Thesis

Etude de l'impact de l'administration de cisapride ou d'un placebo sur la vidange gastrique et la nutrition entérale précoce chez des patients de soins intensifs sous ventilation mécanique

CARTIER FAESSLER, Vanessa

Abstract

Un stress métabolique intense est observé chez les patients hospitalisés aux soins intensifs. Le catabolisme qui en résulte s'additionne à la pathologie de base et concoure à en aggraver l'évolution par une dénutrition. Plusieurs raisons sont invoquées pour expliquer le lien existant entre le catabolisme et la dénutrition. Elles peuvent être regroupées en deux catégories : les troubles en relation directe avec le catabolisme (redistribution du métabolisme, inflammation etc.) et ceux altérant la progression du bolus alimentaire. Le présent travail tente de diminuer les effets observés dans la seconde catégorie. Après avoir revu les bases pathophysiologiques ainsi que les effets du métabolisme augmenté lors de la maladie aiguë du patient de soins intensifs, une étude clinique est présentée. Elle teste l'hypothèse que l'administration de cisapride, médicament procinétique, augmente la vidange gastrique chez les patients bénéficiant d'une ventilation mécanique. Les résultats obtenus ont confirmé cette hypothèse sans effets secondaires remarquables.

Reference

CARTIER FAESSLER, Vanessa. *Etude de l'impact de l'administration de cisapride ou d'un placebo sur la vidange gastrique et la nutrition entérale précoce chez des patients de soins intensifs sous ventilation mécanique*. Thèse de doctorat : Univ. Genève, 2005, no. Méd. 10429

URN : urn:nbn:ch:unige-3316
DOI : 10.13097/archive-ouverte/unige:331

UNIVERSITE DE GENEVE

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Thèse préparée sous la direction du docteur Jacques-André ROMAND, CC

ETUDE DE L'IMPACT DE L'ADMINISTRATION DE CISAPRIDE OU D'UN PLACEBO SUR LA VIDANGE GASTRIQUE ET LA NUTRITION ENTERALE PRECOCE CHEZ DES PATIENTS DE SOINS INTENSIFS SOUS VENTILATION MECANIQUE

Thèse
présentée à la Faculté de Médecine
de l'Université de Genève
pour obtenir le grade de Docteur en médecine

par

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de Winterthur (ZH)

Thèse n° 10429

Genève

2005

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ACKNOWLEDGEMENTS

The author would like to recognize and thank those who helped make this research work possible:

Dr Jacques-André Romand
Dr Claude Pichard
Dr Myriam Treggiari
Dr Reza Kethari (Neuchâtel)
Dr Doron Margalit (Neuchâtel)
Dr Joceline Deruaz and her husband, Dr Cedric Deruaz
Dr Valerio Gozzoli
The nurses from the Hôpital des Cadolles (Neuchâtel) and the Geneva University Hospital
Mrs Briner, the pharmacist from the Hôpital des Cadolles (Neuchâtel)
Mrs Bill, the libriarian from the Hôpital des Cadolles (Neuchâtel)

And over all

My husband and my sons

Etude de l'impact de l'administration de cisapride ou d'un placebo sur la vidange gastrique et la nutrition entérale précoce chez des patients de soins intensifs sous ventilation mécanique

INTRODUCTION

Ce travail de thèse reprend la physiologie et la patho-physiologie gastro-intestinale avant de se pencher sur le support nutritionnel nécessaire aux patients hospitalisés en milieu de soins intensifs. Dans la deuxième partie, une étude visant à améliorer l'état nutritionnel est détaillée et analysée.

Les patients séjournant en milieu de soins intensifs présentent fréquemment de nombreuses co-morbidités (altérations de l'état nutritionnel et immun préexistant, maladies cardio-vasculaires, respiratoires et métaboliques ainsi que leurs répercussions) en sus de la ou des pathologies motivant leur hospitalisation. Une admission en milieu de soins intensifs implique un traitement agressif nécessitant des accès vasculaires, un tube endo-trachéal éventuel et fréquemment un cathéter urinaire. Un soutient médicamenteux hémodynamique, une antibiothérapie et /ou une sédation s'avèrent souvent nécessaires. Au début de leur séjour, ces patients présentent une phase de stress métabolique majeur et perdent rapidement du poids et de la masse musculaire. Le concept intuitif de support nutritionnel précoce permettant le maintient des défenses corporelles ainsi que la préservation des fonctions des différents organes a été largement étudiée et est admise bien que les évidences scientifiques manquent. Pourtant les supports nutritionnel et calorique sont souvent considérés comme non primordiaux et débutés plusieurs heures voire jours après l'admission. Cette attitude est également motivée par l'observation que la vidange gastrique peut être ralentie par différentes étiologies telles que ventilation mécanique, la défaillance circulatoire, les traitements médicamenteux incluant des opiacés, l'iléus post opératoire, les traumas neurologiques et les autres co-morbidités telles que la gastroparésie diabétique. Pour remédier à ces difficultés, il avait été préconisé dans les années 80 de débuter une alimentation parentérale. La preuve de l'efficacité de cette attitude thérapeutique n'a jamais été démontrée alors que les effets secondaires de l'alimentation parentérale sont observés quotidiennement. Pour cette raison un regain d'intérêt pour l'alimentation entérale est affirmé actuellement car il permettrait le maintient de la flore et de la muqueuse intestinale et éviterait les complications attribuables à l'alimentation administrée par voie parentérale telles qu'infections de cathéters, hyperglycémies, etc.…

Différentes études ont été menées pour d'une part expliquer mais également essayer de corriger les altérations du transit intestinal. En particulier une, l'effet de l'administration d'un médicament qui augmente la vidange gastrique sur la tolérance de la nutrition entérale précoce chez des patients de soins intensifs soumis à une ventilation mécanique, a été étudiée par Spapen et coll. Cette étude prospective, randomisée et contrôlée a confirmé l'hypothèse des auteurs. L'absence d'administration de placebo et le protocole n'étant pas effectué en double aveugle, un biais de sélection ne peut être formellement exclu.

BUT DE L'ETUDE

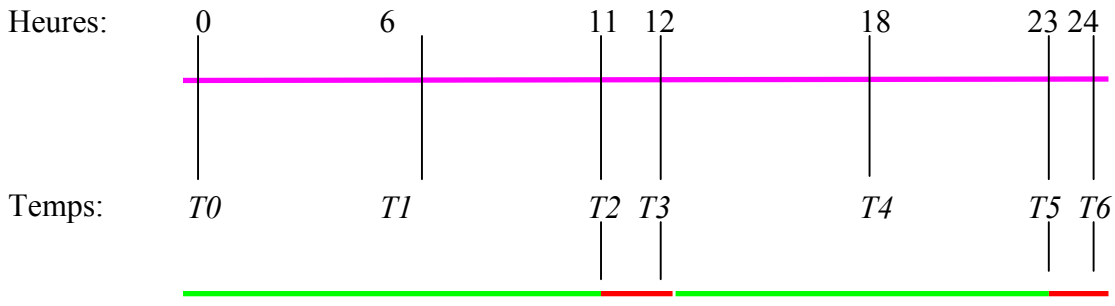
Nous avons conduit une étude similaire à celle de Spapen mais de manière randomisée-contrôlée en double aveugle afin de confirmer ou d'infirmer ses résultats. Les objectifs de l'étude étaient d'estimer la tolérance au support nutritionnel entéral mesurée par les résidus gastriques et la quantité journalière d'alimentation entérale administrée.

MATERIEL ET METHODE

De mai 1997 à mars 1999, nous avons enrôlé 34 patients de milieu de soins intensifs (Hôpital des Cadolles-Neuchatel, Soins Intensifs de Chirurgie-HUG) remplissant les critères d'éligibilités suivants : Ventilation mécanique débutée depuis moins de 24 heures, absence de contre-indication à l'alimentation entérale et durée du support nutritionnel entéral estimée à 5 jours ou plus.

Design de l'étude :

Le support nutritionnel devait être initié durant les vingt quatre premières heures suivant le début de la ventilation mécanique via une sonde naso-gastrique de type Salem 14 Fr ou 16 Fr. Le positionnement correct de la sonde était établi initialement par un cliché radiologique puis vérifié deux fois par jour par l'inflation d'air et l'auscultation du bruit gastrique subséquent.
Le protocole consistait en l'administration quatre fois par jour soit de 10 mg de cisapride ou de son placebo en double aveugle via la sonde naso-gastrique (cf. figure ci dessous ; T1-T3-T4-T6). Une nutrition entérale était débutée dès que possible en continu 11 heures sur 12 heures (T0 à T2) suivies de 1 heure de jeûne (T2 à T3), à répéter sur les 12 heures suivantes (T3 à T5 puis T5 à T6). La vidange gastrique était évaluée par aspiration au travers de la sonde naso-gastrique deux fois par jour suite à l'heure de jeûne (T3 et T6). Selon la quantité de résidu gastrique mesurée, la nutrition entérale était poursuivie ou stoppée selon un protocole prédéfini. Le cisapride ou son placebo étaient administrés après la mesure du résidu gastrique ainsi que 6 heures plus tard.



