nutrition may produce optimal benefits when started early and in patients with multiple organ failures (12, 13). Most authors and professional organizations define "early nutrition" as nutritional support started within 24 to 48 hours after ICU admission (5, 14, 15). Early nutrition may contribute to diminish nosocomial infection rates, stay lengths, and healthcare costs (2, 11, 16-29).

Despite the scientific evidence of benefits from nutritional support via *the enteral route*, substantial gaps persist between everyday practice in many ICUs and widely disseminated clinical practice guidelines. In a 2010 multicenter observational study that included nearly 3000 patients, almost 40% of patients were still without nutritional support 48 hours after ICU admission, 35% of patients eligible for enteral nutrition were receiving parenteral nutrition, and mean calorie and protein intakes amounted to only 60% of recommended targets (30). Inadequacies were more marked among surgical patients than among medical patients (31). Although delayed initiation of early enteral nutrition thus appears to be a common contributor to malnutrition, variability in administration modalities combined with calorie deficiencies also emerge as key factors in poor patient outcomes (19, 32-39). Before 2011, a multicenter study from Germany in a cohort of patients with very severe critical illnesses (54% mortality rate) showed that 35.1% of patients received parenteral nutrition only, 34.6% received combined enteral and parenteral nutrition, and only 20.1% received enteral nutrition only (19). This inadequate use of enteral nutrition can be ascribed to at least two factors: legitimate or exaggerated concern about complications related to the enteral route and the absence of sound scientific evidence demonstrating that one route is superior over the other.

The most common complication of early enteral nutrition is upper gastrointestinal intolerance, which occurs in 50% of patients. Concern about nosocomial pneumonia and undernutrition related to this complication remains a major deterrent to the use of early enteral

nutrition (32-35, 38, 40-44). 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 (45-52). The dreaded sequence of incomplete gastric emptying, gastroesophageal reflux, aspiration, and nosocomial pneumonia is a constant concern for healthcare workers. Ventilator-associated pneumonia (VAP) remains a major complication of mechanical ventilation seen in 8% to 27% of patients and responsible for longer ICU stays and an increased risk of death in some patients (53). The measure most commonly used to prevent or decrease the risk of intolerance consists in discontinuing or markedly decreasing the flow rate of enteral feed. This measure diminishes the energy and nutrient intakes, which no longer meet the needs of the patient. In a prospective observational study, a negative energy balance in surgical ICU patients was associated with undernutrition, which in turn correlated with a higher rate of infections and with increased mortality in the most severely ill patients (54). In contrast, parenteral nutrition appears to be the safest means of delivering the required amounts of energy and protein.

The lower intestinal tract can also be the site of complications characterized by ischemia despite patency of the blood vessels, a condition known as nonocclusive mesenteric ischemia (NOMI) (55). NOMI may affect 20% to 30% of ICU patients with severe circulatory failure. Intense splanchnic vasoconstriction designed to preserve blood flow to essential organs (the brain, heart, and kidneys) can result in necrotizing enterocolitis, a condition that is fatal in 70% to 100% of cases (56, 57). The main causative factors are medications (catecholamines, vasoconstrictors, cardiovascular drugs), patient characteristics (chronic hemodialysis, heart surgery, multiple trauma), and critical complications (acute respiratory distress syndrome, septic shock, cardiogenic shock, fluid and sodium overload) (58-60). The potential role for enteral nutrition in the development of NOMI remains controversial. A study involving superior mesenteric artery blood-flow measurement 3 h after the introduction of nutritional support in volunteer ICU patients failed to conclusively resolve this issue (61). Enteral nutrition was associated with a greater than 50% blood-flow increase and parenteral nutrition with a greater than 60% decrease, indicating a theoretical risk of a mismatch between oxygen supply and demand in the splanchnic territory in patients with acute circulatory failure receiving enteral nutrition.

Another contributor to the current underuse of early enteral nutrition in many patients is the conflicting nature of findings from available studies. In addition, no study to date has demonstrated that a specific nutritional modality is associated with decreased mortality.

International recommendations rest chiefly on metaanalyses whose interpretation is rendered difficult by the heterogeneity of the included studies (2, 13, 14). These studies included a predominance of surgical patients, many of whom were not receiving ventilatory assistance and had low critical-illness severity. The most recent metaanalysis, published in 2009, underlines the heterogeneity and sample-size inadequacies of the study populations, which preclude definitive conclusions about treatment benefits in some cases (14). In a metaanalysis confined to trials that used the intention-to-treat approach, i.e., nine of 465 trials, mortality was higher with enteral nutrition (62). In this metaanalysis, mortality in patients given early parenteral nutrition (within 24 h after ICU admission) was 56% lower than in patients given late enteral nutrition (more than 48 h after ICU admission). The uncertainty surrounding current recommendations has been acknowledged by their authors, who have emphasized the need for adequately powered and randomized trials in homogeneous patient populations.

Several recent studies evaluated supplemental parenteral nutrition in patients with failure to reach their target nutrient intakes due to poor tolerance of early enteral nutrition. The optimal time for initiating combined parenteral and enteral nutrition is controversial, with North-American societies recommending delayed introduction of parenteral nutrition after the first week and European societies arguing for early combined nutrition designed to rapidly reach the theoretical energy target (4, 6). A very recent, large, randomized, multicenter trial (EPaNIC trial) compared these two strategies (63). All patients having a Nutritional Risk Screening score >3 were included, i.e., over 4500 patients. The primary outcome measure was ICU stay length, which was shorter by 1 day in the group given late parenteral nutrition. The nosocomial infection rate and mechanical ventilation duration were higher in the early-parenteral-nutrition group. In contrast, no significant differences were found for ICU or hospital mortality rates. The authors concluded that early addition of parenteral nutrition to enteral nutrition, within the first ICU week, provided no benefits and increased the length of stay. These results should be interpreted in the light of the low overall ICU mortality rate (6.2%) and limited duration of mechanical ventilation (2 days) related to the predominance of heart-surgery patients, which preclude definitive conclusions regarding mortality. In contrast, in a randomized trial from Switzerland that has so far been reported only during meetings, the early adjunction of parenteral nutrition in patients whose nutritional targets were not achieved by enteral nutrition was associated with a significant decrease in the nosocomial infection rate (64). Although these two studies reflect the current high level of interest in early nutritional support in ICU patients, neither was designed to compare the parenteral to the enteral route. Instead, both studies sought to determine whether supplemental parenteral nutrition in patients

with intolerance to enteral nutrition should be started early or only after the first week. Thus, neither study provides any information on the possible superiority of one route over the other. To date, no large prospective randomized trial has demonstrated that early enteral nutrition improves survival in ICU patients, a fact that leaves room for active controversy (65-67).

The current situation can be summarized as follows.

1. International recommendations indicate that early enteral nutrition should be preferred over parenteral nutrition.

2. Adherence to this guideline is poor in many patients, for a number of reasons:

   a. Concern about potential complications of the recommended strategy and/or the need to manage these complications when they occur result in an increased work load and in delayed or absent use of early enteral nutrition.

   b. The available data (metaanalyses) are conflicting.

   c. The authors of the recommendations acknowledge that their guidelines rest on converging arguments and indirect studies but not on sound evidence, most notably from randomized trials having adequate statistical power and using relevant clinical outcome measures.

   d. The highly conflicting results of recent studies on supplemental early parenteral nutrition constitute indirect evidence that the issue remains unresolved.

3. There is therefore a pressing need to conduct a study capable of determining whether the enteral route is superior over the parenteral route for early nutritional support in ICU patients. This study must be conducted in a population of selected patients at high risk for death and/or secondary complications, most notably infections, in whom the implementation of optimal nutritional support is likely to have the greatest consequences and to raise the greatest difficulties.

Patients with shock requiring both invasive mechanical ventilation and vasoactive amines have a particularly high level of illness severity associated with high risks of death, secondary complications, intolerance to early enteral nutrition, and mesenteric vascular complications. For these patients, most recommendations indicate that early enteral nutrition should not be started until the hemodynamic situation is controlled (2, 4, 6). Therefore, either enteral nutrition is delayed or parenteral nutrition is given initially (19). However, the greatest benefits from enteral nutrition were reported in this type of population. In a retrospective analysis of data from 1174 patients treated with mechanical ventilation and vasoactive agents

(68), early enteral nutrition (within 48 h after starting mechanical ventilation) was associated with a lower mortality rate compared to the group given late enteral nutrition. In the subgroup analysis, the benefits from early enteral nutrition were greatest in the sickest patients (usually those having the greatest dependency on vasoactive agents) and in the patients who failed to improve promptly (i.e., who had marked vasoactive agent dependency throughout the first 48 h of treatment). Another retrospective study of 2528 patients requiring mechanical ventilation for longer than 48 h produced similar findings (12). In the patients with the worst severity-of-illness scores (APACHE II>25, SAPS II>56, and MPM-0<0.54) at baseline, ICU and hospital mortality rates were significantly lower with early vs. late enteral nutrition. Thus, severe illness and established circulatory failure do not contraindicate early enteral nutrition, provided the initial life-sustaining interventions are appropriate. Nevertheless, regarding the nutritional strategy in this type of patient, adherence to recommendations is extremely variable and the recommendations themselves are unclear because they do not rest on a body of sound evidence allowing definitive conclusions.

The objective of this research project is therefore to obtain unequivocal confirmation, in an appropriate number of patients and using a prospective multicenter randomized controlled trial design, of the hypothesis that early first-line enteral nutrition decreases day-28 all-cause mortality in patients with shock treated with mechanical ventilation and vasoactive amines, compared to early first-line parenteral nutrition.

The NUTRIREA2 trial provides the opportunity to answer two additional questions, via an ancillary study for each.

