Protocole NUTRIREA 1

NCT Number : NCT01137487

« Study of Impact of Not Measuring Residual Gastric Volume on Nosocomial Pneumonia Rates »

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Version No. 3 dated 18 February 2010

CLINICAL TRIAL PROTOCOL

NUTRIREA1

TRIAL CODE	PHRI2010 – JR/NUTRIREA1
STRATEGY	No monitoring of gastric residue
FULL TITLE	Absence of gastric residue measurement and risk of nosocomial pneumonia in patients undergoing mechanical ventilation and enteral nutrition – Randomised multicentre equivalence trial
INDICATION(S) (TARGET)	Patients undergoing invasive mechanical ventilation
PRINCIPAL INVESTIGATOR	**Dr Jean REIGNIER** Multidisciplinary Intensive Care Unit Departmental Hospital Centre La Roche -sur-Yon
PROTOCOL VERSION NO.	Version No. 3
DATE OF PROTOCOL	18 February 2010
CPP	POITIERS WEST III
AFSSAPS	Not applicable

SUMMARY

SIGNATURE OF INVESTIGATOR COORDINATOR

I have read all the pages of the clinical trial protocol. I confirm that it contains all the information necessary to conduct the trial. I undertake to conduct the trial in accordance with the protocol and the terms and conditions set out therein.

I also undertake to ensure that the investigators and other qualified members of my team have access to copies of this protocol and the documents relating to the conduct of the trial so that they can work in accordance with the provisions contained in these documents.

NAME: Dr Reignier

Signature: …….. Date: _____

SUMMARY

TITLE	Absence of gastric residue measurement and risk of nosocomial pneumonia in patients on mechanical ventilation and enteral nutrition: Randomised multicentre equivalence trial - NUTRIREA1
COORDINATING INVESTIGATOR	**Dr Jean REIGNIER** Multidisciplinary Intensive Care Unit Departmental Hospital Centre La Roche -sur-Yon Tel: 02.51.44.62.12 Fax: 02.51.44.62.94 jean.reignier@chd-vendee.fr
PROTOCOL VERSION	Version no. 3
JUSTIFICATION/CONTEXT	Early enteral nutrition is part of the basic treatment for patients on mechanical ventilation. However, despite its established benefits and widely disseminated professional recommendations, studies show that the use of enteral nutrition is far from systematic and that the achievement of nutritional goals is unpredictable. These difficulties are mainly attributable to the intolerance experienced by around 50% of patients and the associated risks of nosocomial pneumonia and malnutrition. This intolerance is attributed to gastric hypokinesia, which causes poor gastric emptying and increased gastric residue, with a high risk of gastro-oesophageal reflux and nosocomial pneumonia. These affect 8 to 27% of ventilated patients and are associated with high mortality (25 to 50%). In order to reduce these risks, regular monitoring of gastric residual volume is a key measure in the monitoring of enteral nutrition. However, the validity of this measurement is increasingly being questioned: the technique is not standardised; its "normal" value is unknown; increasing its threshold value does not affect the occurrence of signs of intolerance, the frequency of regurgitation, or the frequency of gastric content inhalation. No limit value for gastric residue has been set above which the risk of regurgitation and pneumonia increases. Measuring gastric residue therefore appears to be of little relevance in reducing the risk of nosocomial pneumonia. By leading to unjustified interruptions in nutrition, it may also result in poorer enteral nutrition delivery.
MAIN OBJECTIVE	To verify that the rates of patients with at least one case of ventilator-associated pneumonia (VAP) are equivalent regardless of whether gastric residue is monitored or not.
SECONDARY OBJECTIVES	The secondary objectives are to compare the following between the two groups: ▪ the incidence density of VAP. ▪ the VAP rate. ▪ the rate of patients who vomited at least once. ▪ the rate of patients who experienced diarrhoea. ▪ the rate of patients who achieved daily calorie goals during the first week. ▪ The number of calories administered enterally. ▪ Mortality in intensive care, at 28 days, 90 days, and in hospital. ▪ Albumin levels at the end of mechanical ventilation, on day 7 (if mechanical ventilation continued beyond 7 days), and upon discharge from intensive care. ▪ The frequency of other nosocomial infections: o Bacteremia.

	○ Central venous catheter infections. ○ Urinary tract infections. ▪ Descriptive bacteriological data. ▪ Length of stay in intensive care ▪ Duration of mechanical ventilation
PRIMARY ENDPOINT	Percentage of patients who developed at least one VAP
SECONDARY ENDPOINTS	▪ Incidence density of nosocomial pneumonia per 1,000 days of mechanical ventilation ▪ Rate of VAP per 100 patients ▪ Rate of patients who vomited at least once per 100 patients ▪ Rate of patients who experienced diarrhoea per 100 patients ▪ Rate of patients who achieved daily caloric goals during the first week per 100 patients ▪ Number of calories administered enterally ▪ Mortality in intensive care, at 28 days, 90 days, in hospital. ▪ Albumin levels at the end of mechanical ventilation, on day 7 (if mechanical ventilation continued beyond 7 days), and on discharge from intensive care. ▪ Percentage of patients who developed at least one bacteraemia and incidence rate per 1,000 days of hospitalisation in intensive care. ▪ Percentage of patients with at least one central venous catheter infection and incidence rate per 1,000 days of catheterisation. ▪ Percentage of patients who developed at least one urinary tract infection and incidence density per 1,000 days of catheterisation. ▪ Descriptive bacteriological data ▪ Length of stay in intensive care ▪ Duration of mechanical ventilation ▪ Rate of intolerant patients in the "residual monitoring" group
METHODOLOGY/STUDY DESIGN	Randomised, multicentre, open-label equivalence trial
SUBJECT INCLUSION CRITERIA	▪ Patients undergoing invasive mechanical ventilation ▪ All patients requiring nasogastric tube feeding within 36 hours of intubation and for a foreseeable period of at least 2 days ▪ Aged over 18 ▪ Who have received information and do not object to participating in the study ▪ Affiliated with a social security scheme
SUBJECT EXCLUSION CRITERIA	▪ Invasive mechanical ventilation started more than 36 hours ago ▪ Expected duration of intubation less than 48 hours ▪ Patients treated with prone positioning at the time of inclusion (prone positioning after inclusion in the study will not be a reason for exclusion from the study) ▪ Recent digestive surgery (<1 month) ▪ History of gastrectomy, oesophagectomy, duodenopancreatectomy ▪ Presence of gastrostomy or jejunostomy ▪ Active digestive haemorrhage ▪ Moribund ▪ Minor (<18 years old) ▪ Legally incapacitated (under guardianship, curatorship) ▪ Pregnant, labouring or breastfeeding woman.