En cas d'intolérance à la vitesse d'administration de l'alimentation entérale (définie par un résidu gastrique supérieur à 250 mL), la solution de cisapride versus son placebo continuait d'être administrée aux temps prévus selon le protocole et les résidus gastriques notés. Si la nutrition entérale était redémarrée selon une nouvelle échelle de temps, les heures d'administration du cisapride et de son placebo étaient adaptées en fonction.

Etaient considérés comme intolérants à l'administration de nutrition entérale les patients présentant plus de 3 résidus gastriques supérieurs à 250 mL consécutifs et/ou des vomissements plus d'une fois par jour. Dans ce cas, un essai d'administration de cisapride 10 mg par voie non aveugle en maintenant le même protocole horaire était tenté. Dans le cas où ce test s'avérait inefficace, le patient était considéré comme intolérant à l'alimentation entérale précoce.

L'étude était considérée comme terminée lorsque le support nutritionnel entéral était stoppé, que l'apport oral était repris ou que le patient était transféré hors de l'unité de soins intensifs où avait lieu l'étude.

Les données collectées comportaient les caractéristiques démographiques des patients, leur évolution durant leur séjour ainsi que différents scores de gravités. Par ailleurs des tests de laboratoires usuels ainsi qu'un bilan azoté étaient effectués. Les apports caloriques et protéiques, ainsi que la quantité de nutrition entérale étaient relevés en plus des résultats des résidus gastriques, ainsi que la présence de nausées, vomissements ou diarrhées. Une gastroscopie était pratiquée dans la mesure du possible afin de confirmer la justesse de la mesure du résidu gastrique. Un cliché radiologique pratiqué lors de la mise en place de la sonde naso-gastrique n'était répété qu'en cas de suspicion de complication pulmonaire.

Les résultats principaux étaient :

- L'apport calorique journalier
- La tolérance à l'alimentation entérale reflétée par les résidus gastriques, la présence de nausées, vomissements ou diarrhées.
- La longueur du séjour en milieu intensif et en milieu hospitalier ainsi que l'évolution clinique.

RESULTATS ET DISCUSSION

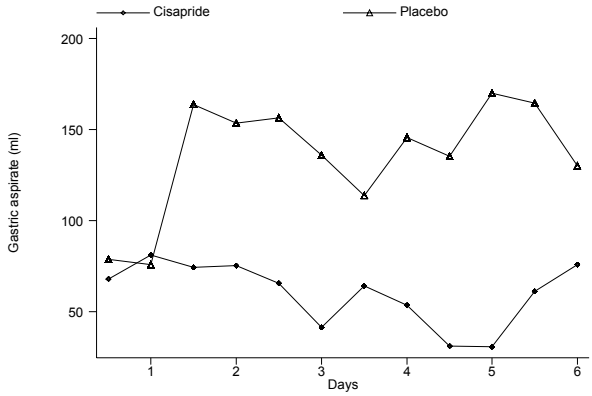
Trente-deux patients (28 à Neuchâtel et 4 à Genève) furent recrutés consécutivement et randomisés pour recevoir en double aveugle soit du cisapride (n=16) ou son placebo (n=16). Les caractéristiques démographiques de ces patients (âge, sexe, scores SAPS II, SOFA, diagnostic d'admission, durée de séjour en milieu intensif et hospitalier ainsi que leur devenir) étaient similaires et les deux groupes étaient comparables. Le délai d'initiation du support nutritionnel entéral, la durée de ce support et la durée d'intubation oro-trachéale en raison de la ventilation mécanique étaient aussi similaires. L'intervalle entre l'admission et l'initiation de l'alimentation entérale était de 13 heures dans chaque groupe. Six patients ont été déclarés intolérants à l'alimentation entérale (3 dans chaque groupe) et ont nécessité une alimentation par voie parentérale.

Effet du cisapride sur le résidu gastrique journalier:

Les valeurs moyennes et médianes des résidus gastriques mesurés étaient de 71mL ±23mL et 76mL (intervalle min-max: 33-99mL) respectivement dans le groupe cisapride et de 132mL ±36mL et 136mL (intervalle min-max : 70mL-181mL) respectivement dans le groupe placebo avec une valeur statistique de $p<0.005$.

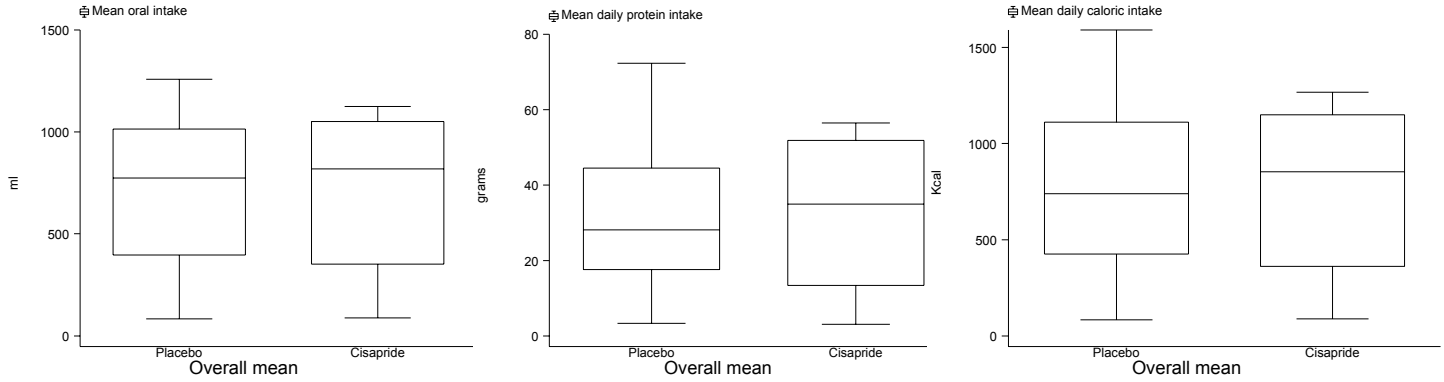
Résidu gastrique moyen au départ et durant les 6 jours suivants chez les patients randomisés à recevoir du cisapride (n=16) ou son placebo (n=16) (graphique # 1)**.**

Graphique # 1



Effet de l'administration de cisapride sur l'apport entéral en terme de millilitres d'apport entéral (graphique # 3), de grammes de protéines (graphique # 4) et de calories (graphique # 5).

Graphique # 3 Graphique # 4 Graphique # 5



Comme les résidus gastriques étaient systématiquement réinjectés dans l'estomac via la sonde naso-gastrique exceptés si supérieurs à 250 ml, l'apport entéral compte de la quantité d'apport entéral prescrite ajoutée au résidu gastrique réinjecté. Les données concernant l'apport protéique et calorique sont dérivées de l'apport entéral total par patient. Ni l'apport total entéral, ni l'apport protéique journalier ou l'apport calorique ne sont statistiquement différents entre les groupes de patients recevant du cisapride ou du placebo.

Effet du cisapride sur les marqueurs biologiques de l'activité métabolique :

La balance azotée mesurée chez 22 patients (11 dans chaque groupe) n'est pas différente de manière statistiquement significative (p=0.59), bien que les valeurs du bilan azoté soient moins négatives dans le groupe cisapride.
L'apport calorique minimal a été atteint chez un petit nombre de patient et de manière similaire sans différence statistiquement significative entre les deux groupes : chez 35% des patients après 3.8 jours respectivement dans le groupe cisapride et chez 25%

des patients après 4 jours en moyenne respectivement dans le groupe placebo ($p=0.55$).

Finalement, aucune complication liée soit à l'alimentation entérale, excepté quelques cas de vomissements, soit à l'administration de cisapride (en particulier aucune arythmie sur le monitoring cardiaque continu) n'a été observée.

CONCLUSION

Cette étude montre que si le cisapride est ajouté à un protocole de nutrition entérale chez des patients de soins intensifs soumis à une ventilation mécanique, la vidange gastrique est doublée. La tolérance à la nutrition entérale, reflétée par les résidus gastriques aspirés, est améliorée par l'administration de cisapride, ceci sans effet secondaire. D'autre part l'observance stricte d'un protocole d'alimentation entérale pré-défini est nécessaire au succès de ce type de support nutritionnel et permet de compenser le retard de vidange gastrique en termes de calories. Le délai d'introduction du support nutritionnel entéral peut par ailleurs être réduit si un protocole strict est appliqué.