1. Is enteral nutrition associated with better preservation of gut mucosa integrity compared to parenteral nutrition?

Published studies suggest that enteral nutrition may help to preserve gut mucosal integrity and function. More specifically, enteral nutrition may maintain normal gut permeability and preserve the gut lymphoid tissue (11, 23, 69). In addition, experimental data suggest that the risk of bacterial translocation may increase with parenteral nutrition and decrease with enteral nutrition (16, 70-72). These effects of enteral nutrition may diminish the risk of systemic inflammatory response syndrome and organ failure (29, 73). These theoretical benefits may, however, be offset by the risk of gut mucosal ischemia possibly associated with enteral nutrition (61, 74). Furthermore, they have not been demonstrated in critically ill patients, particularly those with mechanical ventilation and shock. The NUTRIREA2 trial provides a valuable opportunity to compare the effects of enteral and parental nutrition on gut integrity

and function in this population. Such a comparison can be performed readily in everyday practice by assaying two molecules recently identified as reliable markers for gut failure as seen in some critically ill patients (75-77). Citrulline is an amino acid produced from glutamine by enterocytes. Plasma citrulline levels reflect the mass of functional enterocytes. Intestinal fatty acid-binding protein (I-FABP, also known as FABP2) is a small protein found in the cytosol of small-bowel enterocytes that is released into the capillaries when the enterocytes are damaged. Plasma I-FABP is a marker for enterocyte lysis. Assaying both plasma citrulline and plasma I-FABP may provide an evaluation of gut failure in critically ill patients and may allow discrimination between enterocyte damage (low plasma citrulline and high plasma I-FABP) and enterocyte dysfunction (low plasma citrulline and normal plasma I-FABP), although both mechanisms may be interlinked (78). The hypothesis underlying this ancillary study is that gut mucosal integrity and function are better in patients given first-line enteral nutrition compared to those given parenteral nutrition. Higher plasma citrulline levels and lower plasma I-FABP levels in the enteral-nutrition group than in the parenteral-nutrition group would support this hypothesis.

2. Is enteral nutrition associated with a higher risk of gastric-content aspiration compared to parenteral nutrition?

Risk factors for gastric-content microaspiration in critically ill patients include gastroesophageal reflux, gastric distension, damage to the inferior and superior esophageal sphincters, and impairment of the glottic closure reflex that normally prevents aspiration (79, 80). Several studies involving technetium 99m (^{99m}Tc) labeling of gastric contents have established that gastric-fluid microaspiration is common in critically ill patients receiving both endotracheal ventilation and enteral nutrition (81-84). However, to our knowledge, no studies have specifically addressed the role for enteral nutrition in the occurrence of microaspiration. The objective of this ancillary study is to compare the frequency of gastric-content microaspiration in patients given enteral versus parenteral nutrition during the NUTRIREA2 trial. The new knowledge of risk factors for microaspiration provided by this study may help to improve strategies for preventing microaspiration and VAP.

5.6 Overview of potential benefits and, where applicable, of predictable and known risks for the patients participating in the research project

By comparing two strategies for nutritional support initiation, this study will strive to standardize the initiation of nutritional support in patients treated with mechanical ventilation and one or more vasoactive amines. At the acute phase of their ICU management, the study patients will receive a single nutritional modality, i.e., either parenteral nutrition (early parenteral group, P group) or enteral nutrition (early enteral group, E group) for at least 72 h and no longer than 7 days. Each of these two modalities will be used according to a pre-defined protocol that will include an estimate of energy needs based on body weight. Beyond the first study week, the ICU teams will give preference to the enteral route, except in patients with acute bowel disease constituting an absolute contraindication to enteral nutrition. Thus, parenteral and enteral intakes will be combined according to each patient's needs.

The standardization of nutritional support will constitute in itself a source of benefits to the study patients (15). This study generates no additional risks to the patients. Nutritional support, whether delivered enterally or parenterally, is among the first-line treatments used routinely in the ICU. Raising healthcare worker awareness about good clinical practice in the area of nutritional support receives careful attention as a matter of course in ICUs. Finally, to date, no study has produced definitive information on the risks and benefits of enteral versus parenteral nutrition.

Similarly, the ancillary studies will pose no additional risks to the patients. More specifically, they will require no additional biological-sample collections. The citrulline and I-FABP assays in Ancillary Study 1 will be performed on a fraction of the blood samples drawn for the routine management of critically ill patients. These blood samples will simply need to be increased slightly (by about 2 mL). The pepsin and salivary amylase assays needed for Ancillary Study 2 will be performed on tracheal aspirates obtained as part of the standard care of patients receiving mechanical ventilation. Thus, no additional procedures are required.

5.7 Statement that the research project will be conducted in compliance with the study protocol and with good clinical practice guidelines

The investigator undertakes to ensure that this research is conducted

- in compliance with the study protocol and
- in compliance with current French and international good clinical practice guidelines.

5.8 Description of the study population

This study will include adults admitted to the ICU and eligible for enteral or parenteral nutrition within 24 h after endotracheal intubation (or within 24 h after ICU admission if intubation occurred before ICU admission), for a predicted duration of at least 2 days. Furthermore, eligibility for study inclusion will require a serious critical illness defined as a need for vasoactive amine therapy to treat shock combined with invasive mechanical ventilation started within the past 24 h. The controlled nutritional-support strategy will be used only during the acute phase of intensive care, defined as the first 7 days in the ICU. Section 5 describes the inclusion and exclusion criteria used to select the study patients.

3) STUDY OBJECTIVES

5.9 Primary objective

The primary objective of this research project is to assess the hypothesis that a strategy involving first-line early enteral nutrition decreases day-28 all-cause mortality in mechanically ventilated patients receiving vasoactive amine therapy for shock, compared to a strategy involving first-line early parenteral nutrition.

5.10 Secondary objectives

The secondary objectives consist in comparing the following variables in the two groups:

- Nosocomial infections:
  - VAP: proportion of patients with at least one VAP episode, VAP incidence density, number of VAP episodes
  - Bacteremia: proportion of patients with at least one episode of bacteremia, incidence density of bacteremia
  - Central venous catheter (CVC)-related infections: proportion of patients with at least one CVC-related infection, incidence density of CVC-related infections
  - Urinary tract infections: proportion of patients with at least one urinary tract infection, incidence density of urinary tract infections
  - Soft tissue infections: proportion of patients with at least one soft tissue infection, incidence density of soft tissue infections
- Descriptive bacteriological data (organisms recovered and antibiotic resistance profile for each nosocomial infection)
- Proportion of patients with at least one episode of vomiting or regurgitation
- Proportion of patients with at least one episode of diarrhea
- Proportion of patients with at least one episode of constipation
- Proportion of patients with at least one episode of documented bowel ischemia
- Number of calories delivered enterally and parenterally each day
- Volume of enteral and parenteral feed delivered each day
- Ratio of prescribed over delivered calories
- ICU mortality, day-90 mortality, and hospital mortality

- Changes in nutritional markers during follow-up (measured at the end of mechanical ventilation, on day 7 in patients on mechanical ventilation for more than 7 days, and at ICU discharge)
- Proportion of patients with at least one episode of liver dysfunction (liver function will be evaluated at the end of mechanical ventilation, on day 7 in patients on mechanical ventilation for more than 7 days, and at ICU discharge)
- ICU stay length
- Hospital stay length
- Total time on mechanical ventilation
- Body weight changes from ICU admission to day 7 and from ICU admission to ICU discharge

5.11 Objectives of the ancillary studies

– Ancillary study 1
  - Primary objective: To demonstrate that a strategy involving early first-line enteral nutrition is associated with improved preservation of gut mucosal integrity, as assessed based on the plasma citrulline level at H72, compared to a strategy involving early first-line parenteral nutrition
  - Secondary objectives: To compare the effects of enteral and parenteral nutrition on the course of organ failures, bacteremia, gastrointestinal intolerance, bowel transit time, and plasma citrulline and I-FABP levels

– Ancillary study 2
  - Primary objective: To evaluate the impact of enteral nutrition on microaspiration of gastric content
  - Secondary objective: To evaluate the impact of enteral nutrition on microaspiration of pharyngeal secretions

5.12 Impact

If the study hypothesis is confirmed, then early enteral nutrition will become the reference standard method of nutritional support in mechanically ventilated patients with

shock, based on improvements in morbidity and mortality rates and in the overall outcome of patients at the acute phase of ICU management.

The ancillary studies will clarify the impact on gut function of the route of administration of nutritional support, as well as the pathophysiology of gastric-content aspiration, in patients receiving mechanical ventilation.

4) STUDY CONCEPTS

5.13 Detailed descriptions of the primary endpoint and, where applicable, of the secondary endpoints

4.1.1 Primary endpoint

The primary endpoint is all-cause mortality by day 28 (D28). Information on this endpoint will be collected on the 28th day after inclusion of the patient in the study. For patients who have been discharged, information on the primary endpoint will be collected by a telephone call to the patient at home.

4.1.2 Secondary endpoint

- Proportion of patients with at least one VAP episode (numerator in each group: total number of patients with at least one VAP episode during mechanical ventilation or within 2 days after extubation; denominator: total number of patients included in the relevant group).

  The diagnosis of VAP will be suspected based on the development or persistence of lung infiltrates on the chest radiograph with at least two of the following criteria: body temperature ≥38.5 or ≤35.5ºC, leukocytosis (>10 000/mm^3) or leukopenia (<4000/mm^3), and purulent tracheobronchial aspirate. The diagnosis will have to be confirmed by a positive *semi-quantitative* bacteriological test: bronchoalveolar lavage (>10^{-4} cfu/mL), brush (>10^{-3} cfu/mL), tracheal aspirate (>10^{-6} cfu/mL), or protected distal specimen (>10^{-3} cfu/mL) (53, 69).
- VAP incidence density per 1000 days of mechanical ventilation, i.e., ratio of the number of patients with at least one VAP episode during mechanical ventilation or within 2 days after extubation over the period at risk defined as follows:
  - total number of mechanical ventilation days in patients without VAP
  - mechanical ventilation days before the first VAP episode in patients with VAP
- Number of VAP episodes per patient
- Other nosocomial infections:
  - Bacteremia: proportion of patients with at least one episode of bacteremia and incidence density per 1000 ICU days

  - CVC-related infections: proportion of patients with at least one CVC-related infection and incidence density per 1000 CVC days
  - Urinary tract infections: proportion of patients with at least one episode of urinary tract infection and incidence density per 1000 urinary-catheter days
  - Soft tissue infections: proportion of patients with at least one soft tissue infection and incidence density per 1000 ICU days
  - Other nosocomial infections: proportion of patients with other nosocomial infections and incidence density per 1000 ICU days
- Proportion of patients with at least one nosocomial infection
- Descriptive bacteriological data: organisms recovered in the overall population of nosocomial infections and antimicrobial resistance profiles
- Proportion of patients with at least one episode of vomiting or regurgitation while on mechanical ventilation
- Proportion of patients with at least one episode of diarrhea defined as liquid stools in a volume greater than 300 mL/24 hours in patients with a fecal collector or as more than four loose stools/24 hours (15).
- Proportion of patients with at least one documented episode of bowel ischemia defined 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 [CTA], angiography, or magnetic resonance angiography [MRA]) or presence of 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) by endoscopy (rectosigmoidoscopy or colonoscopy) (70)

- Number of calories (in Kcal) delivered enterally and parenterally:
  - daily mean during the first week
  - daily mean throughout the time on mechanical ventilation
- Ratio (as a %) of prescribed over delivered calories delivered enterally and parenterally:
  - daily mean during the first week
  - daily mean throughout the time on mechanical ventilation
  - proportion of patients who achieved their calorie target on each follow-up day
- Volume of liquid feed (in mL) delivered
  - daily mean during the first week
  - daily mean throughout the time on mechanical ventilation