	▪ Patient hospitalised without consent. ▪ Patient deprived of liberty by court order. ▪ Patients admitted to a health or social care facility. ▪ Prior inclusion in a randomised research protocol, the primary endpoint of which is the tolerance of enteral nutrition or the prevention of nosocomial pneumonia. ▪ Contraindication to the administration of prokinetics (hypersensitivity to metoclopramide or erythromycin, heart rhythm disorders such as QT prolongation or torsades de pointes).
STRATEGIES/PROCEDURES	In both groups, intolerance to enteral nutrition will be monitored based on the presence or absence of vomiting. In the "residue" group, it will also be monitored by checking gastric residue every 6 hours according to a well-established protocol.
NUMBER OF PATIENTS	420 patients in total, i.e. 210 in each arm
DURATION OFLA RECHERCHE	Duration of the inclusion period: 18 months Duration of participation for each patient: duration of mechanical ventilation. Total duration of the study: 24 months.
EXPECTED OUTCOMES	If the hypothesis is confirmed, this study will make it possible to discontinue gastric residue measurements during enteral nutrition in ventilated patients. The nursing workload will be reduced. Strategies for preventing ventilator-associated pneumonia can be refocused on measures that have been proven effective. Patients will also likely be better nourished.

List of abbreviations

AFSSaPS	French Health Products Safety Agency
AMM	Marketing Authorisation
ARC	Clinical Research Associate
BPC	Good Clinical Practice
CPP	Committee for the Protection of Individuals
CNIL	French Data Protection Authority
CRF	Case Report Form
EvIG	Serious Adverse Event
EIG	Serious Adverse Effect
EIGI	Unexpected Serious Adverse Effect
ICH	International Conference on Harmonisation
IDE	State-registered nurse
INSERM	la SantéNational Institute of Health and Medical Research
MR	Reference Methodology
RCP	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEC	Clinical Research Technician

1. General information

1.1. Title

Absence of gastric residue measurement and risk of nosocomial pneumonia in patients undergoing mechanical ventilation and enteral nutrition: Randomised multicentre equivalence trial - Acronym: NUTRIREA1

1.2. Study coordination and monitoring

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1.3. Investigators

1.3.1. Coordinating investigator

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2. Scientific justification and general description of the research

In everyday resuscitation practice, nutrition is part of the treatments routinely prescribed and administered. Enteral administration is recommended and should be preferred[1-4] . It appears to be associated with better preservation of the digestive mucosa, lower rates of bacterial translocation, fewer secondary infections and a reduction in length of stay and mortality[5-23] . Its beneficial effects are said to be even more noticeable when administered early after admission to intensive care and to critically ill patients with multiple organ failure[24, 25] .

Nevertheless, despite its established benefits and widely disseminated professional recommendations, studies show 1) that the use of early enteral nutrition is far from systematic, 2) that its methods of administration vary greatly from one department to another, and 3) that even in units with established practices, the achievement of nutritional goals is unpredictable[9, 26-33] . A recent German multicentre study of a cohort of critically ill patients (mortality rate of 54%) showed that 35.1% of patients were fed exclusively by parenteral nutrition, 34.6% received combined enteral and parenteral nutrition, and only 20.1% received exclusive enteral nutrition[9] . These difficulties in generalising and using a treatment with supposed benefits can be attributed to several factors. Some are related to the published studies themselves: the benefits of enteral nutrition demonstrated primarily in surgical patients; the absence of large-scale randomised studies; and the conclusions of the recommendations based on meta-analyses that are difficult to interpret[34, 35] . Others are related to the difficulties in establishing enteral nutrition due to intolerance in approximately 50% of patients and the associated risks of nosocomial pneumonia and malnutrition[26, 30, 32, 36] . This intolerance is attributed to gastric hypokinesia, which causes poor gastric emptying and increased gastric residue, with a high risk of gastro-oesophageal reflux and therefore inhalation of gastric contents and nosocomial pneumonia[37-44] .

The fear of digestive intolerance and its potential consequences, primarily pulmonary infections, is a major obstacle to the satisfactory administration of early enteral nutrition[26, 29-32, 36, 45-48] . The sequence of incomplete gastric emptying, gastro-oesophageal reflux, inhalation and nosocomial pneumonia is on everyone's mind and feared by healthcare teams. Nosocomial pneumonia remains a major complication of mechanical ventilation. It affects 8 to 27% of patients and is associated with an increase in the length of stay in intensive care and a high risk of mortality (25 to 50%)[49] . To protect patients from these disadvantages, regular monitoring of residual gastric volume is a key measure in the supervision of enteral

nutrition[24, 47, 49-56] . An increased residual gastric volume is thought to reflect incomplete gastric emptying and is a warning sign of complications. For the most part, it therefore serves as a warning sign that enteral nutrition should be discontinued. However, repeated interruptions in enteral nutrition administration due to exceeding a given residual gastric volume value are a major obstacle to achieving nutritional goals[57] . Furthermore, the validity of residual gastric volume measurement is increasingly being questioned[58] .