SUMMARY

The present medical thesis revisited the gastro-intestinal physiology and pathophysiology before focusing on nutrition treatment in critically ill patients. In the second part a study aim at improving nutritional status was conducted and analyzed.

Critically ill, mechanically ventilated patients admitted to the Intensive Care Units for medical or surgical problems often present comorbidity in parallel of their main admission diagnosis. The former includes the nutritional and immune status before the admission, cardio-vascular, respiratory and metabolic disorders and their repercussions. Moreover, admission in the Intensive Care Unit implies an invasive management of the patient with intra-vascular accesses, intra-tracheal tube impairing coughing, and urinary catheter, eventually a vaosactive or inotropic support, an antibiotic therapy and/or a medical sedation. Nutritional support is often considered of lower priority than vital support and only begun after several hours or even days after admission. This, even though patients experience metabolic stresses and rapidly lose body weight and muscle mass. Early nutrition may also be delayed because of impaired gastric emptying resulting from various etiologies.

It is now well recognized that enteral nutritional support is better than parenteral nutrition. To improve it's tolerance, Spapen *et al* designed a prospective randomized controlled study to investigate the effect of cisapride on tolerance to early enteral nutrition assessed by gastric emptying measurement in critically-ill, mechanically ventilated patients. They showed an improvement in the gastric emptying. However, the study design was not optimal (absence of blinding, no placebo). We decided to conduct a similar study in a double blind-randomized controlled manner in order to confirm or refute their results.

We enrolled thirty-four critically ill, mechanically ventilated patients who received either 10 mg of cisapride or its matched placebo via a naso-gastric tube four times a day. Enteral nutrition was started as early as possible after admission and gastric emptying was evaluated by gastric aspiration through the naso-gastric tube twice a day.

The conclusion of the study was that if cisapride is added to a standard enteral feeding protocol, gastric emptying is doubled and tolerance to an early enteral nutrition reflected by the gastric aspirate is improved. Finally, this improvement was observed without secondary effects.

INTRODUCTION

1. Review of the physiology of the transit of the gastrointestinal tract

The gastrointestinal system is a boundary between the external and the internal environments. Indeed, the food is prepared for passage to the internal environment through the stomach by digestion (nutrients are broken into smaller units) and absorption through the intestinal mucous membrane.

1.1: Motor function of the gastrointestinal tract

The gastrointestinal transit results from two types of movement: mixing and propulsion or peristaltic movements. It moves forward the alimentary bowl at a rate appropriate to digestion and absorption along the intestine. Myenteric plexus, stimulated and modulated by the parasympathetic system, promotes the departure, intensity and rate of the bowel movements. Atropine, a anticholinergic drug, removes the totality of the nerve impulse and paralyzes the myenteric plexus.

Swallowing of the alimentary bowl is a reflex that transfers the chewed food from the mouth to the esophagus. A swallowing movement is made of three parts: a first part: voluntary, who initialized the process; a second part: pharyngeal, involuntary, which transfers the alimentary bowl from the pharynx to the esophagus; and a third part, involuntary, which allows the food to go from the esophagus to the stomach.

1.1.1: Stomach

The proximal stomach presents two types of bowel movement: primary, reflex to the peristaltic movement of the esophagus and secondary, resulting from distension of the esophagus, which still contains part of alimentary bowl. These movements are under control of the parasympathetic system and are initiated by a relaxation of the whole stomach and the gastro-esophageal sphincter. The main role of this sphincter, located at the junction between the esophagus and the stomach (five last cm), is to prevent regurgitation of the gastric bowl in the esophagus by tonic contraction of the lower part of the esophagus (circular muscle). A vagal reflex secondary to the increased intragastric pressure reinforces this tonic contraction.

Anatomy of the stomach

(See Fig. #1)

Illustration found on the Internet: Stomach anatomy

The stomach can be divided into two functional compartments. The proximal part (fundus and upper body) where food is stored and the distal stomach (lower body and antrum). The distal part is primarily responsible for the mixing and breakdown of solids that are transformed into chyme and then slowly evacuated in the small intestine. The evacuation rate is determined by the quality (osmolality, type of fatty acids, proteins or polypeptides) [1] and type of food ingested (liquid or solid), and by the degree of activity of the peristaltic impulse starting from the antrum, and spreading to the pylorus and the duodenum (relaxing-reflex of the sphincter of the pylorus and the proximal duodenum). The emptying of liquid from the stomach is function of the pressure gradient between the stomach and the duodenum. The

stomach dilation by the bowl produces an increase of the rate of chyme evacuation (vagal-reflex stimulated by distension of the wall).
Two types of contraction in the proximal stomach are observed: slow sustained contractions and, superimposed on these, more rapid, phasic contractions.

Motor activity of proximal stomach responsible for gastric emptying

(See Fig #2)

Adapted from [2]

The sustained contractions are responsible for the basal pressure within the stomach. Deglutition and gastric distension will result in prompt relaxation of the proximal gastric wall by inhibition of the sustained contractions. This receptive and adaptive relaxation permits the fundus and upper body of the stomach to act as a reservoir while maintaining low intragastric pressures. Inhibitory vagal neurons, which are noncholinergic, nonadrenergic and partially dopaminergic mediate this reflex.

The stomach contains pacesetter cells located in the smooth muscle cells in the upper body of the stomach on the greater curvature. This gastric pacemaker generates slow cyclic depolarizations, which are propagated distally to the pylorus. A basal activity of 3 to 4 cycles per minute is observed. Superimpose are more vigorous peristaltic waves which are generated by excitatory stimuli such as neurotransmitters.

Electrical and motor activity of distal stomach responsible for gastric emptying of digestible solids

(See Fig #3)

Adapted from [2]

The muscular contraction results in circular rings, which increase in amplitude and velocity as they move distally. During the postprandial state, rhythmic sets of peristaltic waves that constitute the digestive pattern of the distal stomach are observed. These contractions have two functions: first to transport, and second a mixing and grinding effect on solid foods. As the peristaltic wave approaches the distal antrum, the terminal antrum and pylorus close. Large solid particles retained in the stomach by the antropyloric closure are retropelled and triturated in the antrum. Through this grinding action, along with acid-peptic digestion, most solid particles are reduced to chymous-like consistency, allowing outflow into the duodenum. As with the proximal stomach, the distal stomach is controlled via both neural (vagal and sympathetic fibers) and hormonal mechanisms: gastrin increases the frequency of the gastric pacemaker and facilitates generation of action potential, its net effect is to slow down gastric emptying.

Solids that cannot be broken (>2.0mm) are eliminated from the stomach by a different mechanism: the migrating motor complex (MMC). This interdigestive myoelectric complex, which recurs approximately every 2-h and takes place during the fasting state, begins in the proximal stomach and migrates aborally through the small bowel. It is composed of four phases. Phase 1: a period of motor inactivity lasting 45-60mn. During phase 2, there are intermittent peristaltic contractions that increase in

frequency and amplitude over a 30-45mn period. In the 5-15mn periods, designated as phase 3, there is a salvo of peristaltic contractions (3 per minute) generated by action potentials occurring with every pacesetter potential. In the fasting state, the pylorus remains open as phase 3 interdigestive contraction approaches and the contraction sweeps indigestible solids out of the stomach. Phase 4 is a short transition period between the electromechanical surge of phase 3 and the inactivity of phase 1.

Motor activity responsible for gastric emptying of indigestible solids

(See Fig #4)

Adapted from [2]

These interdigestive cycles are switched off by neural and hormonal mediators: the periodicity is thought to be determined by signals from the central nervous system, Motilin plays an initiating role, truncal vagotomy delays the onset of a pattern of gastric contractions and gastrin inhibits fasting electromechanical cycles. Virtually any peptide, hormone or transmitter substance in the gut is involved in the regulation of fasting motility [3]. Animal studies have shown that inhibitors of nitric oxide synthase (NOS) initiate premature phase IIIs of the MMC, whereas donors of nitric oxide (NO) disrupt the MMC. Russo *et al*, [4], in there work used an inhibitor of NOS in healthy human volunteers. Their study confirms that NO mechanisms play a role in the regulation of fasting small intestinal motor activity in humans.

1.1.2: Small intestine

Illustration of small intestine cells

(See Fig #5)

Illustration found on the Internet: GI Tract Anatomy and Morphology of the Small Intestine

The small bowel, where most of the absorption of the digested food takes place, contains receptors, which inhibits gastric emptying, when stimulated via neural and/or hormonal pathway. Gastrin, cholecystokinin, GIP-gastric inhibitory polypeptide, secretin, glucagon, VIP-vasoactive intestinal polypeptide and somatostatin mediate the hormonal pathways.