- ICU mortality, 90-day mortality, and hospital mortality; to confirm deaths by day 90, we will search the epidemiological causes-of-death database (CépiDc, *Centre d'épidémiologie sur les causes médicales de décès*).
- Mean changes in serum albumin, prealbumin, transthyretin, and C-reactive protein (CRP) measured at baseline, at the end of mechanical ventilation, on day 7 (in patients on mechanical ventilation for more than 7 days), and at ICU discharge
- Proportion of patients with at least one episode of liver dysfunction during follow-up; liver function will be evaluated at the end of mechanical ventilation, on day 7 (in patients on mechanical ventilation for more than 7 days), and at ICU discharge; liver dysfunction will be defined as serum bilirubin >50 µmoL/L and/or elevation >3N in one or more liver enzymes (γ-glutamyltransferase, alkaline phosphatase, and ASAT-ALAT).
- ICU stay length
- Hospital stay length
- Time on mechanical ventilation
- Changes in mean body weight determined at baseline, on day 7, and at ICU discharge

4.1.3 Endpoints for the ancillary studies

– <u>Ancillary study 1</u>
  - Primary outcome measure: plasma citrulline level at H72
  - Secondary outcome measures: SOFA score; plasma levels of citrulline and I-FABP on D0, D3, and D8; proportion of patients whose plasma I-FABP is ≥100 pg/mL on D0, D3, and D8; proportion of patients whose plasma citrulline is ≤10 µL/L on D0, D3, and D8; mean plasma I-FABP; mean plasma citrulline; proportion of patients with at least one episode of bacteremia; proportion of patients with at least one episode of gastrointestinal intolerance; proportion of patients with at least one episode of diarrhea; in the enteral-nutrition group, cumulative calorie intake over the first 3 days and on D7; impossibility of administering enteral nutrition.

– <u>Ancillary study 2</u>

- Primary outcome measure: proportion of patients with abundant microaspiration
- Secondary outcome measures: salivary amylase levels in tracheal aspirates

5.14 Description of the research project methodology with a study diagram including scheduled visits and investigations

4.2.1 Study design

This multicenter randomized controlled open trial will compare two parallel groups of patients receiving mechanical ventilation and vasoactive amine therapy and given early nutritional support according to one of two strategies (first-line enteral nutrition versus first-line parenteral nutrition) at the acute phase of ICU management (D1 to D7).

4.2.2 Conduct of the study

4.2.2.1 Inclusion

Patients will be included in the study within 24 h after intubation, or within 24 h after ICU admission if they were intubated before ICU admission. Study inclusion will occur after the usual initial life-sustaining interventions required in patients with shock managed using ventilatory support. The study will include patients requiring vasoactive amine therapy after volume expansion if indicated and any evaluation procedures dictated by the clinical condition. These initial treatment and evaluation decisions will be at the discretion of the physician in charge of each patient, who will follow standard procedures in the relevant study ICU.

Information about the study and collection of consent to study participation will involve the patient if he or she is conscious and the next of kin otherwise. If informed consent is obtained from the next of kin, informed consent will be sought from the patient as soon as he or she recovers a sufficient level of consciousness.

A log of patients considered for study participation will be kept and will include any reasons for non-inclusion and refusals of consent.

After checking the inclusion and non-inclusion criteria, as well as consent to participation given by the patient or next of kin, the investigator will be able to include the patient. At inclusion, demographic data, patient characteristics, and vital signs will be collected: date of birth, sex, date of ICU admission, reason for ICU admission, McCabe and Knaus scores, chronic co-morbidities, body weight, height, BMI, SOFA score, and SAPS II.

4.2.3 Nutritional support protocol

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

a. General principles

Nutritional support will be started as soon as possible after the initiation of invasive mechanical ventilation and no later than 24 hours after intubation or after ICU admission in patients intubated before ICU admission.

The calorie target for each patient will be estimated based on body weight as 20-25 Kcal/Kg/day during the acute phase (7 days at the most) then 25-30 Kcal/Kg/day from day 7 to extubation. In obese patients (BMI> 30 Kg/m²), the body weight yielding a BMI of 30 will be used to estimate the calorie target.

Nutritional support will be prescribed as a flow rate (mL/hour) and started at the prescribed flow rate (as opposed to increased gradually). The feed will be delivered continuously, over the 24-hour cycle, with no interruptions. Actual feed delivery will be monitored regularly based on the volumes delivered relative to the predefined daily calorie targets. In addition, special attention will be directed to avoiding delays. Any interruption in feed delivery will be reported to the ICU physician in charge. Except in special situations, nutritional support will not be interrupted while transporting the patient. However, when enteral or parenteral nutrition must be interrupted (e.g., for a specific gastrointestinal or radiological investigation), the flow rate will not be increased to compensate for the interruption. Finally, the patient will be in the semi-recumbent supine position with the torso at 30° to 45° from the horizontal plane.

b. Enteral nutrition

Isoosmotic isocaloric normal-protein polymeric preparations will be used during the first week, after which the choice of feed will be at the discretion of the physician. The enteral nutrition preparation will be delivered continuously, over the 24-hour cycle, with no

interruptions, via a 14-French silicone gastric tube. Tube position in the middle of the stomach will be 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 will be directed to the risk of tube obstruction, particularly when administering medications: the tube will be flushed regularly with 20-30 mL of water.

A predefined protocol will be used to manage upper gastrointestinal intolerance to enteral nutrition (Appendix 1) (71). The tolerance of enteral nutrition will be monitored based only on episodes of significant vomiting or regurgitation (passage of enteral nutrition formula into the mouth, outside the mouth, or into the endotracheal tube in the absence of care procedures or mobilization). The residual gastric volume will not be monitored. Intolerance to enteral nutrition will be defined as the presence of significant vomiting or regurgitation. Minimal regurgitation or vomiting triggered by tracheal aspiration or oral cavity care will not be taken to indicate intolerance. Intolerance to enteral nutrition will lead to the following two measures:

- First, initiation of treatment with a prokinetic agent *after confirmation that there are no contraindications and after obtaining a prescription by a physician*. The study ICUs will use the prokinetic agent of their choice, according to their standard practice. The prokinetic agent will be continued until enteral nutrition at the highest prescribed flow rate has been well tolerated for 48 hours. The prokinetic agent will then be discontinued.
- Second, if the intolerance persists despite prokinetic therapy, the flow rate will be decreased by 25 mL/h, every 6 hours, until the signs of intolerance resolve. Therefore, enteral nutrition will be stopped (and the gastric tube placed under suction) only in patients with intolerance despite a flow rate ≤25 mL/h. All interruptions in enteral nutrition delivery must be reported to the intensivist in charge. This precaution is particularly important in patients receiving insulin. Enteral nutrition will be resumed at the prescribed flow rate (appropriate to the patient's needs) after 6 hours have elapsed with no further signs of intolerance. (71).

c. Parenteral nutrition

Ternary admixtures packaged in bags and containing the three groups of macronutrients will be used according to standard practice in each participating center. Supplemental electrolytes will be supplied in a solution separate from the parenteral feed, according to the needs of each patient. Parenteral nutrition will be delivered continuously, over the 24-hour

cycle, with no interruptions, via a central venous catheter (CVC). Special attention will be directed to preventing infections by complying with the standard protocols for CVC insertion and maintenance used in each of the participating centers. Proper positioning of the CVC will be checked using a radiograph.

d. Additional intakes (water, electrolytes, trace elements, and vitamins)

Additional water and electrolytes will be given intravenously according to the needs of each individual patient as assessed by the physician in charge and in compliance with standard practice in each study ICU.

Intravenous vitamins, trace elements and, when appropriate, will be given according to the needs of each individual patient, using the standard preparations and protocols available in each study ICU.

These components will not be added to the parenteral nutrition bags. Instead, they will be given using a separate intravenous bag and line, continuously over the 24-hour cycle; if needed, this separate preparation will be shielded from light using aluminum foil.

4.2.4 Study intervention: first-line enteral or parenteral nutrition

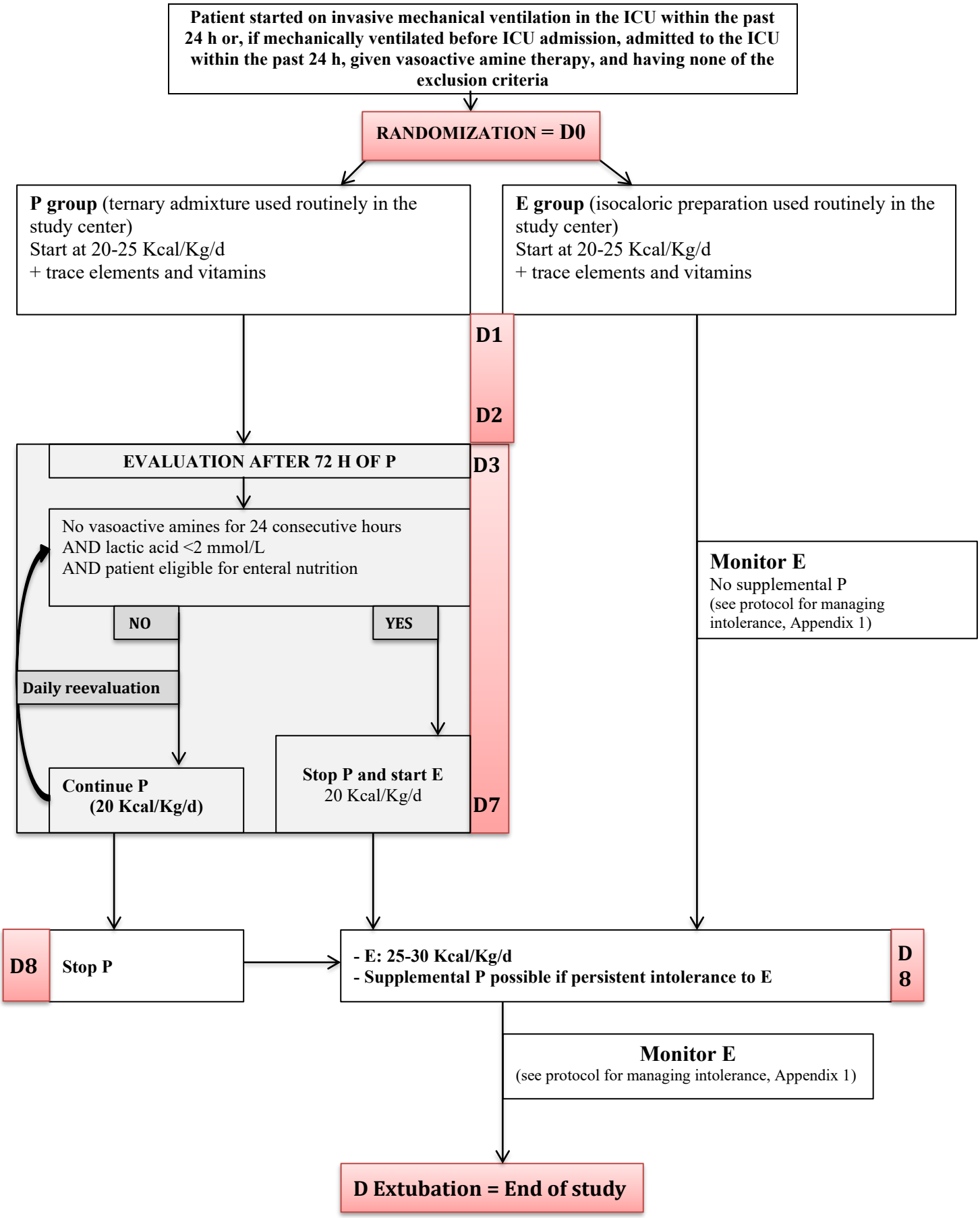
After study inclusion, patients will be allocated at random to one of two nutritional-support strategies (Figure 1).