The "normal" residual gastric volume is unknown. It varies depending on the rate of administration of the nutritional solution and gastric emptying, which is itself physiologically regulated by the enterogastric reflex linked to the arrival of nutrients in the proximal intestine. Furthermore, it is likely that gastric volume is not constant and experiences peaks that are not necessarily taken into account when measurements are taken at regular intervals (usually every 6 hours). Modelling of gastric emptying has shown that residual gastric volume is highly variable, that there is no "normal" value, and that the decision to stop administering nutritional solutions at an arbitrarily set residual value has no physiological basis[59] . Furthermore, residual gastric volume is not correlated with other clinical signs of digestive intolerance to nutrition (distension, pain, radiographic abnormalities)[60] . Increasing its threshold value does not affect the occurrence of signs of intolerance, the frequency of regurgitation, or the frequency of gastric content inhalation[61, 62] . Furthermore, no limit value for gastric residue has been set above which the risk of regurgitation and pneumonia increases[63] . Recommendations remain very vague on this point. The American text specifies that "enteral nutrition requires adequate gastric motility" and that "a residual gastric volume greater than 150 ml requires a reduction in the rate of administration, consideration of intravenous administration, or even direct administration of the solution into the small intestine", "the role of prokinetic agents such as cisapride or erythromycin not being established"[1] . The French consensus defines a gastric residue limit of 200 ml[4] . The Canadian recommendations state that the use of a prokinetic agent "may be considered" in order to improve enteral nutrition administration; they do not specify the criteria used to define enteral nutrition intolerance[2] . European recommendations only mention that "prokinetic administration should be considered in cases of enteral nutrition intolerance," specifying "in cases of increased gastric residue," but without defining the measurement technique, frequency of monitoring, or threshold value[2] . These data explain why the residual gastric volume values used to suspect digestive intolerance vary in the literature from 50 to 500 ml and are *ultimately* chosen arbitrarily by healthcare teams. Furthermore, the technique for measuring residual gastric volume is not standardised, and

gastric residue measured by aspiration through a gastric tube, a technique commonly used at the patient's bedside, does not necessarily reflect the actual gastric residue. For this to be the case, each aspiration through the gastric tube would have to remove all gastric contents. This is never certain and depends on factors such as the calibre of the tube and its position[58, 64] . The residual gastric volume may therefore be underestimated by this technique. Currently, the only other techniques available use the measurement of the concentration of dyes or radioactive markers after their dilution in the gastric contents and are not validated or applicable in routine bedside practice[65-70] . Finally, the causal link between regurgitation of enteral nutrition fluid and nosocomial pneumonia is being questioned. A recent study found no correlation between the risk of nosocomial pneumonia and the frequency of regurgitation or inhalation of gastric contents[61] . Bacterial colonisation and inhalation of pharyngo-laryngeal secretions appear to be more decisive factors than those of gastric contents[49] .

In summary, measuring gastric residue appears to be irrelevant in preventing the risks of regurgitation and nosocomial pneumonia. It may also lead to poorer enteral nutrition delivery. A study conducted in the general intensive care unit atLa Roche sur Yon showed that the introduction of an enteral nutrition administration protocol that did not include monitoring of residual gastric volume allowed for the administration of more enteral nutrition without increasing the risk of vomiting and nosocomial pneumonia[71] . However, this study has methodological limitations that reduce its scope: it is a single-centre, before-and-after study with an insufficient number of patients to draw definitive conclusions about the absence of nosocomial pulmonary infection risk.

The objective of this research is therefore to verify, in a prospective, multicentre, randomised and controlled study, the hypothesis that monitoring residual gastric volume does not reduce the risk of ventilator-associated pneumonia in patients receiving early enteral nutrition.

2.1. Summary of the benefits, if any, and the foreseeable and known risks for individuals participating in the research

This study aims to standardise the practice of enteral nutrition in patients treated with mechanical ventilation: patients will be fed according to specific protocols that comply with

current recommendations. This standardisation of enteral nutrition delivery will in itself be beneficial to patients participating in the study[72] .

This study does not pose any additional risk to patients. Gastric residue monitoring is routinely performed in some departments, but is not standard practice in all.

2.2. Statement indicating that the research will be conducted in accordance with the protocol and good clinical practice

The investigator also undertakes to ensure that this research is conducted:
- in accordance with the protocol,
- in accordance with current French and international good clinical practice.

2.3. Description of the population to be studied

This study will therefore focus on adult patients admitted to intensive care who require nasogastric tube feeding within 36 hours of intubation and for a foreseeable period of at least two days. The selection criteria are described in Chapter 5.

3. Objective s of the research

3.1. Main objective

The primary objective of this research is to test the hypothesis that the rates of patients with at least one case of ventilator-associated pneumonia (VAP) are equivalent regardless of whether gastric residue is monitored or not.

3.2. Secondary objectives

The secondary objectives are to compare the following between the two groups:

- the incidence density of VAP.
- the VAP rate.
- the rate of patients who vomited or regurgitated at least once.
- the rate of patients who experienced diarrhoea.
- the rate of patients who achieved daily calorie goals during the first week.

- The number of calories administered enterally.
- Mortality in intensive care, at 28 days, 90 days, and in hospital.
- Albumin levels at the end of mechanical ventilation, on day 7 (if mechanical ventilation continued beyond 7 days), and upon discharge from intensive care.
- the frequency of other nosocomial infections:
    - bacteremia
    - central venous catheter infections.
    - Urinary tract infections.
- Descriptive bacteriological data.
- length of stay in intensive care
- Duration of mechanical ventilation

4. Impact

If the study hypothesis is confirmed, gastric residue measurement could be removed from protocols, which would limit interventions on patients, prioritise care proven to be effective in preventing nosocomial pneumonia, reduce the nursing workload and, probably, improve nutrition for critically ill patients.

5. Research design

5.1. Precise statement of the main evaluation criteria and, where applicable, secondary evaluation criteria

5.1.1. Primary endpoint

The primary endpoint is the proportion of patients who developed at least one VAP (numerator for each group: number of patients who developed at least one VAP after the start of mechanical ventilation and less than 2 days after extubation; denominator: total number of patients included in the group concerned).