List of hormones acting on the physiology of the gastrointestinal tract:

Hormone	**Produced by**	**Major function (s)**
Gastrin	Gastric antrum Duodenum	Acid secretion, contraction of the gastro-esophageal sphincter, secretion of glucagon
Secretin	Mucosa	Pancreatic secretion of water and electrolytes
Cholecystokinin	Mucosa	Gall bladder and pancreatic secretion
GIP	Mucosa	Inhibits gastric acid secretion
Motilin	Mucosa	Contraction of gastro-esophageal sphincter
Substance P	Mucosa Nerves	Unknown
Somatostatin	Gastric antrum Pancreatic δ cells	Endocrine/paracrine; inhibits secretion of gastrin, secretin, GIP, motilin, pancreatic secretion, glucagon, insulin
VIP	Nerve cells Endocrine cells	Pancreatic secretion
Glucagon	Pancreatic α cells	Stimulates release of insulin and pancreatic somatostatin
Insulin	Pancreatic β cells	Anabolic hormone

Adapted from [5]

The different receptors include acid receptors (proximal duodenum and jejunum), osmotic receptors sensitive to electrolytes, carbohydrates and amino acids except for L-tryptophan (duodenum), and L-tryptophan receptors (all portion of duodenum and jejunum). Increasing osmolarity of solution results in slower gastric emptying, although some hypoosmolar solutions may also inhibit elimination. Fatty acids, monoglycerides and diglycerides delay gastric emptying. The emptying of carbohydrates and amino acids, except for L-tryptophan (which always delays gastric emptying), is determined by the osmolality of the solution via the osmoreceptors.

The propagation of the chyme in the small intestine is simpler than in the stomach, as the walls of the duodenum, jejunum and ileum have three muscular layers to help churn, mix and propel. A peristaltic reflex is initiated by distension of the walls as soon as the nutrients passe through the intestine.

Physiology of gastric and small intestine emptying

(See Fig #6)

Adapted from [2]

1.1.3: Large intestine

In the large intestine, final absorption of electrolytes and water takes place. The remaining content at the end of the large intestine is the feces, which is stored until exoneration takes place. The movements of the layer are relatively slow, but resemble that of the small intestine (mixing and propulsion). Defecation starts when the bowl

arrives in the rectum, with reflex contraction of the rectum and relaxation of the anal sphincters; it is stopped until voluntary relaxing of the external anal sphincter takes place.

The propulsive movements appears after meal and are partially related to the gastro-colic reflex and duodeno-colic reflex coming from distension of the stomach and duodenum. Transmission is made through the myenteric plexus and the parasympathetic system [2, 6].

1.2: Bacterial population of the Gut

Gastrointestinal motility is also a major, natural defense mechanism against infection of the gut [7]. Microorganisms are relatively scarce in the esophagus, stomach, duodenum and jejunum, due either to the basal condition of the "interior-milieu" (acidity) and to the migrating motor complexes, which periodically flush the luminal content of the proximal gut towards the colon. As movement of the intestinal contents slows in the terminal ileum, the quantity of bacteria rises tremendously [8]. In contrast to the stomach and small intestine, the contents of the colon teem with bacteria, predominantly strictly anaerobes.

Bacterial Populations in the Digestive Tract of Normal Humans:

	Stomach	Jejunum	Ileum	Colon
Viable bacteria per gram	$0\text{-}10^3$	$0\text{-}10^4$	$10^5\text{-}10^8$	$10^{10}\text{-}10^{12}$
pH	3.0	6.0-7.0	>7.5	6.8-7.3

1.3: Secretory function of the Gut

The whole gut contains secretory gland with specific function varying in each part. The two main functions are enzyme secretion (from the mouth to the terminal ileon) to make some nutrients soluble and participate to the digestion of macro-elements, and mucus secretion (from the mouth to the anus). Mucus contributes to mucosal defense by providing a physical barrier to bacteria, thereby reducing bacterial adherence to the epithelium and invasion of the mucosa. Mucus also acts as lubricant to reduce physical abrasion of the mucosa and participates to the protection of the mucosa from damage induced by acid and other luminal toxins. An increase in mucus thickness is a normal defensive response to luminal insult. Water and electrolytes are also secreted in the gut lumen. This fluid secretion reduces bacterial adherence, dilutes and flushes away any potential noxious substances in the lumen. Global secretion function help propel the digestive bolus along the digestive tract.

In the stomach, the cardia contains glands, which secrete mucus. The body, which is the main secreting area, contains chief or pepsin secreting cells, parietal oxyntic cells, secreting HCl and intrinsic factor, and mucus cells in the duct. The pyloric part contains mainly mucus secreting cells. There are finally epithelial cells, which product small amounts of enzymes and watery secretions.

The tubular glands, which product mucus in the small intestine and the colon, are the Lieberkühn glands. Other glands situated in the salivary glands, pancreas and liver, product the secretions necessary for digestion and emulsification of nutrients. The salivary and pancreatic glands are acinus glands.

Beside mucus secretion, gut cells secretion is initiated by several stimuli such as presence of food or chemical irritation, distension of the gut wall, increase in gut

motility, parasympathetic stimulation and hormonal regulation (nutriments in the gut lumen promote gastro-intestinal hormones secretion as mentioned above). Mucus secretion is permanent, but nitric oxide (NO) is an important regulator of mucus quality and quantity secretion in the stomach (stimulation of guanylyl-cyclase in the epithelial cell) [9]. NO seems also to play an important role in the modulation of epithelial fluid secretion. The latter, is also osmotically driven by the active transport of chloride ions into the lumen [9].

The resulting total volume of daily gut secretion is of 7200mL (saliva: >1500mL, gastric secretion: 2000mL, pancreatic secretion: 1200mL, biliary secretion: 700mL, intestinal secretion: 2000mL and colic secretion: 100mL). The ingested fluid is about 1500mL per day. More than 7000mL are then absorbed in the small intestine and normally 500ml leaves the small intestine and enters the colon [6].

1.4: Immune function of the Gut

Immune function of the gut has only been observed in animal studies. Conclusions are extrapolated to human, without clinical trials.

Several mechanisms protect the mucosal cell from potential pathogens, preventing invasive infection and bacterial access into the systemic circulation. Mucus production (direct mechanical surface protection), gastric acidity and intact peristaltism prevent bacteria from penetrating the mucosal cell and producing sepsis. If microorganisms are able to penetrate through the mucus and fluid secreted by the epithelium; the tight junction between adjacent epithelial cells forms the next barrier they encounter. This junction is regulated by NO [9].

The gastrointestinal tract contains also an immune tissue: the GALT (Gut-Associated Lymphoid Tissue). This tissue is located in the mucosal layer along the gastro-intestinal tract (diffuse isolated cells) and forms Peyer's patches under the mucosal layer in the distal part of the small intestine. This tissue contains 70 to 80% of all immunoglobulin-secreting cells of the body [10]. IgA, the primary immunologic product of this system, is a critical component of mucosal immunity and barrier integrity and accounts for 50% of the body's total immunoglobulin production. IgA are secreted from IgA+ plasma cells after sensitization in the Peyer's patches and are homed into the lamina propria. The IgA produced in the lamina propria are immediately transported by means of mucosal epithelial cells by secretory components onto the mucosal surface [11].

Secretory IgA (S-IgA), of which ninety percent are secreted in bile, intestinal secretion, saliva, tears and breast milk, prevents adherence of bacteria, viruses, and enterotoxins to the mucosal surfaces (intestinal microvilli). They also prevent the uptake of enteric antigens and may play a role in eliminating infectious agents that have penetrated epithelial cell layers [11, 12]. Intestinal secretory-IgA levels correlates inversely with bacterial overgrowth, bacterial translocation, and changes in intestinal permeability in animal models [13].

Illustration of stimulation and homing of S-IgA

(See Fig #7)

Adapted from [12]

A reduction in the luminal level of secretory-Ig A (as seen in case of exclusive parenteral nutrition) results in a greater frequency of gastrointestinal microorganism proliferation and, coupled with impaired reticuloendothelial function often seen in critically ill patients, may predispose to systemic bacteremia. The feeding of an oral diet appears to be especially important for the maintenance of secretory-IgA antigenic stimulation of the intestine [11, 12].

2. Assessment of gastric emptying in normal and pathological conditions

The general methods currently used in evaluating gastric emptying are intubative techniques (gastric or duodenal intubation, with or without marker), imaging techniques (radiological: liquid barium sulfate or radiopaque meals; scintigraphy; ultrasonography; MRI), and indirect absorption techniques (blood tests, breath tests).

The intubative techniques have provided valuable information regarding emptying of solid and liquid meals in various disease states. But they are largely abandoned in clinical practice because of inaccuracy and invasiveness. Furthermore, gastric aspiration studies measure only liquid emptying, and the result may vary secondary to the position of the tube tip.