In the parenteral-nutrition group (P group), the patients will receive first-line parenteral nutrition for at least 72 hours. After these 72 hours, the course of action will depend on the results of the daily hemodynamic status evaluation. If the hemodynamic condition is stable (no vasoactive amines for 24 consecutive hours and arterial lactic acid level below 2 mmol/L) and the enteral route can be used, parenteral nutrition will be stopped and immediately replaced by enteral nutrition at the flow rate needed to achieve the previously defined calorie target. If on the contrary the patient still requires vasoactive amine therapy and/or the arterial lactic acid level is equal to or greater than 2 mmol/L, parenteral nutrition will be continued for a total of 7 days (168 hours). On day 8, in the absence of contraindications to enteral nutrition, parenteral nutrition will be stopped and enteral nutrition started. Supplemental parenteral nutrition may be added subsequently in the event of intolerance to enteral nutrition precluding the achievement of the predefined calorie targets.

In the enteral-nutrition group (E group), the patients will receive first-line enteral nutrition. In the event of persistent gastrointestinal intolerance precluding achievement of the

predefined calorie targets, supplemental parenteral nutrition may be added starting on day 8 in compliance with North-American recommendations and with the recently published study by Casaer (6, 72). Isoosmotic isocaloric normal-protein polymeric preparations will be used during the first week, after which the choice of the preparation will be at the discretion of the physician. To minimize the risk of gastric intolerance and consequently of vomiting, the volume of supplemental water given enterally will be as small as possible during the first study week.

Figure 1: Protocol



4.2.5 Monitoring of intestinal transit

The volume and appearance of the stools will be monitored daily.

The occurrence of constipation (no stool for more than 6 days) or diarrhea (more than 300 mL of liquid stool or 4 loose stools per day) will be reported and will lead to the appropriate diagnostic and therapeutic management (Appendix 2) (15, 73, 74).

4.2.6 Special situations

- Patients in the prone position: intolerance to enteral nutrition is particularly common in this position and will be prevented via prophylactic prokinetic treatment started at the first turn in the prone position (75, 76).
- Patients receiving insulin therapy: very close monitoring and strict application of the insulin-therapy protocol used in each study-center institution are crucial. Blood glucose targets will be at the discretion of each study center according to their usual practice and protocols. In addition,
    - in the event of a decrease in the enteral feed flow rate due to poor tolerance of enteral nutrition (regurgitations), blood glucose levels will be determined at least hourly during the first 2 hours following the flow rate reduction; if blood glucose levels remain stable, the patient will be returned to the frequency of monitoring specified in the insulin-therapy protocol;
    - In the event nutritional support is discontinued, blood glucose levels will be determined hourly for as long as the patient remains off enteral nutrition.
- Patients who are re-intubated or re-admitted to the ICU: if this event occurs at the acute management phase (<7 days after first use of mechanical ventilation), the patient will be managed in the same way as during the first period of intubation, until the end of the acute phase. Thus, a patient allocated at random to the enteral-nutrition group (E group) will remain in this group for at least the first 7 days of management. If the event occurs after the end of the acute phase, the method of nutritional support will be at the discretion of the physician in charge.

4.2.7 Patient follow-up

The following will be recorded until the patient is extubated: vital signs, nutrition monitoring data, laboratory tests, and data relevant to nosocomial infections. The patient will

be followed-up to hospital discharge, D28, and D90. At these time points, vital status will be recorded. Below is a flowchart of patient follow-up.

	Inclu-sion	Rando-mization	D0*	D1 to Dn	End of study	D28	D90
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			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

*from time at inclusion to 11:59 pm

Design of the ancillary studies

Ancillary study 1

The plasma citrulline and I-FABP assays on D0, D3, and D8 will be performed using blood drawn as part of the standard care of critically ill patients; the volume of each blood sample will be increased slightly (by about 2 mL) to allow these assays. For amino acid chromatography, blood will be drawn in a lithium heparin tube, which will be transported on ice as promptly as possible to the medical biochemistry laboratory. At arrival at the laboratory and within 2 hours after blood collection, the sample will be centrifuged (4°C, 1900 rpm, 10 minutes) and the plasma stored at -70 °C until the analysis.

The samples will be centralized at the Biology Center of the Besançon Teaching Hospital. After thawing and deproteinization, ion-exchange chromatography will be performed on a Hitachi L-8800 analyzer (Hitachi, Tokyo, Japan).

I-FABP will be assayed using a blood sample drawn into an EDTA tube, which will be taken as rapidly as possible to the medical biochemistry laboratory. At arrival at the laboratory, the sample will be centrifuged (4°C, 1500 rpm, 15 minutes) and the plasma stored at -70°C until analysis by ELISA (Hycult Biotech, Uden, The Netherlands) at the Biology Center of the Besançon Teaching Hospital.

Ancillary study 2

Tracheal aspiration will be performed according to standard practice in the study centers. All tracheal aspirates obtained within 48 hours after randomization for the NUTRIREA2 trial will be stored frozen at each study center. The frozen aspirates will be sent to the Biochemistry Department of the Lille Teaching Hospital (Dr. M. Balduyck, Dr. F. Zerimech, and Dr. P. Maboudou), where the pepsin and salivary amylase assays will be performed.

The measures taken to prevent microaspiration will comply with current recommendations and with standard practice in each study center. They will consist of the following:

- Endotracheal tube cuff pressure kept at about 25 cm H_2O;
- Semi-recumbent patient position;
- Application of at least 5 cmH_2O of positive end-expiratory pressure (PEP) in patients without contraindications;
- Daily evaluation of criteria for weaning off mechanical ventilation, to minimize the duration of mechanical ventilation;
- No routine prophylactic treatment of stress-induced ulcers; and
- Limited use of sedation and application of a sedation management protocol.

5.15 4.3 Description of measures taken to minimize and avoid biases

4.3.1 Random allocation

The randomization scheme will be stratified on the study site. Patient category (postoperative or medical) will not be used for stratification, as the distribution between postoperative and medical patients is expected to be heavily skewed (based on earlier studies, surgical patients are expected to contribute only 10% of the study population). Random allocation will be performed using the electronic case-report form available at each study center.

4.3.2 Blinding methods

The trial will be open, since nutritional support requires the intervention of a nurse and involves two different routes of administration (enteral or parenteral), one for each group of study patients.

Given the absence of blinding, the secondary endpoints relevant to nosocomial infections will be validated by an adjudication committee. Nosocomial infections are of the utmost clinical importance, and the results of our study may have a major impact on future patient management. Consequently, a very high level of uniformity in data collection is crucial to ensure that highly reliable results are obtained.

4.4 Expected duration of study patient participation and description of the time sequence and duration of all trial periods, including follow-up, where applicable

The duration of participation of each patient in the study will depend on the time to extubation. The vital status of each patient will be recorded at ICU discharge, at hospital discharge, on D28, and on D90. For patients discharged before D28 and/or D90, a telephone interview will be arranged.

Study recruitment is expected to last 30 months, yielding a total patient follow-up time of 36 months.

4.5 Reasons for permanent or temporary study discontinuation

4.5.1 Patient withdrawal from the study

The patients or next of kin may ask to withdraw from the study at any time and for any reason. In the event of secondary withdrawal of consent to participation in the research project, none of the data collected since study inclusion of the patient will be used, in compliance with the wishes of the patient or next of kin. Withdrawal of a patient from the study will have no impact on the standard care delivered to the patient for the condition that prompted the hospital admission. The laboratory tests specific to the study nutritional-support protocol will not be performed. All investigations and treatment decisions will be at the discretion of the physician in charge of the patient.

Should a patient be lost to follow-up, all data for that patient collected since study inclusion will be used, and the investigator will make every effort to contact the patient.

4.5.2 Discontinuation of all or part of the study

Given that this study investigates standard practice, no study discontinuation criteria have been defined in advance, except the following:

1. scientific publication resulting in a consensus that challenges the primary study hypothesis or the method used to treat mechanically ventilated patients;
2. interim analysis conducted by the independent data monitoring committee and showing an early significant difference in the primary endpoint .

4.6 Data collection

All the study data are collected routinely in ICUs for the management of mechanically ventilated patients with shock.

<u>Demographics and clinical data</u>

- At inclusion: date of birth, sex, date of ICU admission, reason for ICU admission, McCabe and Knaus scores, chronic co-morbidities, body weight, height, BMI, and SOFA score
- at H24: SAPS II and SOFA score

- follow-up: date of final extubation, date of ICU discharge, date of hospital discharge (Acute care hospital), vital status at ICU discharge, and vital status at hospital discharge

Nutritional data, every day, *until extubation of the patient*: name of the enteral or parenteral preparation; target number of calories; volume and calories delivered each day; vomiting (yes/no every 4 hours, with the time of any vomiting episodes); decrease or discontinuation of nutritional support (yes/no); reason for decreasing or discontinuing nutritional support (vomiting, diarrhea, acute pseudoobstruction of the colon, other acute abdominal symptoms, abdominal complication, imaging study/other); presence, volume, and appearance of the stools (yes/no every 4 hours, exact volume in mL and, where applicable, qualitative description as normal/liquid/mucopurulent/mucous/bloody); and diarrhea with its presumed cause (intolerance to nutritional support, medication, *Clostridium difficile*, other).