A diagnosis of VAP will be suspected when parenchymal opacity appears or persists on chest X-ray, associated with at least two of the following criteria: body temperature ≥38.5 or ≤35.5ºC, hyperleukocytosis (>10,000/mm^{33}) or leukopenia (<4000/mm^3), and purulent tracheobronchial aspirates. The diagnosis must be confirmed by a positive *semi-quantitative*

bacteriological examination: LBA (>10^{-4} cfu/ml), brush (>10^{-3} cfu/ml), tracheal aspiration (>10^{-6} cfu/ml) or PDP (>10^{-3} cfu/ml).

This method of diagnosing VAP, which includes the requirement for a semi-quantitative bacteriological criterion, is part of standard resuscitation practice and is used in all six departments participating in the study[49, 73] . In addition, all VAP diagnoses will be confirmed by an adjudication committee.

5.1.2. Secondary evaluation criteria

- Incidence density of nosocomial pneumonia per 1,000 days of mechanical ventilation: the incidence density will be defined as the ratio between the number of patients who developed at least one VAP after the start of mechanical ventilation and less than 2 days after extubation and the risk period. The risk period will be defined as:
    - the sum of days of exposure to mechanical ventilation for patients who did not develop VAP
    - the days of exposure preceding infection only for patients with VAP.
- Average number of VAP (numerator for each group: total number of VAP occurring after the start of mechanical ventilation and less than 2 days after extubation; denominator: total number of patients included in the group concerned).
- Rate of patients who vomited or regurgitated at least once per 100 patients (numerator in each group: total number of patients who vomited or regurgitated; denominator: total number of patients included in the group concerned).
- Rate of patients who experienced at least one episode of diarrhoea per 100 patients (numerator in each group: total number of patients who experienced diarrhoea; denominator: total number of patients included in the group concerned). Diarrhoea is defined as the occurrence of more than 300 ml of liquid stool if the patient has a faecal collector or more than 4 loose stools per day[72] .
- Percentage of patients who achieved daily calorie goals during the first week per 100 patients (numerator in each group: number of patients who received 100% of the prescribed goal each day of the first week of enteral nutrition; denominator: total number of patients included in the group concerned)
- Number of calories administered enterally:
    - cumulative total during the first week

  - daily average during the first week of nutrition
  - Daily average throughout the entire period of mechanical ventilation.
- Mortality in intensive care, at 28 days, 90 days, and in hospital.
- Albuminemia at the end of mechanical ventilation, on day 7 (if mechanical ventilation continued beyond 7 days), and upon discharge from intensive care.
- Other nosocomial infections:
  - Bacteremia: percentage of patients who developed at least one episode of bacteremia and incidence rate per 1,000 days of hospitalisation in intensive care.
  - Central venous catheter infections: percentage of patients who had at least one central venous catheter infection and incidence rate per 1,000 days of catheterisation.
  - Urinary tract infections: percentage of patients who developed at least one urinary tract infection and incidence rate per 1,000 days of catheterisation.
- Descriptive bacteriological data: germs identified as causing VAP and antibiotic resistance profiles.
- Length of stay in intensive care
- Duration of mechanical ventilation
- Rate of patients intolerant to enteral nutrition per 100 patients in the "residual" group. Intolerance in the intervention group is defined by the occurrence of significant regurgitation or vomiting or a residual volume >250 ml.

5.2. Description of the research methodology, accompanied by a schematic presentation specifying in particular the planned visits and examinations

5.2.1. Experimental design

This is a randomised, controlled, multicentre, open-label equivalence trial comparing two groups of patients treated with invasive mechanical ventilation and receiving early enteral nutrition: one where residual gastric volume is monitored, the other where it is not.

5.2.2. Study procedure

5.2.2.1.Inclusion

Patients must be included in the study within 36 hours of intubation. Information will be provided and consent to participate in the study will be sought from the patient if they are conscious or from their relatives if they are not. If the information has been provided to relatives, consent will be sought from the patient as soon as their level of consciousness allows.

A table tracking patients who have been offered the study will be kept up to date, noting any reasons for non-inclusion and objections to participation.

After verifying the inclusion and exclusion criteria and obtaining the consent of the patient or their relatives, the investigator may include the patient. Upon inclusion, the patient's demographic data, characteristics and vital signs will be collected: date of birth, sex, date of admission to intensive care, reason for admission to intensive care, McCabe and Knaus scores, previous chronic conditions, weight, height, BMI, SOFA.

5.2.2.2. enteral nutrition protocol

The enteral nutrition protocol and gastric residue monitoring must be standardised according to the elements defined below.

Enteral administration should begin as soon as possible after invasive mechanical ventilation is initiated, and must begin within 36 hours of intubation. The prescribed solutions will be iso-osmotic, isocaloric and normoproteic (such as Nutrison, Normoréal, Isosource) during the first week, then left to the discretion of the practitioner. Additional enteral water intake will be limited as much as possible during the first week of the study. The calorie target for each patient will be calculated based on weight and will be 20-25 kcal/kg/day during the acute phase (limited to a maximum of 7 days) and then 25-30 ml/kg/day. In obese patients (BMI> 30), it will be limited to the patient's theoretical weight for a BMI of30. L The actual administration of enteral nutrition must be monitored regularly based on the volumes administered and their adequacy in relation to the predefined daily targets. Nutrition will be prescribed in terms of flow rate (ml/hour) and started immediately at the prescribed flow rate (no gradual increase). Nutrition must be administered at a continuous flow rate over 24 hours, without interruption, via a 14 French silicone gastric tube. Particular attention must be paid to the risk of tube obstruction, especially when administering medication: regularly flush the tube with 20 to 30 ml of water.