Radiological techniques are considered unsatisfactory for use in gastric emptying studies. Although, duodenal dye dilution techniques are excellent as research tools, they require time and expertise [14]. Scintigraphy remains the most reliable method to measure gastric emptying [15]. Ultrasonography is able to demonstrate antropyloroduodenal motility and flow contents. In particular, 3-D ultrasonography is able to estimate gastric volume, and secondary gastric emptying rate (correlates only with liquid emptying) and duplex technique measure transpyloric flow. But these techniques rely on the experience of the performer [14, 16, 17]. Gastric emptying curves of liquid meals obtained with MRI correlate very well with scintigraphic curves [18]. But this rather new technique is expensive and cannot be performed at the bedside [17].

Indirect techniques to measure gastric emptying include the paracetamol (or acetaminophen) absorption test and 13C breath tests. Paracetamol test is frequently used to measure gastric emptying of liquids. It is based upon pharmacokinetic evidence that paracetamol in solution is not absorbed in the stomach but is rapidly absorbed from the small intestine after passage through the pylorus [19, 20]. A fixed dose of paracetamol is given orally at T0, through the naso-gastric tube. Arterial blood samples are taken before the administration of paracetamol and then at repeated intervals, during six hours after administration. Paracetamol concentrations in blood samples are then measured to determine the area under the paracetamol absorption curve, the time to peak paracetamol plasma concentration and the peak paracetamol concentration [21, 22]. But there is no correlation between paracetamol absorption and volumes of gastric aspirates [23]. 13C breath tests (13C acetate [24] or 13C octaonate [25]) can measure the gastric emptying of liquids and solids respectively and can achieve accuracy comparable with gastric scintigraphy.

Correlation between gastric emptying and the volume of gastric aspirate or the presence of bowel sounds has not been proved and is questioned [26]. But it is generally admitted that a gastric residue lower than 120 to 150mL correlate with a satisfactory gastric emptying. However, Cohen *et al*, [27], showed that paracetamol absorption test may be normal in patients with relatively high gastric residual volumes

(more than 150mL after 8 hours, or more than twice the hourly infusion rate in that study of critically ill patients).

3. Delayed gastric emptying: etiology, prevalence, symptoms and pathophysiology

Delayed gastric emptying states can result from many factors: mechanical, metabolic and endocrine, gastric disease, post-gastric surgery, medications and idiopathic origin.

3.1: Etiology
The delayed gastric emptying can be transient or chronic.

	Transient delayed gastric emptying	**Chronic delayed gastric emptying**
Mechanical factors	Mechanical ventilation	Gastric carcinoma and tumor associated, pyloric or prepyloric ulcers, idiopathic hypertrophic pyloric stenosis, pseudo-obstruction resulting from amyloidosis, muscular dystrophies, dermatomyositis, sclerodermia
Gastric diseases	Viral gastroenteritis	Gastroesophageal reflux, gastric ulcer disease, atrophic gastritis ± pernicious anemia
Metabolic and endocrine origin	Acute diabetic ketoacidosis, pregnancy	Diabetes mellitus, Anorexie nervosa? Bulimia nervosa?
Post gastric surgery	Postoperative gastro-colo paresis	Post vagotomy and/or post gastric resection
Medications	Morphine, anticholinergics, levodopa, β-adrenergic agonists, L-dopa Hormones in pharmacological studies: gastrin, cholecystokinin, somatostatin dopamine	Cigarette smoking
Idiopathic origin		Idiopathic, idiopathic autonomic degeneration, chronic idiopathic intestinal pseudo-obstruction, gastric dysrhythmias-tachygastria, gastroduodenal dyssynchrony
Central nervous system origin		Spinal cord injury, brain stem lesions and traumatic brain injury, Parkinson's disease, depression?
Electrolytes abnormalities	Hypokalemia, hyperglycemia, hypercalcemia, hypocalcemia, hypomagnesemia	

3.2: Prevalence
The reported prevalence of delayed gastric emptying varies between studies. For diabetes mellitus it varies from 22% to 50% (whether insulin dependent or non-insulin dependent); for gastroesophageal reflux, solid food retention can be seen in 57% of patients, whereas 38% have normal emptying of solids and 5% displayed rapid emptying.

3.3: Symptoms
Many patients with grossly delayed gastric emptying have few or no symptoms. Delayed and more rapid gastric emptying may also result in similar symptoms.

Clinical manifestations of gastric emptying disorders include nausea, vomiting, abdominal discomfort, early satiety, "dumping" and diarrhea. Posprandial symptoms are usually worse, but symptoms may also be delayed. Moreover, esophageal, small intestinal, colonic and anorectal motor dysfunction are often associated with disordered gastric emptying. Thus, dysphagia, diarrhea, constipation and fecal incontinence are observed [2, 28].

3.4: Pathophysiology
Pathophysiologic mechanisms of delayed gastric emptying include defective pumping through weak contraction and abnormally high resistance to emptying.

Subnormal fundic tones, weak or absent antral pumping contractions and proximal duodenal retention because of duodenal pump failure, are causes of defective pumping through weak contractions.

Abnormally high resistance to emptying is due to persistently obstructive or retropulsive contractions of antrum and pylorus, excessively frequent localized pyloric contractions-pylorospasm and obstructive patterns of duodenal contraction. The preponderance of nonexplusive antral contractions (antral phase 3 activity is absent) is found in case of idiopathic gastroparesis. In case of diabetes mellitus, marked antral hypomotility (abnormal gastric pacemaker function) and a preponderance of nonexplusive antral contractions (same mechanism as in case of gastroparesis) have been demonstrated. Gastric surgery produces transient or permanent impairments of the ability of the stomach to grind solid food, to retain it within the stomach and to pump meals into the duodenum. In only a minority of patients these anatomical modifications cause majors symptoms due to delayed gastric emptying, more rapid emptying of liquids and/or alkaline reflux gastritis [28].

3.4.1 Delayed gastric emptying following traumatic brain injury
In case of traumatic brain injury, difficulties in feeding and poor tolerance to gastro-enteral feeding are often observed [29]. They are either due to a hypermetabolic state, which appears immediately after trauma, or to swallowing disorders that frequently follow acute brain injury, or are secondary to gastroparesis. This poor tolerance may persist from 14 days until 4 to 6 months after brain injury [30]. At the beginning, a significant inverse relation ship is observed between daily intracranial peak pressure and time to tolerance of feeding [31]. Similar findings have been described by Garrick *et al*. [32], who demonstrated that gastric motility is inhibited and amplitude of gastric and duodenal contractions are reduced by over 80% and 60% respectively, by increased intracerebroventricular pressure in a rabbit model. This effect is of rapid onset and is reversed by a cholinergic agonist, suggesting a neural mechanism involving vagal inhibitory pathways. In human, the relative intolerance to enteral/oral

nutrition has been attributed to prolonged paralytic ileus, abdominal distension, aspiration pneumonia and diarrhea [33, 34], and an adverse effect of elevated intracranial pressure above 20 mmHg is suggested [31]. Saxe *et al*. [35] showed that lower esophageal sphincter dysfunction accompanies acute head injury and disappears if the Glasgow Coma Scale (GCS) is over 12. After spinal cord injury patients present also significant prolonged gastric emptying of solid meal in case of high-level injury (quadriplegic) [36].

3.4.2 Delayed gastric emptying due to medications

Morphine and other opiate analgesics are notorious for causing gastric retention. Exogenous and endogenous opiates exert their influence directly on gastrointestinal receptors (opiates μ receptors) and via the central nervous system [2]. They are first associated with an increase in amplitude of gastric contractions, which is then followed by a prolonged decrease in gastric propulsive activity. The influence of the central nervous system has been questioned. Indeed, Murphy *et al*. [37] showed in their study that the use of methylnaltrexone (a quaternary derivative of the opiate antagonist naltrexone, which does not cross the blood-brain barrier) attenuates the morphine–induce delay in gastric emptying. Methylnaltrexone had the potential to decrease the side effects of opioid medications, which are mediated peripherally, while maintaining the central analgesia effect of the opioid. Even small dose of morphine, such as 0.05mg/kg, which is already effective to produce analgesia, inhibits gastric emptying in human healthy volunteers, compared to placebo [38].

β-Adrenergic agonists, such as isoproterenol and salbutamol, have been shown to delay gastric emptying, and propranolol was shown to reverse the action of isoproterenol. Propranolol, by-itself, was found to accelerate gastric emptying significantly. This suggests that under physiologic conditions, there may be β-adrenergic inhibition of gastric activity [2].

Dopamine is known to decrease gastric tone. Moreover, it also increases the motility of the proximal part of the small intestine in humans [39]. However, delayed gastric emptying is universally observed. At a dose of 2 μg/kg/min, it produces a transient fall in gastric pressure in all healthy humans, and a persistent fall in some. At 8 μg/kg/min, it reduces intragastric pressure and delay gastric emptying. The probable explanation is that dopamine produces β-adrenergic stimulation. Levein *et al*. [40] studied the effect of a continuous infusion of dopamine (5 μg/kg/min) on gastric emptying and oro-caecal transit time in human healthy volunteers. They showed that dopamine delays gastric emptying and prolongs oro-caecal transit time. It must be highlight that dopamine agonists have however plexiform effects on the digestive tract. For example the process of adaptive relaxation, whereby the stomach relaxes to receive a bolus of food, is mediated by the vagus nerve with dopamine as neurotransmitter [41].