Treatments given: Every day, *until extubation of the patient*: prokinetic agent (dose/24 h), polyethylene-glycol (dose/24 h), neostigmine (dose/24 h), sedation (dose/24 h and nature of the hypnotic and/or opioid agents), neuromuscular blockers (dose /24 h), catecholamines (dobutamine, noradrenaline, or adrenaline; yes/no regardless of duration and dose), renal replacement therapy (yes/no), antibiotics (yes/no), insulin (total dose/24 h), volume of IV fluids (total/24 h), and gastric anti-secretory agents (sucralfate, proton-pump inhibitors, histamine receptor antagonists, other).

Laboratory data

- D1: hemoglobin, leukocytes, platelets, Na, K, Ca^{2+}, Ph, PaO_2, $PaCO_2$, pH, arterial lactic acid, bicarbonate, urea, creatinine, bilirubin, ASAT-ALAT, gamma-glutamyl transpeptidase, alkaline phosphatase, and total protein
- Daily from D1 to D7 (if extubation before D7: on the day of extubation then stop): PaO_2, arterial lactic acid, bilirubin, ASAT-ALAT, gamma-glutamyl transpeptidase, alkaline phosphatase, glucose, protein, Na, K, Ca^{2}+, Ph,, creatinine, and SOFA
- Albumin, pre-albumin, transthyretin, and CRP on D1 and D7 or on the day of extubation

Nosocomial infections (one data-collection form per infection): VAP (date, organism, resistance profile), bacteremia (date, organism, resistance profile), intravascular catheter-related infection (date of the diagnosis, organism, resistance profile), urinary tract infection (date of the diagnosis, organism, resistance profile), soft tissue infection (date of the diagnosis, organism, resistance profile); and other (type, date of the diagnosis, organism, resistance profile).

Invasive devices: endotracheal tube (dates of insertion and removal), intravascular catheters (dates of insertion and removal), and urinary catheters (dates of insertion and removal)

Additional data collected during the ancillary studies

- Ancillary study 1

Plasma citrulline and I-FABP assays on D0, D3, and D8. Blood will be drawn by the nurse in charge of the patient as part of standard care. Each blood sample will be labeled with the number assigned to the patient, the first initial of the patient's last and first names, the patient's date of birth, the date and time of sample collection, and the number assigned to the sample.

For amino acid chromatography, the blood samples will be centrifuged within 2 hours after collection (4°C, 1900 rpm, 10 minutes) and the plasma stored at -70 °C at the study center.

For the I-FABP assay, the blood samples will be centrifuged (4°C, 1500 rpm, 15 minutes) and the plasma stored at -70°C until the analysis.

An accredited transporter will take the samples to the Biology Center of the Besançon Teaching Hospital, where they will be processed. The samples will be destroyed after the assays are performed.

- Ancillary study 2

D0, D3, and D8: pepsin and salivary amylase assays in all tracheal aspirates

The tracheal aspirate samples will be collected by the nurse in charge of the patient, according to standard practice. Each sample will be labeled with the number assigned to the patient, the first initial of the patient's last and first names, the patient's date of birth, the date and time of sample collection, and the number assigned to the sample. Each tracheal aspirate sample (about 1-2 mL per aspirate) will be stored at -20 °C at the biochemistry department of each

study center. An accredited transporter will take the samples to the Biology and Pathology Center of the Lille Teaching Hospital, under the responsibility of Dr Balduyck, Dr Zerimech, and Dr Maboudou, for blinded assays of pepsin and salivary amylase. Pepsin levels will be measured using an ELISA, under the responsibility of Dr. Zerimech and Dr Balduyck, at the Molecular Biochemistry-Biology Laboratory headed by Pr. N. Porchet, Biochemistry Department, Lille Teaching Hospital. The amylase assays will be performed under the responsibility of Dr Maboudou at the Biochemistry, Proteins, and Predictive Biology Laboratory headed by Pr N. Porchet, Biochemistry Department, Lille Teaching Hospital. A colorimetric enzyme assay will be used. The level of salivary amylase will be computed as the difference between total and pancreatic amylase levels. The samples will be destroyed after the assays are performed.

5 SELECTION AND EXCLUSION OF PATIENTS FOR THE STUDY

5.16 Inclusion criteria to be met by study participants

- Invasive mechanical ventilation for an expected duration of at least 48 hours
- Nutritional support started within 24 h after intubation
- Treatment with a vasoactive amine (adrenaline, dobutamine, or noradrenaline) via a central venous catheter
- Age older than 18 years
- Informed about the study and having consented to participation in the study
- Covered by the French public health insurance system

5.17 Noninclusion criteria to be absent in study participants

- Invasive mechanical ventilation started more than 24 h earlier
- Patient admitted for an acute gastrointestinal condition that contraindicates enteral nutrition
- 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 pre-existing long-term home enteral or parenteral nutrition
- Active gastrointestinal bleeding
- Dying patient – not-to-be-resuscitated order or other treatment-limitation decision at ICU admission
- Adult under guardianship
- Pregnancy, recent delivery, or lactation
- Department of corrections inmate
- Institutionalized patient
- Prior inclusion in a randomized trial designed to compare enteral and parenteral nutrition
- Contraindication to parenteral nutrition: known hypersensitivity to egg or soybean proteins or to another component, inborn error in amino-acid metabolism, or severe familial dyslipidemia affecting triglyceride levels

5.3 Recruitment modalities

Participation in the study will be suggested to all patients admitted to the study ICUs, given vasoactive amine therapy, placed under invasive mechanical ventilation for an expected duration of at least 48 h, and requiring early enteral or parenteral nutritional support.

5.4 Contraindication to participation in another research project

Patients included in this study will not be eligible for participation in other studies that compare enteral and parenteral nutrition and/or that have the same objectives.

5.5Critères d'inclusion des personnes qui se prêtent aux études ancillaires

Patients meeting the criteria for inclusion in the NUTRIREA2 trial will be eligible for inclusion in the ancillary studies, after the patient, a relative, or a surrogate receives information and states that he/she has no objection to inclusion in the ancillary studies (see the specific patient information document in the appendix).

6 PRODUCTS ADMINISTERED TO THE STUDY PARTICIPANTS

6.1 Study intervention

We will evaluate two strategies for initiating nutritional support: first-line parenteral nutrition and first-line enteral nutrition. Patients allocated at random to the enteral-nutrition group (E) will receive enteral nutrition only; and those allocated at random to the parenteral-nutrition group (P group) parenteral nutrition only for at least 72 hours and until day 7 of invasive mechanical ventilation, except if the physician in charge decides that the clinical situation mandates continued parenteral nutrition. In both groups, nutritional support will be started within 24 h after intubation. The selection of nutritional preparations will be at the discretion of the investigators according to availability and standard protocols used in each ICU.

The daily calorie target in both groups is 20-25 Kcal/Kg/day at the acute phase of ICU management, in compliance with current recommendations (4-6, 77). This calorie intake is adequate in over 90% of ICU patients with systemic insults and equals 1.3- to 1.5-fold the mean resting energy expenditure (REE) estimated using simplified equations. In addition, this calorie intake avoids overnutrition, which may induce deleterious effects (metabolic and hepatobiliary complications) (77-79).

In the enteral-nutrition group (E group), the patients will receive first-line enteral nutrition. In the event of persistent intolerance precluding achievement of the calorie targets, supplemental parenteral nutrition may be added starting on day 8 (6, 72).

In the parenteral-nutrition group (P group), the course of action will be guided by the hemodynamic evaluations conducted daily starting 72 hours after parenteral nutrition initiation and until day 7. A stable hemodynamic status is defined for this study as discontinuation of the vasoactive amines and a normal level of arterial lactic acid (<2 mmol/L). As soon as these two criteria are met, the patient will be switched from parenteral to enteral nutrition, in the absence of absolute contraindications to the enteral route. The calorie targets and mode of nutritional-support initiation are identical to those in the early enteral-nutrition group (E group). Starting on D8, in patients without contraindications to enteral feeding, the enteral route will be substituted for the parenteral route.

After extubation, regardless of the time since randomization, decisions about the continued need for, and optimal route of, nutritional support will be at the discretion of the physician in charge of the patient.

6.2 Treatments that may be used

All the medications whose use is standard practice for ICU patients will be used according to the specific needs of each patient.

6.3 Treatments that may not be used

Given that this study evaluates standard care, no medication used according to its marketing authorization is contraindicated.

7 STATISTICS

The statistical analysis will be carried out at the CIC INSERM 202 under the responsibility of Bruno Giraudeau. The analyses will be performed using SAS 9.2 and R software.

7.1 Description of planned statistical methods, with the schedule of planned interim analyses

The statistical analysis will be conducted according to a predefined plan. The analysis will follow the intention-to-treat (ITT) approach, as recommended for superiority studies. Two interim analyses will be performed, given the need for a large number of included patients. A statistical analysis report will be written to describe all the findings to be communicated, according to CONSORT Statement recommendations, while taking into account the specific features of the trial, i.e., the nonpharmacological nature of the intervention (http://www.consort-statement.org/).

7.1.1 Description of the groups at baseline

The groups established by randomization will be compared using descriptive statistics. No statistical tests will be performed.

7.1.2 Analysis populations

The ITT approach will be used: each patient will remain in the group assigned by randomization, regardless of subsequent events.

7.1.3 Analysis of the primary endpoint

Day-28 mortality will be reported as the point estimate with the 95% confidence interval in each group. Day-28 mortality will be compared between the two groups using the chi-square test.

7.1.4 Analysis of secondary endpoints

- For the analysis of patients with at least one nosocomial infection,
  - we will use a competitive-risk model, with death as the competing risk, since patients who have died cannot experience nosocomial infections;
  - in addition, the proportion of patients having at least one nosocomial infection will be analyzed in the same way as the primary endpoint, in order to obtain a sensitivity analysis of observed results.