It is important not to fall behind schedule. Any interruption in feeding must be reported to the resuscitation physician. Unless specifically indicated, enteral nutrition should not be stopped during a CT scan. However, if it is absolutely necessary to stop enteral feeding (for a digestive examination, for example), the flow rate should not be increased to make up for the delay.
In addition, the mid-gastric position of the tube will be verified by X-ray upon admission to intensive care or as soon as the tube is inserted, and whenever the tube is changed or repositioned. Finally, the patient should be placed in a supine position in a semi-sitting position, inclined between 30° and 45°.

5.2.2.3. Study-specific intervention: monitoring or non-monitoring of gastric residue

Enteral nutrition tolerance will be studied:

- *in the group without residue:* only by monitoring significant regurgitation or vomiting (occurring outside of any care or mobilisation, of enteral nutrition solution in the mouth, outside or in the intubation tube)
- *in the residue group:* by regularly measuring gastric residue every 6 hours and monitoring significant regurgitation or vomiting. The measurement of gastric residual volume (residue group only) will be performed:
    - by aspirating all residue through the gastric tube using a 50 ml syringe with a conical tip.
    - every 6 hours at fixed times: 6 a.m., 12 p.m., 6 p.m. and midnight. The value is recorded on the monitoring sheet.

The aspirated gastric residue must be reinjected after measurement unless it is >250ml. If the gastric residue is > 250ml:

- it must be measured in its entirety
- it must not be reinjected
- it must be deducted from the volume of enteral nutrition administered

As patients will be cared for by teams that may vary from one day to the next, every effort will be made to ensure that caregivers know which randomisation arm the patient has been assigned to. In particular, a signalling system will be put in place in the patient's file in terms of prescriptions and monitoring signs.

Diarrhoea will also be monitored. It is defined as the occurrence of more than 300 ml of liquid stools or more than 4 loose stools per day[72] . Its observation requires a diagnostic and therapeutic approach (Appendix 2).

5.2.2.4.Treatment of intolerance

Intolerance will be defined in both groups by the patient vomiting or regurgitating significantly. Simple regurgitation of a minimal amount (frequent in the prone position), vomiting caused by tracheal aspiration, and oral care will not be considered signs of intolerance. In addition, in the "residue monitoring" group, a gastric residue volume > 250 ml will also be considered intolerance.

Enteral nutrition intolerance requires two measures:

- Firstly: to start treatment with a prokinetic agent *after confirming that there are no contraindications and following a doctor's prescription*. Investigating departments will use the prokinetic agent of their choice, according to their usual care protocol. This treatment will be continued until a period of 48 hours of good tolerance to the maximum prescribed flow rate has been achieved. It must then be discontinued.
- Secondly, if the patient remains intolerant, the flow rate will be reduced by 25 ml/h every 6 hours for as long as the patient remains intolerant. *Enteral feeding will therefore only be stopped (and the gastric tube placed in suction) if poor tolerance is observed at a flow rate ≤ 25 ml/h.*

The doctor must be notified of any interruption in feeding. This precaution must be particularly observed for patients treated with insulin. Enteral feeding is resumed at the prescribed flow rate (in accordance with the patient's needs) after 6 hours without any new signs of digestive intolerance.

CAUTION:

Patients on DV

Systematic PROKINETICS from day 1 ER DV

NE group <u>WITH VGR</u>: DECISION TREE

MEDICAL PRESCRIPTION OF LA NUTRITION ENTERALE

IMPERATIVE:

Radiological control of the mediogastric position of the tube before each start of enteral feeding, then systematically at each change or repositioning of the tube.

START OF ENTERAL NUTRITION
As early as possible (<36 hours after intubation)
Maximum flow rate from the outset according to the prescribed objective

LA TOLERANCE DIGESTIVE MONITORING
➔GASTRIC RESIDUE
Measured every 6 hours
➔VOMITING/REGURGITATION

Resume **maximum flow** rate after 6 hours unless otherwise prescribed

IF INSULIN THERAPY
Capillary blood glucose monitoring every hour Until resumption

NO

RESIDUE G
≤ 250 ml

Reinject
The residue

Continue enteral nutrition at maximum flow rate or increase it back to maximum flow rate if

REGURGITATION VOMITING
Or
RESIDUE G > 250 ml
Aspirate all residue
<u>DO NOT REINJECT</u>
Subtract the

I ère start PROKINETIC on P.M. up to 48 hours of tolerance at the maximum prescribed flow rate

REGURGITATION VOMITING
Or
RESIDUE G > 250 ml
Aspirate all residue
<u>DO NOT REINJECT</u>
Subtract the
discarded volume

YES

II nd Modification of enteral nutrition flow rate

If flow rate > 25 ml/h **DECREASE** the

Notify the doctor

If Flow rate ≤ 25

CAUTION
PATIENTS IN DV
Systematic PROKINETIC treatment from the first DV on medical prescription
Stop 6 hours after last vomiting

NE group without residue: DECISION TREE

MEDICAL PRESCRIPTION OF LA NUTRITION ENTERALE

IMPERATIVE:

Radiological check of the mediogastric position of the tube before each start of enteral feeding, then systematically at each change or repositioning of the tube

START OF ENTERAL NUTRITION
As early as possible (<36 hours after intubation)
Maximum flow rate from the outset according

LA TOLERANCE DIGESTIVE MONITORING
➔**VOMITING/REGURGITATION**
Significant outside of care and mobilisation

NO

REGURGITATION VOMITING

YES

I^st^ start PROKINETIC on P.M.
up to 48 hours of tolerance at the prescribed flow rate