4. Treatment of delayed gastric emptying in critically ill patients

Before prescribing drugs, simple methods to facilitate the gastric emptying must be used. First, semi-recumbent position is advantageous to diminish gastroesophageal reflux (GER). Avoiding supine position prevents some regurgitation by gravity. Indeed, if the head is not maintained above the abdomen, the gastric content will always have a tendency to flow back in the mouth. 30% of patient kept in supine position are estimated to have GER even in the absence of a naso-gastric tube. The naso-gastric tube also predispose the patient to reflux by interfering with the lower

esophageal sphincter function, as well as prolonging esophageal contact time with refluxed gastric content [42]. Furthermore, avoiding a contact between nasogastric tubes and the pylorus may prevent pyloric hyper-contractions and thus gastric food retention. If these simple measures do not improve gastric emptying then pharmacological treatment may be prescribed.

4.1: Review of the usual prokinetic drugs employed and of their efficiency in critically ill patients

The most effective approach to treat gastroparesis is the use of drugs designed to increase the rate of gastric emptying by facilitating gastroduodenal motility. [43]. The gastrokinetic drugs available are:

- Metoclopramide
- Domperidone
- Cisapride
- Erythromycin

Their gastrokinetic effect is due to direct dopamine receptor blockade (domperidone, metoclopramide), stimulation and blockade of subtypes of 5-hydroxytryptamine receptors (metoclopramide, cisapride) and stimulation of motilin receptors (erythromycin). Most of these effects appear to be modulated by the final common path of increased acetylcholine release at gastric neuromuscular junctions. All these drugs increase the amplitude of antral contractions [28]. Bethanechol, a cholinomimetic drug, increases the rate of gastric emptying and gastric motor activity in some patients with gastroparesis, but overall its clinical efficacy has been disappointing [43].

- Metoclopramide has both central and peripheral antidopaminergic properties. It releases acetylcholine from the myenteric plexus, without affecting gastric acid secretion. It also has central antiemetic properties. Its use is limited by neurological side effects (central antidopaminergic effects), such as anxiety, drowsiness and lassitude (up to 20% of patients); dystonic reactions occur in about 1%. Secondary hyperprolactinemia is also well known [28].
- Domperidone is a peripheral dopamine antagonist like metoclopramide, but lacks cholinergic activity. Neurologic side effects are rare, since it penetrates the blood-brain barrier poorly. Hyperprolactinemia occurs occasionally [28]. Domperidone is also believed to possess cardiac electrophysiological effects similar to those of cisapride and class III antiarrhytmic drugs [44].
- The next chapter will be allotted to cisapride.
- Erythromycin stimulates gastrointestinal motility by acting as an agonist of receptors for the gastrointestinal peptide motilin, effect that is unrelated to its antibiotic properties [45]. The effect of erythromycin on gastric motor activity is dose-dependent [46]: small dose stimulates antral activity (phase III), which migrates into the duodenum, and higher dose induces strong contractions of the antrum, which are not propagated [47].

Effects on gastric motility of cisapride, erythromycin and metoclopramide are well studied in critically ill mechanically ventilated patients [48-51]. The study of Jooste *et al.* [49] shows that a single dose of metoclopramide improves gastric emptying (paracetamol absorption test). The benefit of such effect is however questioned. Indeed, Yavagal *et al*. [52] found no benefit after administration of metoclopramide on the prevention of aspiration pneumonia, mortality rate or the length of ICU stay in mechanically ventilated patients receiving enteral tube feeding.

The administration of erythromycin, which is also effective in improving gastric emptying in patients intolerant to nasogastric feeding [51], is followed by an increase in antral motility (manometric study) and an acceleration of gastric emptying (paracetamol absorption test) in the study of Dive *et al*. [48].

The study of McLaren *et al*. [50] compares sequential single doses of cisapride, erythromycin and metoclopramide (paracetamol absorption test and gastric residual volumes) in critically ill patients intolerant to enteral feeding. They found that gastric residual volumes during the study are not significantly different between agents, and that metoclopramide or cisapride are effective for promoting gastric emptying. Metoclopramide seems to provide a quicker onset than cisapride. However, cisapride, which is as efficient as metoclopramide for gastric emptying, is more appropriate than the latter in critically ill patients, who need gastric emptying and stimulation of entire gut motility. Cisapride is also devoid of central effects.

4.2: Focus on cisapride

4.2.1 Pharmacokinetic aspects
Cisapride, a substituted piperidinyl benzamide, can be administered via oral, parenteral or rectal way; only the oral formulation is authorized in Switzerland.

Peak plasma concentrations of cisapride are achieved 1 to 2 hours after oral administration of a single 5 to 20 mg dose. The absolute bio-availability of the oral formulation of the drug is 40 to 50%. The volume of distribution is 2,4 l/kg and cisapride is 98% bound to plasma protein in vitro. Cisapride is metabolized in the hepatocytes (oxidative-N-dealkylation) and its major metabolite, norcisapride, has no pharmacological activity. The elimination half-life is about 7-10 hours in healthy volunteers (lengthened in patients with hepatic disease and some elderly subjects who can accumulate the drug). There is no evidence of significant alterations of its elimination in case of renal insufficiency. [53, 54].

4.2.2: Pharmacodynamic aspects
Mechanism of action:
Cisapride stimulates gastrointestinal motor activity through an indirect mechanism involving the release of acetylcholine mediated by postganglionic nerve endings in the myenteric plexus of the gut [53]. The release of acetylcholine stimulates the gastric motility in a fashion similar to the natural progression of the interdigestive migrating motor complex. Cisapride also acts on serotonin receptors (serotonin = 5-hydroxytryptamine = 5-HT). It is an agonist at the 5-HT4 receptor as well as antagonist at the 5-HT3 receptor. Studies indicate that the intestinal effect is most likely to result from activation of 5-HT4 receptors, although other, as yet unidentified serotonin receptors may also be involved [54]. The main site of action of cisapride in the stomach is supposed to be the proximal portion where the acceleration in gastric emptying occurs [55].

Efficiency on the different parts of the gut:
Cisapride increases the lower esophageal sphincter pressure (LOSP) and esophageal motility by about 20 to 50% in healthy adult volunteers and patients with gastroesophageal reflux disease [54]. It also reduces the duration of esophageal pH<4 [55]. It has been shown to reduce the exposure of the esophagus to gastric acid (effect attributed to the action on the LOSP, esophageal clearing peristalsis and gastric emptying). Its efficiency is similar or superior to metoclopramide in reducing esophageal exposure time to acid [53].

In case of functional dyspepsia, the relief of symptoms is better with cisapride than a placebo [53], and similar to metoclopramide [54]. Patient suffering from functional dyspepsia compared to healthy volunteers, have delayed gastric emptying of solids, but not of liquids, when monitored by 13C breath tests. The use of cisapride significantly accelerates gastric emptying of solids, which remains still slower in case of functional dyspepsia. The effect of cisapride adjunction on gastric emptying of liquids is controversial: Duan *et al.* [56] found no modification, but a more recent study by Borovica *et al.* [57] found an acceleration of liquid gastric emptying.

Cisapride enhances gastro-intestinal and colic motility [58]:

- Comparative trials on the efficiency of cisapride with or without other active agents on gastroparesis are numerous and often contradictory or even non conclusive. The only conclusion one can draw is that cisapride efficiency is similar or superior to metoclopramide in reducing gastric transit time in healthy volunteers and in patients with idiopathic gastroparesis [53, 54]. Gastric emptying is accelerated in:
  - Healthy subjects and patients with idiopathic gastroparesis [53, 59, 60],
  - Gastroparesis associated with gastro-esophageal reflux disease [55],
  - Gastroparesis following surgery [61].

  The volume threshold required for antral stimulation is decreased.
- Antro-duodenal motility and coordination are improved following single or multiple doses of cisapride in healthy volunteers and patient with dyspepsia (fasting and fed conditions) [53].
- There are few trials evaluating the efficacy of cisapride on postoperative gastrointestinal atony. Wiseman *et al*. [54] in their review showed only an efficacy to relieve symptoms in case of Roux-en-Y gastro-jejunostomy. They found no efficacy to relieve nausea and vomiting in the early postoperative phase compared to a placebo. In case of cholecystectomy, Tollesson *et al*. [61], who studied the postoperative colonic motility, found that cisapride induced a significantly earlier return of propulsive motility in the right colon. An earlier first passage of feces occurred in the cisapride group (significant result).
- In pharmacodynamic studies, cisapride restored colonic propulsive action and accelerated colonic transit in the caecum and ascending colon. Cisapride enhance the propagative motility of the colon (clinical trial) [61], reduce the transit time through the small and large intestine in healthy volunteers and patients with deficiencies in propulsive activity (diabetic autonomic neuropathy, quadriplegic patients) and cause a significant increase in stool frequency compared with both baseline and placebo [53, 62]. In a study on colonic transit time, the number of bowel movements increased in healthy volunteers and in patients with constipation [54].