- VAP
  - proportion of patients with at least one VAP episode: the method used will be the same as for nosocomial infections, with not only death as a competing risk, but also time to extubation +2 days, since after this point any episode of pneumonia would not be classified as a VAP episode;
  - VAP incidence density as the point estimate with the 95% confidence interval;
  - number of VAP episodes per patient analyzed using a negative binomial regression model with no offset variable
- Bacteremia, central venous catheter (CVC)-related infections, urinary tract infections, soft tissue infections: each of these categories of infection will be analyzed using the same method as for the pooled nosocomial infections
- Descriptive bacteriological data (organisms recovered with their resistance profiles for each nosocomial infection): only descriptive analyses will be performed
- Proportion of patients with at least one episode of vomiting or regurgitation: the method will be the same as for the primary analysis
- Proportion of patients with at least one episode of diarrhea: the method will be the same as for the primary analysis
- Proportion of patients with at least one episode of constipation: the method will be the same as for the primary analysis
- Proportion of patients with at least one documented episode of acute pseudoobstruction of the colon (Ogilvie syndrome): the method will be the same as for the primary analysis
- Proportion of patients with at least one documented episode of bowel ischemia: the method will be the same as for the primary analysis
- Proportion of patients with at least one mechanical complication of CVC insertion: the method will be the same as for the primary analysis

- Proportion of patients with at least one episode of CVC obstruction or other dysfunction requiring a change of CVC: the method will be the same as for the primary analysis
- The number of calories delivered each day by the enteral and parenteral routes: changes over time in delivered calories will be represented graphically by boxplots created each day on the same graph; changes over time will be compared between the two groups using a mixed linear model, after data transformation if necessary
- Volume of enteral and parenteral feeds delivered each day: the analysis method will be the same as for the number of calories
- Ratio of prescribed over delivered calories: the proportions of patients who achieved their daily calorie target will be determined at each follow-up time point (in days) and will be compared between the two groups using a logistic random effects model
- ICU mortality, 90-day mortality, and hospital mortality: 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
- Nutritional markers and body weight: changes over time in nutritional markers and body weight will be analyzed using the method described above for the number of calories delivered
- Proportion of patients with at least one episode of liver dysfunction: the method will be the same as for the primary objective
- Times in the ICU, in the hospital, and on mechanical ventilation will be compared between the two groups using nonparametric Wilcoxon tests

7.1.5 Analysis of the outcome measures for the ancillary studies

– ANCILLARY STUDY 1

  - Analysis of the primary outcome measure

Plasma citrulline levels at H72 will be analyzed using the approach described for the calorie intake.

- Analysis of the secondary outcome measures

- SOFA score: SOFA score changes over time will be evaluated graphically by placing daily boxplots on the same graph. For between-group comparisons of SOFA score changes over time, a mixed linear model will be built, after transformation of the data if needed.
- Plasma citrulline and I-FABP levels at D0, D3, and D8: the changes in these variables over time will be evaluated graphically by placing daily boxplots on the same graph. For between-group comparisons, a mixed linear model will be built, after transformation of the data if needed.
- Proportion of patients whose plasma I-FABP is ≥100 pg/mL on D0, D3, and D8: the analysis method will be the same as for the primary NUTRIREA2 outcome measure.
- Proportion of patients whose plasma citrulline is ≤10 µL/L on D0, D3, and D8: the analysis method will be the same as for the primary NUTRIREA2 outcome measure.
- Proportion of patients with at least one episode of bacteremia: the analysis method will be the same as for the primary NUTRIREA2 outcome measure.
- Proportion of patients with at least one episode of gastrointestinal intolerance: the analysis method will be the same as for the primary NUTRIREA2 outcome measure.
- Proportion of patients with at least one episode of diarrhea: the analysis method will be the same as for the primary NUTRIREA2 outcome measure.

– ANCILLARY STUDY 2

- Analysis of the primary outcome measure

The chi-square test will be applied to compare the proportion of patients with abundant microaspiration in the two groups. The odds ratio with its 95% confidence interval will be computed.

- Analysis of the secondary outcome measures

Patient characteristics in the two groups will be compared. Qualitative variables will be compared using either the chi-square test or Fisher's exact test. Shapiro-Wilk's test will be applied to determine whether the quantitative variables are normally distributed. These quantitative variables will then be compared using Student's *t* test if normally distributed and the Mann-Whitney U test otherwise.

7.2 Estimated sample size, and estimated numbers of patients recruited at each study center, with supporting statistical information

This clinical randomized controlled superiority trial will seek to demonstrate that the D28 mortality rate in patients admitted to the ICU and treated with mechanical ventilation and vasoactive amines is lower in patients given early enteral nutrition than in patients given early parenteral nutrition. Assuming a 37% D28 mortality rate in the parenteral-nutrition group and a 5% decrease in mortality with early enteral nutrition (i.e., a D28 mortality rate of 32%), with the alpha risk set at 4.9% and the beta risk at 20%, 1427 patients are needed in each group (Newcombe, Statist Med 1998; 17:873-890), i.e., a theoretical total of 2854 patients.

The mortality rates used for the sample size estimation are those obtained in the NUTRIREA-1 randomized controlled trial in nine centers (CRICS network), in which similar inclusion criteria were used.

Ancillary studies

– *Ancillary study 1*

The primary outcome measure is the plasma citrulline level at H72. To demonstrate a significant difference between plasma citrulline levels of 16 µmoL/L (enteral-nutrition group) and 12 µmoL/L (parenteral-nutrition group), with a standard deviation of 8 µmoL/L, a two-tailed test, the alpha risk set at 0.05, and 90% power, 85 patients will be needed in each group (170 patients in all).

– *Ancillary study 2*

The primary outcome measure is the proportion of patients with abundant microaspiration. We expect that the proportion of patients with abundant microaspiration will be 50% in the enteral-nutrition group and 30% in the parenteral-nutrition group. With the alpha risk set at 0.05, to obtain 80% power, 94 patients will be needed in each group (188 patients in all), with simple random sampling.

7.3 Degree of statistical significance planned for the study

The statistical tests will be performed using a significance threshold of 1% for the interim analyses and 4.9% for the final analysis.

7.4 Statistical rules for study discontinuation

We will perform two interim analyses, after inclusion of the first 1000 and the first 2000 patients, respectively. We will use Peto's boundary (*Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612. PMID*):

- the significance level associated with the first interim analysis is 0.01;
- the significance level associated with the second interim analysis is 0.01;
- the significance level associated with the final analysis is 0.049.

This method yields an overall Type I error of 5%.

7.5 Handling of missing, unused, or invalid data

In this study, patients from whom consent to the study was not obtained and those who secondarily withdrew their consent will not be included in the analyses. Apart from these two situations, the likelihood that patients will be lost to follow-up is small. The study patients will be admitted to ICUs, and the primary endpoint is objective (D28 mortality). However, should there be any patients for whom information on the primary endpoint is missing, then these patients would be considered as having died before D28, in both randomized arms.

7.6 Handling of changes to the initial statistical analysis plan

The statistical analysis plan will be finalized when the database is locked.

7.7 Selection of patients to be included in the analyses

The analyses will be conducted using the intention-to-treat (ITT) approach.

8 RATIONALE FOR REQUESTING CATEGORIZATION OF THE TRIAL AS A STUDY OF STANDARD CARE

Given the characteristics of the research project, the chief investigator considers that this project is primarily a **study of standard care**, based on the following arguments:

- all the nutritional-support interventions and protocols will be performed according to standard ICU practice;
- the study consists in evaluating combinations of diagnostic and prophylactic interventions and medical strategies (nutrition administration and monitoring protocol, diagnosis of VAP) that are used in everyday practice, i.e., whose indications are defined by professional consensus;
- the study does not involve any techniques or strategies that are innovative or obsolete;
- the combination of interventions (enteral or parenteral nutrition) is not new;
- the study consists in comparing two medical strategies (enteral and parenteral nutrition) for which no available data indicate that one is better than the other in terms of safety or efficacy.

  Indeed,

  - international guidelines recommend a specific management strategy (prefer early enteral nutrition over parenteral nutrition)
  - but this strategy is either not used at all or used improperly in a large number of patients, for the following reasons:
    1. it is in itself a source of potential complications, and concern about this risk and/or the need to manage the complications should they occur result in an increased workload and in delayed or absent use of early enteral nutrition;
    2. the available studies (metaanalyses) have produced conflicting results;
    3. and the authors of the recommendations acknowledge that their guidelines rest on converging data and indirect studies and not on sound evidence, most notably from randomized trials that are adequately powered and use relevant clinical objectives;
  - the widely conflicting results of recent studies on early supplemental parenteral nutrition constitute indirect evidence that the issue remains unsettled.
- Finally, the specific modalities used in the study are expected to minimize risks (by increasing the stringency of the enteral and parenteral nutrition delivery protocols) and place only negligible constraints on study participants (Article R 1121-3 of the French Public Health Code [CSP], decree n° 2006-477, 26 April 2006).

The Poitiers Ouest III ethics committee (*Comité de Protection des Personnes de Poitiers Ouest III*) has categorized the NUTRIREA-II trial as a study of standard care and has approved the conduct of the NUTRIREA-II trial (approval date, 26 January 2012, see letter enclosed).

9 RIGHT OF ACCESS TO THE STUDY DATA AND SOURCE DOCUMENTS

9.1 Access to the study data

The medical data about each patient will be communicated only to the institution with which the chief investigator is affiliated or to a person appointed by the chief investigator under conditions that ensure the confidentiality of the patient data.

9.2 Source documents

If needed, the institution to which the chief investigator is affiliated may request direct access to the medical record to check the study procedures and/or data, without violating confidentiality rules and within the limits set by laws and regulations.

9.3 Data confidentiality

Individuals having direct access to the study data will take all the necessary precautions to ensure the confidentiality of the data pertaining to the study participants, most notably regarding their identity and the results obtained during the study.

These individuals, together with the study investigators, are under an obligation to maintain confidentiality (under the conditions defined in articles 226-13 and 226-14 of the French penal code). During or at completion of the study, the data collected from the study participants and communicated by the individuals involved in the study will be rendered anonymous.

Under no circumstances will the names or addresses of the study participants be included in the study data.

Only the first letter of the last name and the first letter of the first name of each patient will be recorded, and these letters will be combined with a number to form a study-specific identifier reflecting the order of patient inclusion.

10 QUALITY ASSURANCE

To optimize the conduct of the study, a Clinical Research Assistant (CRA) will be in charge of performing the following tasks:

- preparation of the file to be submitted to the ethics committee (*Comité de Protection des Personnes*, CPP) and of the files for the CCTIRS and CNIL;
- finalization of the study documents (e.g., case-report form) and communications among individuals involved in conducting the study;
- study initiation in the study centers;
- verification of the data collected for the study;
- and documentation, registering, and reporting of the study data, in compliance with Standard Operating Procedures.

11 ETHICAL EVALUATION OF THE SPECIFIC MONITORING MODALITIES DEFINED IN THE RESEARCH PROTOCOL

11.1 Ethics committee (Comité de Protection des Personnes, CPP)

This research protocol and the patient information and consent documents have been submitted to the Poitiers CPP, which categorized the trial as a study of standard care and approved the conduct of the trial (approval date, 26 January 2012, see letter enclosed).

11.2 Substantial modifications

Any substantial modification to the study protocol will be communicated to the ethics committee (CPP) to ensure that the suggested modifications have no adverse effect whatsoever on the protection afforded to the study participants.