Vomiting REGURGITATION

NO

Resume at **prescribed flow**

YES

II^ème^ Modification of enteral nutrition flow rate

DECREASE the flow rate by 25 ml/h

Dextro/h
For 2 hours

If Flow rate ≤25 ml/h

IF INSULIN THERAPY
Capillary blood glucose monitoring/hour
Until resumption

Notify the Doctor

STOP Feeding
For 6 hours
SNG suction

Special situations

- Patients in the prone position: intolerance to enteral nutrition, which is particularly common in these patients, should be prevented by prophylactic treatment with prokinetics from the first session in the prone position[74, 75] .
- Patients treated with insulin: They must be closely monitored and it is important to adhere strictly to the insulin therapy protocol. In addition:
    - in the event of a decrease in enteral nutrition flow due to poor tolerance of enteral nutrition (residue >250 ml and/or regurgitation), blood glucose levels should be monitored hourly for 2 hours following the decrease in flow. If blood glucose levels remain stable, monitoring should resume at the rate established by the insulin therapy protocol.
    - during any period of feeding cessation, blood glucose levels must be monitored hourly throughout the entire period of enteral nutrition cessation.
- Re-intubated patients: management during the second intubation will be identical to that allocated for the first intubation. Thus, a patient randomised to the "residual" group will be managed in this way throughout their hospitalisation in intensive care.

5.2.2.5. Patient follow-up

Vital signs, nutrition monitoring data, biology and nosocomial infections will be recorded until the patient is extubated. The patient will be followed up until discharge from hospital, on day 28 and day 90, when their status (alive or deceased) will be recorded according to the following flow chart:

FLOW CHART (NUTRIREA 1)

	Inclusion	JO*	D1 to Dn	D28	End of study
Eligibility: check criteria I and E	X				
Information note	X				
Demographic data	X				
Features		X			
Ventilation		X			
Biology		X	X **		
SOFA		X	X		
Nutritional assessment		X	X		
Treatments administered		X	X		
Nosocomial infections			X		
Definitive extubation					X
Permanent cessation of nutrition					X
Living / deceased				X	X

* = from the time of inclusion until 23:59

5.3. Description of measures taken to reduce and avoid bias

5.3.1. Randomisation

Randomisation will be stratified according to the investigating centre. The patient profile (post-operative or medical) will not be taken into account as a stratification factor given the highly uneven distribution between the two types of patients (based on previous studies, the expected proportion of surgical patients is 10%). This randomisation will be carried out directly on the electronic observation log provided in each centre (see Data collection).

5.3.2. Blinding methods

The trial will be conducted openly, as the measurement of gastric residue requires the intervention of a nurse and the result leads to specific management for this group of patients.

This lack of blinding has therefore led us to opt for validation of the primary endpoint by an adjudication committee.

5.4. Expected duration of participation and description of the timing and duration of all trial periods, including follow-up, if applicable

The duration of patient follow-up in the study will depend on the duration of intubation. The patient will be followed up until extubation. Their status (alive or deceased) will be checked upon discharge from intensive care, from hospital, on day 28 and on day 90. For patients discharged before day 28 and day 90, telephone contact will be arranged.

The duration of the study is estimated at 24 months (from 2 May 2010 to 2 May 2012).

5.5. Description of the rules for permanent or temporary discontinuation

5.5.1. Discontinuation of a person's participation in the research

Secondary opposition from the patient or their relatives.

5.5.2. Discontinuation of part or all of the research

With regard to this routine care study, there are no planned criteria for stopping the research, unless a consensus following a scientific publication calls into question the main hypothesis or the management of patients treated with mechanical ventilation.

5.6. Data collected

All of this data is routinely collected in intensive care units for the management of this type of patient:

Demographic and clinical data:

- at inclusion: date of birth, sex, date of admission to intensive care, reason for admission to intensive care, McCabe and Knaus scores, previous chronic conditions, weight, height, BMI, SOFA.
- at H24: IGSII, SOFA
- Follow-up: date of final extubation, date of discharge from intensive care, date of discharge from hospital (MCO), mode of discharge from intensive care (alive or deceased), mode of discharge from hospital.

Nutrition data: Daily assessment at midnight *until patient extubation*: name of enteral nutrition solution, volume target, calorie target, volume and calories actually administered, vomiting (note "yes/no" every 6 hours and time of vomiting), gastric residue (/6 hours) in the group with gastric residue, reduction or cessation of nutrition ("yes/no"), reason for reduction or cessation of nutrition (vomiting, residue, diarrhoea, other acute abdominal symptoms, examination), diarrhoea and its presumed cause (nutritional intolerance, medication, Clostridium difficile, other cause).

Treatments administered each day *until the patient was extubated*: prokinetic (dose administered/24 hours), sedation (dose administered/24 hours of Hypnovel and/or fentanyl and/or Diprivan), curare (dose administered/24 hours), amines (noradrenaline or adrenaline:

"yes/no" regardless of duration), EER ("yes/no"), antibiotics ("yes/no"), insulin (total dose administered/24 hours), total IV fluid volume (/24 hours), gastric antisecretory drugs (sucralfate, PPIs and H2 blockers)

Biological data:

- D1: Haemoglobin, leukocytes, platelets, Na, K, PaO2, PaCO2, pH, arterial lactates, bicarbonates, urea, creatinine, bilirubin, total proteins, albumin, CRP.
- Every day from D1 to D7 (if extubation: on the day of extubation, then stop): PaO2, bilirubinemia, glycaemia, proteinemia, Na, K, creatininaemia, SOFA.
- Albumin and CRP on D1 and D7 or on the day of extubation.

Nosocomial infections (one record sheet per infection): ventilator-associated pneumonia (date, pathogen, resistance profile), bacteraemia (date, pathogen, resistance profile), catheter-related infection (date of diagnosis, pathogen, resistance profile), urinary tract infection (date of diagnosis, pathogen, resistance profile).