Cisapride also has an effect on gallbladder volume (small reduction of volume followed by a faster refilling) compared to placebo [63].

Efficiency in case of opiate administration, diabetes mellitus:
Opioid, such as morphine, are known to delay the emptying of the stomach and the absorption of the orally given drugs. The administration of cisapride (10 mg minimum) prevents the delay in gastric emptying (assessed using the rate of absorption of orally administered paracetamol) secondary to the administration of morphine [64]. In case of administration of morphine in a patient presenting a post-operative paralytic ileus, the administration of cisapride induces earlier return of propagative motility [61].

Diabetes mellitus is known to cause neuropathy and in particularly, diabetic dysautonomia. It includes orthostatic hypotension, baseline tachycardia, cystopathy with urinary troubles, gastroparesis, diarrhea, sudation problems and so on. Cisapride is known to accelerate gastric emptying [59, 65, 66] and antroduodenal coordination [53] in case of diabetic gastroparesis. Borovica *et al*. [57] studied the effect of cisapride in diabetic patients with magnetic resonance imaging. They found no change in antral contractility following cisapride administration, but an acceleration of liquid gastric emptying that may be related to changes in proximal gastric tone or gastric outlet resistance.

Secondary effects:
Concentration of gastrin, insulin, glucose and prolactine do not appear to be altered by the drug. Metabolic control of insulin-dependant diabetes remains unaltered or improves during cisapride therapy [65]. There is an absence of central nervous system depressant effect, such as somnolence or fatigue compared to metoclopramide; and cisapride is devoid of antidopaminergic effects [53].

Cisapride is well tolerated in clinical trials. Side effects, such as transient abdominal cramping, borborygmi and diarrhoea or loose stools, which occurs infrequently, are an extension of its pharmacological action. They have only rarely necessitated treatment withdrawal [53, 67]. Verlinden *et al.* [68] in their review of 42 clinical trials, found a similar incidence of adverse events reported during cisapride treatment (13.7%) compared to placebo administration (11.2%). They found no evidence of any effect of cisapride on the cardiovascular system or on psychomotor function, no neuroendocrine (antidopaminergic like) effects (e.g. prolactine release, extrapyramidal reaction) and no effect on body weight. CNS effects such as somnolence or fatigue arise rarely (1,5%). No clinically significant changes in haematology or blood chemistry are to be found.

Cisapride itself has no cardiac effects if used following recommendations, and specially avoiding drug interactions. Inman *et al*. [69] reviewed 13’233 patients treated with cisapride and 240’381 patients treated under substantially identical conditions without cisapride. They found that the rate of palpitations, tachycardia and extrasystoles recorded during the first month of prescription was 0.8 per 1000 for cisapride compared with a mean rate of 2.5 per1000 in the other patients. They conclude that these events might be coincidental. An effect of the drug on heart rate is not to be expected from its pharmacology (see next paragraph). There is a controversy on spontaneous reports of QT interval prolongation associated with the use of cisapride alone at any dose. For the Committee on safety of medicines and Medicines control agency, none are known [70], but in the literature, case reports are not rare relating long QT syndrome [71] or torsade de pointe [72].

Directions for use:
The recommended dosage in case of gastroparesis or gastro-esophageal reflux disease is 4 times daily 10 mg, 15 to 30 minutes prior to a meal (the presence of food enhance absorption of cisapride) [53, 60].

4.2.3: Drug interactions
Drug interactions result from different mechanisms such as acting on the absorption rate, link to plasmatic proteins, hepatic metabolism (clearly the most important), hepatic and renal clearance and elimination.

Cisapride increases, via his prokinetic effect, the absorption rate and thus the bioavailability of benzodiazepins, acenocoumarol, morphine [73], ranitidine, and cimetidine [74-76] when given concomitantly by oral route.

Cisapride interacts directly with drug metabolised by the cytochrome P450 3A4 such as erythromycin, clarithromycin, fluconazole, itraconazole, ketoconazole and miconazole. These drugs, which inhibit its metabolism (ketoconazole inhibits directly the cytochrome P450 3A4), can enhance the plasmatic rate of cisapride. A high plasmatic rate of cisapride can then promote arrhythmia (report of 2 fatal case of QT prolongation, torsade de pointe and/or ventricular fibrillation) [70, 72, 77]. The exact mechanism of cardio toxicity is unknown but a procainamide-like effect has been suspected as well as an activation of 5HT-4 like receptors [78].

4.3:Administration of cisapride to critically ill patients

Traumatic brain injury is often complicated by gastroparesis, which responds to metoclopramide therapy [34]. If not, the introduction of cisapride is followed by a net improvement in gastric tolerance [79].

Spapen *et al*. [80] studied the effect of adding cisapride to a standard enteral feeding on the gastric emptying in critically ill sedated and mechanically ventilated patient. Their results show that gastric emptying is significantly improved by adding cisapride. Furthermore two other studies from Heyland *et al.* [26, 81]and Goldhill *et al*. [26, 81] made the same conclusion with similar patients[26, 81].

5. Nutrition of the critically ill patient

The association between a poor nutritional status and a poor clinical outcome (mortality, morbidity, cost or duration of hospitalization) is well known. Since the 1960s, it is possible to provide a systematic enteral or parenteral nutritional support to patients not able to eat or who lose weight.

Critically ill patients are endangered to several failures including cardio-circulatory, respiratory, immune and nutritional failures during their stay in Intensive Care Unit (ICU)[82]. Some patients may experience shock state before admission to ICU, which can produce mucosal injury. Furthermore, an immunocompromised state is often observed, especially following surgery. Drug treatment and/or dietary regimens that are administrated are also both able to disrupt the normal ecology of the gut flora. Deitch *et al*. studied rats [83] and confirmed their hypothesis that permeability of intestinal mucosa exist when shock and absence of nutrition is simultaneously present. They extrapolated conclusions to critically ill patients from the animal model: they

suggested that the rupture of the normal ecology of the gut flora could result in subsequent overgrowth of the endogenous micro flora or colonization with exogenous pathogens. The concept of translocation has been an hypothesized theory to explain the development of multiple organ failure appearing weeks after an initial insult.

But rat and human small intestine behave differently when subjected to starvation or mucosal injury. Starvation in the rats can result in small bowel atrophy within 4 days [84], whereas the human bowel may remain nearly normal for nearly 2 weeks of starvation [85]. It is only with electronic microscopy, that a slight but significant decrease in the height of duodenal microvilli is observed.

At their arrival in the intensive care, patients may experience a phase of shock (related to hypovolemia, response to illness) lasting 48 to 96h that is accompanied by a phase of intense catabolism. During this phase, surgical injury, trauma or critical illnesses result in hormone-mediated mobilization of endogenous substrate to protect homeostasis. There is a generalized increase in metabolic activity averaging 30-40% above resting metabolic rate equaling 900-1200 kcal/m^2/day. So critically ill patients are hypermetabolic and have increased nutrient requirements. Endogenously increased metabolic activity is supported by release of stored energy. Under the mobilizing signal of the catecholamines, glucagon, insulin and corticosteroids, endogenous reserves are utilized in support of the metabolic response to injury [86, 87]. Although it is assumed that nutritional support is beneficial in this group of patients, there are no well-designed clinical trials to test this hypothesis. The rationale for nutritional support, therefore, is based upon clinical judgement. It is not known how long a critically ill patient can tolerate what is effectively starvation; the loss of lean tissue, which occurs in catabolic patients (20-40 g nitrogen/day), suggests that depletion to a critical level may occur after 14 days [88].