11.3 Patient information sheet and informed consent form

The patients will receive full and honest information, delivered in understandable terms, about the study objectives and their right to refuse to participate in the study or to withdraw from the study at any time. This information will be given in a patient information and

informed consent document, which will be handed to each patient. An information document dealing specifically with the ancillary studies will also be given to each patient.

12 HANDLING OF THE STUDY DATA AND STORAGE OF THE STUDY DOCUMENTS AND DATA

12.1 Case-report form

An Internet-based data collection tool will be used for this study. This electronic case-report form will be available at each of the study centers. Access to the electronic case-report form will require only an Internet connection and a browser. A document explaining how to use the electronic case-report form will be given to the study investigators.

Tests designed to check data consistency will be performed as an integral part of the electronic format. The electronic case-report form has an audit function that tracks any modifications made to the study data. The audit function also clearly identifies the person who made the modification, as well as the date. The reason for the modification can be supplied as a comment if deemed appropriate.

12.2 Data entry and analysis

The data will be entered into an electronic case-report form via an Internet browser.
The data will be analyzed by a biostatistician at the CIC INSERM202, under the responsibility of Bruno Giraudeau.

12.3 French Data Protection Authority (CNIL)

Approval of the data handling procedure required for the study will be sought from the French Advisory Committee on Data Handling in Healthcare Research (CCTIRS) and, subsequently, permission will be requested from the French Data Protection Authority (CNIL) regarding the handling of personal data with the goal of conducting research on standard care.

13 FUNDING AND INSURANCE

13.1 Study budget

Since this study will investigate standard care, the medical interventions will not require special funding. The expected total duration of the study is 3 years (30 months for patient inclusion and 6 months for follow-up and data verification) for 28 centers. The study will therefore require the following financial resources:

- CRA time for
  - study monitoring and coordination (10% of a full-time salary, for 3 years): 14 265 €;
  - monitoring visits (study initiation and completion visits, four 2-day visits /year/center, i.e., two full-time ARC salaries for 3 years): 285 300 €
- Clinical research technician (CRT) or clinical research nurse (CRN) time in each study center to assist in preparing and implementing the electronic case-report form and in study coordination and logistics, and to enter data into the electronic case-report form (4 to 5 h minimum/patient, i.e., for a mean of 102 patients included in each study center, 10% of a full-time salary/year for 3 years): 376 320 €
- Data handling:
  - Data management time to create the electronic case-report form and to monitor data quality (20% of a full-time salary the first year and 7% for each of the next 2 years): 15 096 €
  - Statistical analysis (1 month full-time, during the last year): 5000 €
- Meetings, coordinator missions (three 1-day-long meetings/3 years – 2 representatives/center for 28 centers; mean cost of 100 € per trip): 16 800 €
- Travel expenses for on-site study initiation, monitoring, and study completion visits (4.5 visits per an and per center on average, i.e., 378 visits each lasting 2 days, with a mean cost of 200 €): 75 600 €
- Stationery for the patient information and consent documents to be given to the patients or next of kin, bedside nutrition monitoring charts: 5100 €
- Study report costs (translation and submission: 2000 €) and costs of study result presentation at one national meeting (1000 €) and one international meeting (2000 €): 5000 €

Total budget: 798 481 € (not counting operating expenses estimated at 10%)

13.2 Insurance

The ethics committee has categorized the trial as a study of standard care, thus indicating that study participation involves no additional risks to the patients, and consequently the insurance held by the facilities delivering medical care to the study patients will cover the activities of the study (article L.1142-2 of the French Public Health Code).

14 STUDY FEASIBILITY

The study will be conducted in the 28 study centers, which include centers belonging to the Clinical Research in Intensive Care and Sepsis (CRICS) network. The feasibility of the NUTRIREA-2 trial was assessed based on the results of the NUTRIREA-1 trial, in which nine CRICS network centers participated during the 8-month study inclusion period. In all, 1736 patients were evaluated for study eligibility and 452 were included. In this population, 239 patients received vasoactive amine therapy. After the exclusion of two centers where previous organizational difficulties – now resolved – resulted in the inclusion of only very few patients, the mean number of patients included per month and per center was 4.3. These data establish the feasibility of NUTRIREA-2 with 28 participating centers and an inclusion period of 30 months at the most.

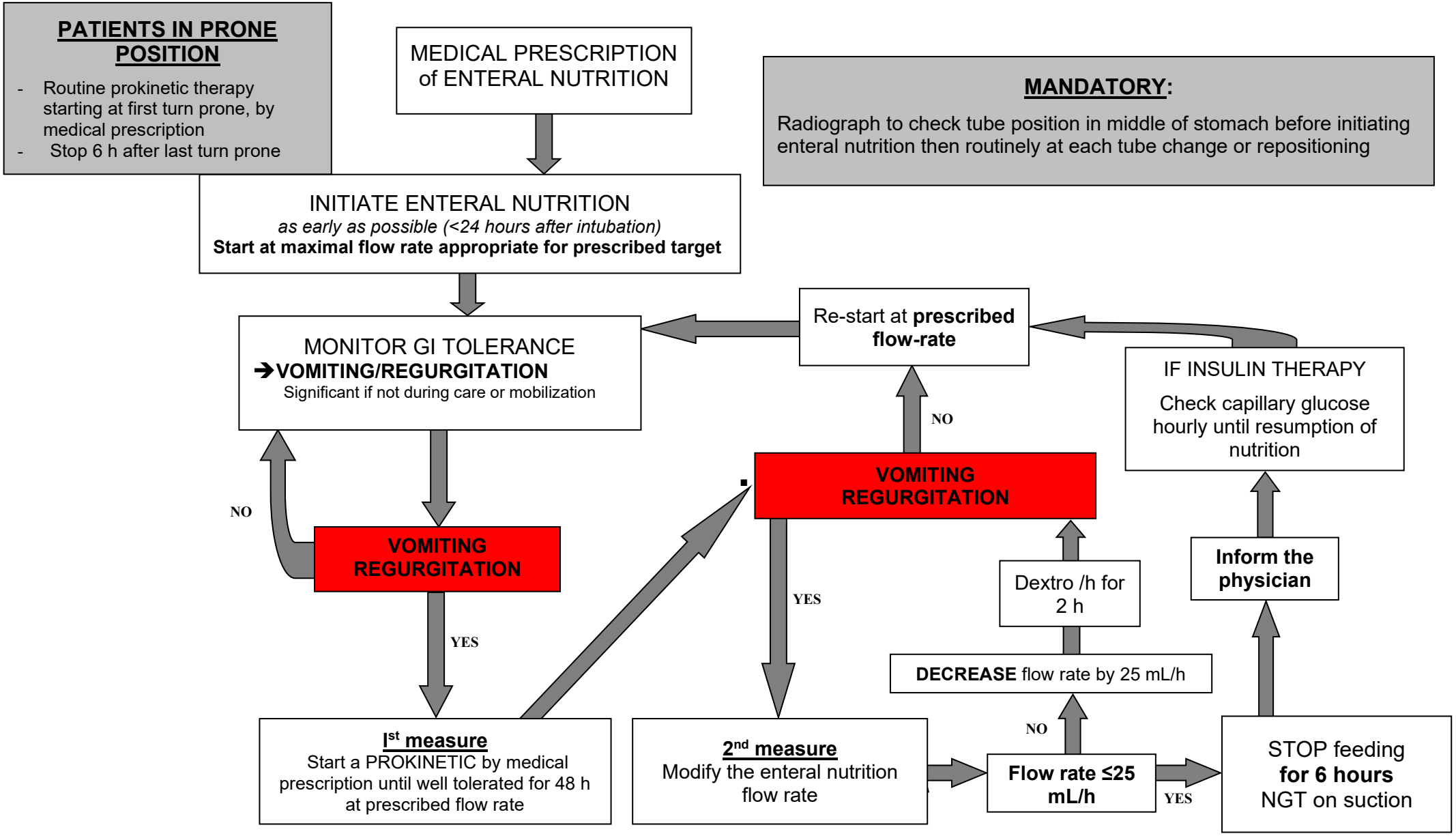
15 PUBLICATION POLICY

Communications and scientific reports relevant to this study will be under the responsibility of the chief investigator, who will obtain the approval of the other investigators. The co-authors of the study report and publications will be the investigators and clinicians involved in the study, in proportion to their contributions to the study, together with the biostatistician and associated investigators.

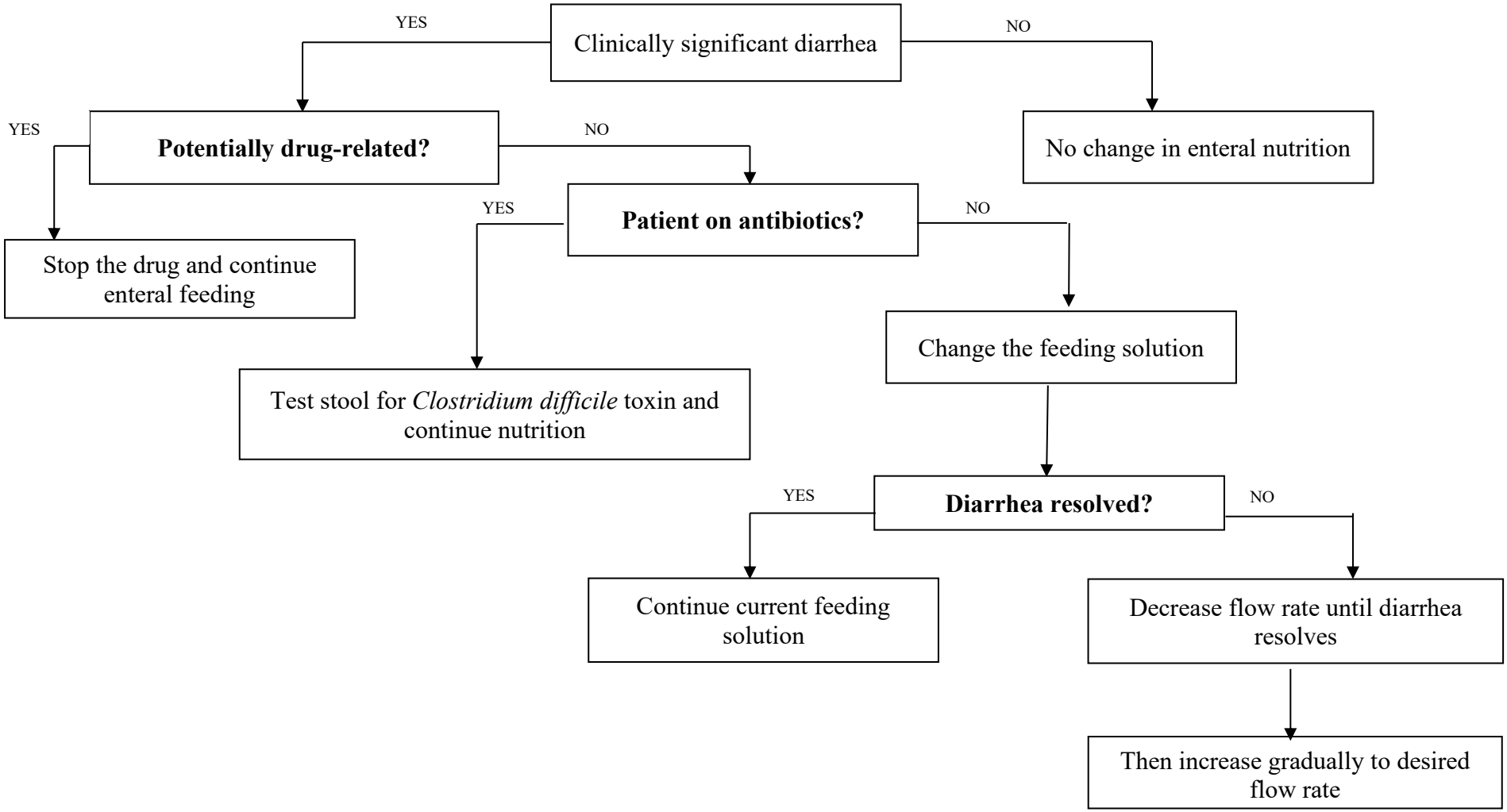
The publication policy will comply with international recommendations (N Engl J Med, 1997; 336:309-315).