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

6. Selection and exclusion of research participants

6.1. Inclusion criteria for individuals participating in the research

- Patients on invasive mechanical ventilation
- who must be fed via nasogastric tube within 36 hours of intubation and for a foreseeable period of at least 2 days
- Aged over 18
- Having received information and not objecting to their participation in the study
- Affiliated with a social security scheme

6.2. Exclusion criteria s for individuals participating in the research

- Invasive mechanical ventilation started more than 36 hours ago
- Expected duration of intubation less than 48 hours
- Patients treated with prone positioning at the time of inclusion (prone positioning after inclusion in the study will not be a reason for exclusion from the study)
- Recent digestive surgery (<1 month)
- History of gastrectomy, oesophagectomy, duodenopancreatectomy, bypass or gastric banding.
- Presence of gastrostomy or jejunostomy
- Active digestive haemorrhage
- Moribund
- Minor (<18 years old)
- Legally incapacitated (under guardianship or curatorship)
- Pregnant, labouring or breastfeeding woman.
- Patient hospitalised without consent.
- Patient deprived of liberty by court order.
- Patients admitted to a health or social care facility.
- Prior inclusion in a randomised research protocol, the primary endpoint of which is the tolerance of enteral nutrition or the prevention of nosocomial pneumonia.
- Contraindication to the administration of prokinetics (hypersensibilité au métoclopramide ou à l'érythromycine, troubles du rythme cardiaque à type d'allongement de QT ou de torsades de pointes,)

6.3. Recruitment procedures

The study will be offered to all patients admitted to intensive care units and treated with mechanical ventilation for a foreseeable period exceeding 48 hours and requiring early enteral feeding.

6.4 Contraindications to participation in other research.

Patients participating in the research may be included in other research studies, except those whose primary endpoint is the tolerance of enteral nutrition or the prevention of nosocomial pneumonia, until the patient is extubated.

7. Products administered to persons participating in research

7.1. Authorised treatments

All drugs commonly used for the management of intensive care patients will be used according to the specific needs of each patient.

7.2. Unauthorised treatments

As this is a routine care study, no drugs used for their indicated purpose are prohibited.

8. Statistics

Statistical analysis will be conducted at CIC INSERM 202 under the supervision of Bruno Giraudeau. Analyses will be performed using SAS 9.1 software.

8.1. Description of planned statistical methods, including the schedule for planned interim analyses

Statistical analysis will be performed according to a pre-established analysis plan. The analysis will be conducted according to the intention-to-treat (ITT) principle and per protocol (PP), as recommended for equivalence trials. No interim analysis will be performed. A statistical analysis report will be prepared incorporating all the elements that must be reported, as recommended by the CONSORT Statement, taking into account the specificities related to the fact that this is a non-pharmacological trial and that the objective is one of equivalence (http://www.consort-s t atement.org/ - Accessed on 20.11.09).

Description of samples at inclusion

The groups resulting from randomisation will be compared using descriptive statistics. No statistical tests will be performed.

Analysis samples

The analysis will be performed using ITT, with each subject remaining in the group to which they were randomised, regardless of what happens.

With regard to thela population PP , the following will be excluded:

- patients extubated before 48 hours of mechanical ventilation or
- patients with a contraindication to enteral nutrition before 12 hours of enteral nutrition

The definition of "la population PP " will be finalised before the baseline freeze as part of a blind review.

Analysis of the primary endpoint

A two-sided 90% confidence interval for the intervention effect (Julious SA. Sample sizes for clinical trials with normal data. Stat Med. 2004 Jun 30;23(12):1921-86. Review. PubMed PMID: 15195324.), i.e. the difference in PAVM rates between the "no monitoring" group and the "residual" group, will be estimated and the limits of this 90% CI will be compared with the a *priori* equivalence zone, as is customary for equivalence trials. The equivalence zone has been set at 10%.

Analysis of secondary endpoints

For binary endpoints, the analyses will be identical to the main analysis.

For quantitative endpoints, after logarithmic transformation of the data if necessary, the effect of the intervention and the associated confidence interval will be estimated using linear regression models in which the randomisation group will be introduced as a covariate. The limits of these 90% CIs will then be compared with the equivalence zone (set at 10%).

8.2. Expected number of people to be included in the study , and expected number of people at each study site with statistical justification

This is an equivalence trial designed to demonstrate that the rates of patients with ventilator-associated pneumonia are the same whether gastric residue is monitored or not. For an expected rate of patients with VAP in the residue measurement group of 19%, an equivalence zone of 10%, an alpha risk of 5% and a beta risk of 20%, the number of patients required is 191 per group (Newcombe. Statist Med 1998;17:873-890), giving a theoretical total of 382. Given an estimated frequency of 10% of patients leaving the study after inclusion (lost to follow-up or mechanical ventilation duration < 48 hours), it will be necessary to include 420 patients for the per-protocol analysis.

8.3. Expected level of statistical significance

As this is an equivalence trial, we will compare the upper limits of the two-sided 90% CI of the intervention effect with the equivalence zone defined above (i.e. 10%).

8.4. Statistical criteria for stopping the research

In the absence of an interim analysis, there are no statistical criteria for stopping the study.

8.5. Method for handling missing, unused or invalid data

In this study, patients for whom consent cannot be obtained will not be included in the analysis. Apart from these patients, it is unlikely that any will be lost to follow-up, as they are hospitalised in intensive care. However, if the endpoint is not available for certain patients, they will be assigned a failure value (i.e. development of VAP), regardless of the randomisation arm.

8.6. Management of changes to the initial strategy analysis plan

The statistical analysis plan will be finalised when the database is frozen.

8.7. Selection of individuals to be included in the analyses

The analysis will be performed using ITT and PP (see above).

9. Justification for the request for validation of routine care research

Taking into account all the elements presented in the project, the research manager classifies it as **routine care research**, since:

- ✓ all enteral nutrition procedures and protocols are performed routinely.
- ✓ the research aims to evaluate combinations of procedures and medical prevention and diagnosis strategies (protocol for the administration and monitoring of enteral nutrition, diagnosis of nosocomial pneumonia) that are standard practice, i.e. subject to professional consensus in accordance with their indications.
- ✓ This research does not focus on techniques or strategies that are either innovative or obsolete.
- ✓ The combination of procedures (monitoring of enteral nutrition with or without measurement of gastric residue) is not an innovative combination.
- ✓ The research focuses on comparing two medical strategies (enteral nutrition monitoring with or without gastric residue measurement), neither of which can, based on current knowledge, be considered superior to the other in terms of safety and efficacy.
- ✓ Finally, the specific implementation procedures in the research must reduce risks (through enhanced protocolisation of enteral nutrition delivery) and represent negligible constraints for the person participating in the research (Article R 1121-3 of the Public Health Code (CSP), Decree No. 2006-477 of 26 April 2006).

The research manager shall therefore submit the study protocol to the OUEST III Committee for the Protection of Persons for a favourable opinion and confirmation of the research's eligibility prior to any implementation of the research, in accordance with Article L 1121-1 of the Public Health Code (CSP) as resulting from Laws No. 2004-806 of 9 August 2004 and No. 2006-450 of 18 April 2006 relating to public health policy.

10. Right of access to source data and documents e

10.1. Access to data

Each patient's medical data will only be transmitted to the organisation to which the person responsible for the research is affiliated or to any person duly authorised by that organisation under conditions that guarantee confidentiality.

10.2. Source documents

Where applicable, the organisation to which the person responsible belongs may request direct access to the medical file to verify the research procedures and/or data, without violating confidentiality and within the limits authorised by laws and regulations.

10.3. Data confidentiality

Persons with direct access shall take all necessary precautions to ensure the confidentiality of information relating to the persons involved, in particular with regard to their identity and the results obtained.

These persons, like the investigators themselves, are subject to professional secrecy (under the conditions defined by Articles 226-13 and 226-14 of the Penal Code).

During or at the end of the research, the data collected on the individuals involved and transmitted by the participants shall be anonymised.

Under no circumstances shall the names or addresses of the persons concerned be disclosed.

Only the first three letters of the subject's surname and the first two letters of their first name will be recorded, accompanied by a coded number specific to the study indicating the order of inclusion of the subjects.

11. Quality assurance

In order to optimise the implementation of the study, a Clinical Research Associate (CRA) may be responsible for:

- preparing the submission file for review by the Committee for the Protection of Persons (CPP)
- finalising the study documents (observation log, etc.) and the channels of communication between the various parties involved
- setting up the study in the centres associated with the study

12. Ethical evaluations of the specific monitoring procedures provided for in the protocol

12.1. Committee for the Protection of Persons

The protocol and the study information and non-objection form will be submitted to the CPP for review.

12.2. Substantial modifications

Any substantial modification to the study protocol must be notified to the Committee for the Protection of Persons in order to verify that the proposed modifications do not in any way alter the guarantees provided to the persons participating in the research.

12.3. Information letter and non-objection form

Patients will be fully and honestly informed, in understandable terms, of the objectives of the study, their rights to refuse to participate in the study, and the possibility of withdrawing at any time. All this information will be included in an information and non-objection form given to the patient.

13. Data processing and storage of documents and data

13.1. Observation log

An online data collection tool will be used for this study. This electronic observation log will be set up in each centre. It only requires an internet connection and a browser. A help document for using this tool will be provided to investigators.
Data consistency checks will be integrated into the electronic format. An audit function is integrated into the electronic notebook, allowing any changes to the study data to be tracked. This function also clearly identifies the person who made the change and the date. A justification can be added as a comment if necessary.

13.2. Data entry and output

Data will be entered electronically via a web browser.
Data analysis will be performed by Bruno Giraudeau.

13.3. CNIL

An opinion on the implementation of the data processing necessary to carry out the study will be requested from the Advisory Committee on the Processing of Information in Health Research (CCTIRS), followed by a request for authorisation from the French Data Protection Authority (la Commission Nationale Informatique et Libertés, CNIL) for the processing of personal data for the purposes of routine healthcare research.

14. Funding and insurance

14.1. Study budget

As this trial is a routine care study, medical procedures are not covered. The costs associated with this research are therefore as follows:

- ARC time required to prepare the submission file for review by the Human Protection Committee and to prepare the CNIL file (1 month full-time) and study coordination (10% FTE over 2 years): €12,000.
- Clinical study technician time for assistance with study coordination and logistics, as well as data entry into the e-CRF: 1 part-time position over 2 years, i.e. €40,000
- Data management:
  - Data management time for creating the electronic observation log and monitoring data quality: 3 months full-time, i.e. € 15,000.
  - Statistical analysis: 1 month full-time, i.e. €50,000
- Meetings, coordinator assignments: €40,000
- Travel expenses for the clinical study technician: €6,000
- Stationery for information letters and letters of non-objection to patients or their relatives, nutrition monitoring sheets at patients' bedsides: €4,000

14.2. Insurance

As the research is classified as routine care research by the CPP (Comité de Protection des Personnes), meaning that there is no additional risk associated with the study, the insurance will be provided by the institution responsible for care (Article L. 1142-2).

15. Feasibility of the study

The study will be conducted in the six investigative centres that make up the Clinical Research in Intensive Care and Sepsis (CRICS) network. These six centres admit a total of 5,200 patients per year on average. Approximately 70% of these patients are treated with mechanical ventilation, i.e. approximately 3,600 patients per year. Given the inclusion and exclusion criteria for the study, we estimate that we can reliably include at least 5 patients per month per department, i.e. 30 patients per month and therefore 360 per year.

As the number of patients expected to be included in the study is 420, the expected duration of the inclusion period will therefore be a maximum of 18 months.

16. Rules relating to publication

Scientific communications and reports relating to this study will be produced under the responsibility of the principal investigator coordinating the study, with the agreement of the investigators in charge. The co-authors of the report and publications will be the investigators and clinicians involved, in proportion to their contribution to the study, as well as the biostatistician and associated researchers.

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

17. References to scientific literature and relevant data used as references for the research

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Appendix 1: Procedure for managing diarrhoea

This procedure was described by Doig in 2008 in JAMA [72]