16 APPENDICES

Appendix 1: Protocol for managing upper gastrointestinal intolerance (71)



Appendix 2: Protocol for managing diarrhea, from Doig et al. (15)



17 REFERENCES

1. Erny P. Nutrition de l'agressé. Conférence de consensus de la société francophone de nutrition entérale et parentérale. *Reanimation Urgences* 1998;7:347-356.

2. 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.

3. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. Espen guidelines for nutrition screening 2002. *Clin Nutr* 2003;22:415-421.

4. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, Ebner C, Hartl W, Heymann C, Spies C. Espen guidelines on enteral nutrition: Intensive care. *Clin Nutr* 2006;25:210-223.

5. Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of critical care medicine and american society for parenteral and enteral nutrition: Executive summary. *Crit Care Med* 2009;37:1757-1761.

6. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G. 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.

7. Thuong M, Leteurtre S. Recommandations des experts de la société de réanimation de langue française. Nutrition entérale en réanimation. *Reanimation* 2003;12:350-354.

8. Beier-Holgersen R, Brandstrup B. Influence of early postoperative enteral nutrition versus placebo on cell-mediated immunity, as measured with the multitest cmi. *Scand J Gastroenterol* 1999;34:98-102.

9. Bortenschlager L, Roberts PR, Black KW, Zaloga GP. Enteral feeding minimizes liver injury during hemorrhagic shock. *Shock* 1994;2:351-354.

10. 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.

11. 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.

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. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: A systematic review. *Crit Care Med* 2001;29:2264-2270.

14. 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.

15. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, Dobb G. Effect of evidence-based feeding guidelines on mortality of critically ill adults: A cluster randomized controlled trial. *JAMA* 2008;300:2731-2741.

16. Braga M, Gianotti L, Costantini E, Di Francesco A, Socci 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.

17. Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: Impact of route of administration and composition of the diet. *Crit Care Med* 1998;26:24-30.

18. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: A meta-analysis. *Am J Clin Nutr* 2001;74:534-542.

19. Elke G, Schadler D, Engel C, Bogatsch H, Frerichs I, Ragaller M, Scholz J, Brunkhorst FM, Loffler M, Reinhart K, Weiler N. 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.

20. 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.

21. Heyland DK, Dhaliwal R. Early enteral nutrition vs. Early parenteral nutrition: An irrelevant question for the critically ill? *Crit Care Med* 2005;33:260-261.

22. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, Kuhl MR, Brown RO. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg* 1992;215:503-511; discussion 511-503.

23. Li J, Kudsk KA, Gocinski B, Dent D, Glezer J, Langkamp-Henken B. Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. *J Trauma* 1995;39:44-51; discussion 51-42.

24. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ* 2004;328:1407.

25. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma--a prospective, randomized study. *J Trauma* 1986;26:874-881.

26. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, Kellum JM, Welling RE, Moore EE. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. *Ann Surg* 1992;216:172-1783.

27. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. Ten versus tpn following major abdominal trauma--reduced septic morbidity. *J Trauma* 1989;29:916-922; discussion 922-913.

28. 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; discussion 260-211.

29. Windsor AC, Kanwar S, Li AG, Barnes E, Guthrie JA, Spark JI, Welsh F, Guillou PJ, Reynolds JV. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998;42:431-435.

30. Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. Nutrition therapy in the critical care setting: What is "best achievable" practice? An international multicenter observational study. *Crit Care Med* 2010;38:395-401.

31. Drover JW, Cahill NE, Kutsogiannis J, Pagliarello G, Wischmeyer P, Wang M, Day AG, Heyland DK. Nutrition therapy for the critically ill surgical patient: We need to do better! *JPEN J Parenter Enteral Nutr* 2010;34:644-652.

32. 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.

33. 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:R218-225.

34. 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.

35. Heyland D, Cook DJ, Winder B, Brylowski L, Van deMark H, Guyatt G. Enteral nutrition in the critically ill patient: A prospective survey. *Crit Care Med* 1995;23:1055-1060.

36. Preiser JC, Berre J, Carpentier Y, Jolliet P, Pichard C, Van Gossum A, Vincent JL. Management of nutrition in european intensive care units: Results of a questionnaire. Working group on metabolism and nutrition of the european society of intensive care medicine. *Intensive Care Med* 1999;25:95-101.

37. Rice TW, Swope T, Bozeman S, Wheeler AP. Variation in enteral nutrition delivery in mechanically ventilated patients. *Nutrition* 2005;21:786-792.

38. Rohm KD, Schollhorn 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.

39. Heyland DK, Schroter-Noppe D, Drover JW, Jain M, Keefe L, Dhaliwal R, Day A. Nutrition support in the critical care setting: Current practice in canadian icus--opportunities for improvement? *JPEN J Parenter Enteral Nutr* 2003;27:74-83.

40. De B, 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.

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. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: A multicenter study. The nutritional and metabolic working group of the spanish society of intensive care medicine and coronary units. *Crit Care Med* 1999;27:1447-1453.

45. 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.

46. 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.

47. 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.

48. Kolbel 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.

49. Landzinski J, Kiser TH, Fish DN, Wischmeyer PE, MacLaren R. Gastric motility function in critically ill patients tolerant vs intolerant to gastric nutrition. *JPEN J Parenter Enteral Nutr* 2008;32:45-50.

50. 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:S80-85.

51. 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.

52. Schuster-Bruce M. Gastric emptying in the critically ill. *Crit Care Med* 2001;29:1293-1294.

53. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165:867-903.

54. Villet S, Chiolero RL, Bollmann MD, Revelly J-P, Cayeux R N M-C, Delarue J, Berger MM. Negative impact of hypocaloric feeding and energy balance on clinical outcome in icu patients. *Clin Nutr* 2005;24:502-509.

55. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: A clinical review. *Arch Intern Med* 2004;164:1054-1062.

56. Stockmann H, Roblick UJ, Kluge N, Kunze U, Schimmelpenning H, Kujath P, Muller G, Bruch HP. Diagnosis and therapy of non-occlusive mesenteric ischemia (nomi). *Zentralbl Chir* 2000;125:144-151.

57. Yasuhara H. Acute mesenteric ischemia: The challenge of gastroenterology. *Surg Today* 2005;35:185-195.

58. Bradbury AW, Brittenden J, McBride K, Ruckley CV. Mesenteric ischaemia: A multidisciplinary approach. *Br J Surg* 1995;82:1446-1459.

59. 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.

60. Thibault R, Pichard C, Wernerman J, Bendjelid K. Cardiogenic shock and nutrition: Safe? *Intensive Care Med* 2010;37:35-45.

61. 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.

62. 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.

63. 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.

64. Heidegger CP, Graf S, Thibault R. Supplemental parenteral nutrition (spn) in intensive care unit (icu) patients for optimal energy coverage: Improved clinical outcome. *Clin Nutr* 2011;6 (suppl 1):2-3.

65. Bistrian BR, McCowen KC. Nutritional and metabolic support in the adult intensive care unit: Key controversies. *Crit Care Med* 2006;34:1525-1531.

66. 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.

67. Wernerman J. Guidelines for nutritional support in intensive care unit patients: A critical analysis. *Curr Opin Clin Nutr Metab Care* 2005;8:171-175.

68. 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.

69. Hubmayr RD, Burchardi H, Elliot M, Fessler H, Georgopoulos D, Jubran A, Limper A, Pesenti A, Rubenfeld 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.

70. Favier C, Bonneau HP, Tran Minh V, Devic J. Endoscopic diagnosis of regressive ischemic colitis. Endoscopic, histologic and arteriographic correlations. *Nouv Presse Med* 1976;5:77-79.

71. Reignier J, Mercier E, Desachy A, Bellec F, Clavel M, Frat JP, Plantefeve G, Boulain T, Quenot JP, Giraudeau B, Group. C. Impact of not monitoring gastric volume in

mechanically ventlated patients receiving early enteral feeding: A multi-center randomized trial. . *Intensive Care Med* 2011;37:S295.

72. 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. *The New England journal of medicine* 2011;365:506-517.

73. Gacouin A, Camus C, Gros A, Isslame S, Marque S, Lavoue S, Chimot L, Donnio PY, Le Tulzo Y. Constipation in long-term ventilated patients: Associated factors and impact on intensive care unit outcomes. *Critical care medicine* 2010;38:1933-1938.

74. van der Spoel JI, Oudemans-van Straaten HM, Kuiper MA, van Roon EN, Zandstra DF, van der Voort PH. Laxation of critically ill patients with lactulose or polyethylene glycol: A two-center randomized, double-blind, placebo-controlled trial. *Crit Care Med* 2007;35:2726-2731.

75. 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.

76. 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.

77. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Leverve X, Pichard C. Espen guidelines on parenteral nutrition: Intensive care. *Clin Nutr* 2009;28:387-400.

78. Klein CJ, Stanek GS, Wiles CE. Overfeeding macronutrients to critically ill adults: Metabolic complications. *J Am Diet Assoc* 1998;98:795-806.

79. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical icu patients: Consistency of care with guidelines and relationship to clinical outcomes. *Chest* 2003;124:297-305.