5.1: Glucose metabolism

A prominent feature of the response to injury or sepsis is hyperglycemia. The initial increase in blood glucose after injury is due to the mobilization of liver glycogen. The hyperglycemia persists beyond the exhaustion of the glycogen supply. There is a marked increase in hepatic glucose production (due to hepatic gluconeogenesis) along with a reduction in glucose clearance. The hepatic gluconeogenesis use: amino acids (breakdown of muscles), lactate and pyruvate (coming from glycogenolysis and glycolysis of muscle), and glycerol (from the metabolism of triglycerides). A resistance to insulin is observed in peripheral tissues, such as skeletal muscle and attributed either to an inhibition of insulin secretion secondary to epinephrine (inhibition of insulin exocytosis) or to a post-receptor blockade. The increased gluconeogenesis and insulin-resistance result in poor utilization of both endogenous and exogenous carbohydrates in stressed patients. Moreover, glucose control with prevention of hyperglycemia is a dominant factor in improving mortality of critically ill patients. Increased insulin administration is associated with an increased risk of death [89, 90]. While there is still no proven mechanism to explain the detrimental effects of hyperglycemia, in vitro data demonstrate that the responsiveness of leukocytes stimulated with inflammatory mediators is inversely correlated with indices of in vivo glycemic control [91]. Other as-yet unproven explanations include exacerbation of polyneuropathy in critical illness or the risk of developing critical illness polyneuropathy, thereby prolonging mechanical ventilation, and undefined alterations in use of cellular energy substrates. Multivariate logistic regression analysis confirmed the independent role of blood glucose control in achieving most of the clinical benefits of intensive insulin therapy and underlines the importance of lowering the blood glucose level to strict normoglycemia [92].

5.2: Fat metabolism

After trauma, patients have increased lipolysis and utilize fat as their major fuel source: muscle lipoprotein lipase activity is increased and adipose tissue lipoprotein lipase is decreased. In case of sepsis, muscle lipoprotein lipase activity is decreased. Moreover, excessive or inappropriate inflammation and immunosuppression are components of the response to surgery, trauma, injury and infection in some individuals and these can lead, progressively to sepsis and septic shock.

The hyperinflammation is characterized by the production of inflammatory mediators, while the immunosupression is characterized by impairment of antigen presentation and of T helper cell type-1 responses. Long chain n-3 fatty acids from fish oil decrease the production of inflammatory cytokines and eicosanoids. They act both directly (by replacing arachidonic acid metabolism) and indirectly (by altering the expression of inflammatory genes through effects on transcription factor activation). Thus, long-chain n-3 fatty acids are potentially anti-inflammatory agents and It is still matter of debate if this can be translated in patients with sepsis [93]. By contrast, in acute respiratory distress syndrome, the debate concerning the use of long-chain fatty acids as opposed to physical mixture of medium- and long-chain fatty acids, specifically regarding their effect on gas exchange and pulmonary hemodynamics, still remains unresolved [94].

5.3: Protein metabolism

Injury (surgical, traumatic and burn) and sepsis result in accelerated protein breakdown, manifested by an increase in urinary nitrogen loss, increased peripheral release of amino acids, and inhibited muscle amino acids uptake observed in sepsis. Labile protein reserves are mobilized in increased amounts. The amino acids are transported to the liver for conversion to glucose (gluconeogenesis) and biosynthesis of new protein necessary to ensure proper recovery. The negative nitrogen balance observed in such patients represents the net result of breakdown (increased) and synthesis (either increased or diminished). Erosion of protein stores (muscle, gut and skin) causes a decrease in the net weight and a muscle loss. This catabolic phase with erosion of protein stores results in a significant added morbidity and mortality [95, 96].

5.4: Nutritional support to critically ill patients

Injured and septic patients do not respond to nutrients like normal or starved patients. The provision of protein to stressed patients is an important aspect of nutritional support. However, it is necessary to provide adequate non protein calories (lipid and carbohydrates), so that the administered and/or endogenous amino acids can be used as substrate for protein synthesis rather than as an energy substrate. This is particularly true because the catabolic state found in burns, trauma and septic patients markedly impairs the efficient utilization of exogenous nitrogen. However, even if adequate proteins are provided, it only partially attenuates the nitrogen losses [96].

Compared to healthy volunteers, critically ill mechanically ventilated patients have delayed gastric emptying, usually associated with the use of opioids for analgesia, and with sedation [97]. But a manometric study done by Dive *et al.* [98], who compares healthy volunteers to mechanically ventilated critically ill patients, shows a loss of peristaltic activity in the stomach and, to a lesser degree, in the duodenum. Theses alterations in the electrical activity of the proximal gut cannot only be attributed to the use of opioids or dopamine or head injury.

In case of head injury, Young *et al*. [99] showed that a profound traumatic response with increased energy expenditures, negative nitrogen balance, weight loss,

hypoalbuminemia and altered substrate oxidation is induced. Head injured patients are also known to have poor gastric tolerance to enteral feeding. The recommendations of nutritional support are to replace 140% of resting metabolism expenditure in non-paralyzed patients and 100% of resting metabolism expenditure in paralyzed patients using enteral or parenteral formulas containing at least 15% of calories as protein by the seventh day after surgery. The preferable option is the enteral way [100].

Nutritional support can be administered via enteral or parenteral way. Kudsk *et al*. [101] compared enteral nutrition to parenteral feeding in a prospective study on patients suffering from abdominal trauma. They found that enteral feeding is associated with significantly fewer cases of pneumonia, intra-abdominal abscess, line sepsis and infection. Only 18% of enteraly feed patients compared to 35% of parenteraly feed develop post-operative septic complications. The difference between groups is the greatest in the most severely injured patients. A meta-analysis on post-operative septic complications conducted by Moore *et al*. [102] compares early enteral feeding to parenteral nutritional support and draws similar conclusions: early enteral nutrition in high-risk surgical post-operative patients is followed by a lower septic morbidity rate compared to total parenteral nutrition.

6. Bacteremia and multiple organ dysfunctions

Systemic blood infections with bacteria have multiple origins: oral or transmucosal passage of bacteria, catheter contamination, wound infections....

Oral microorganisms (more than 500 bacterial species have been encountered in the mouth) are known to cause systemic diseases in every human, but are usually eliminated by the host within minutes [103]. Transmucosal passage of bacteria through the intestinal mucosa is less frequent and could lead, in critically ill patients, to significant incidence if systemic sepsis occurs.

6.1: Bacterial translocation

Bacterial translocation is defined as the passage of viable bacteria or bacterial components from the gastrointestinal tract to extra-intestinal sites, such as the mesenteric lymph node complex, liver, spleen, kidney, and blood stream. Three basic pathophysiological conditions are necessary for bacterial translocation to occur in animal models [104]. These are:

- Disruption of the ecological balance of the normal endogenous microflora, resulting in bacterial overgrowth with Gram positive enteric bacilli
- Impaired host immune defenses
- Physical loss or increased permeability of the intestinal mucosal barrier

Diagram illustrating concomitant factors promoting bacterial translocation

(See Fig #8)

Adapted from [104]

The presence of mucosal atrophy does not mean that intestinal permeability to bacteria or endotoxin, or both, will be increased and, conversely, the prevention of mucosal atrophy is not synonymous with the prevention of bacterial translocation [83].

Diagram illustrating the progressive atrophy of the villous height and crypt depth, bacterial proliferation and then translocation through the atrophied epithelial barrier

(See Fig #9)

These mechanisms can act in concert to promote synergistically the systemic spread of endogenous translocating bacteria to cause lethal sepsis. In animal models without physical damage of the intestinal barrier, bacteria translocate by an intracellular route through the epithelial cells lining the intestines and then travel via the lymph to the mesenteric lymph node complex. In animal models exhibiting damage to the mucosal epithelium, bacteria translocate intercellularly between the epithelial cells to directly access the blood [105]. Histological mechanical damage to the gut mucosal barrier and spread of bacteria from the gut is observed in an animal model of protein malnutrition associated to endotoxemia. The mortality rate is directly related to the degree of malnutrition and histological damage is associated with higher lethal effects of endotoxin [83, 106].

These same conditions are commonly seen in the critically ill or injured patient at risk of developing enteric bacteremia or multiple organ failure. As starvation and protein malnutrition have been reported to: impair host immune and antibacterial defenses, disrupt the normal ecology of the gut microflora and lead to mucosal atrophy, there are many reasons to believe that nutritional variables are important modulators of gut barrier function and bacterial translocation.

6.2 Multiple organ dysfunctions

Multiple organ failure (MOF) is a state often observed in the ICU, which etiology is not clearly established. It usually follows an infection, but the causal relationship between infection and MOF is not proved even if it is frequently observed [107]. Prevention of MOF is now recognized and include aggressive resuscitation of hemodynamically unstable patients, careful assessments to avoid missing clinically significant injuries, early operative treatment of all possible injuries, early nutritional support and early diagnosis and prompt treatment of infectious complications [108]. The treatment of underlying disease remains the cornerstone of the care of critically ill patient to prevent MOF.

The multiple organ failure and its consequences and treatment, which are not of a primary importance for this study, will not be developed further.

7. Importance of the route of nutrition

The route by which patients are fed may influence the immuno-inflammatory and metabolic response to injury, thus affecting the incidence of infectious complications and modulating clinical outcome. The works of Moore *et al.* [102] and Kudsk *et al.* [101] demonstrate an association between total parenteral nutrition (TPN) and a higher incidence of septic complications when compared with total enteral nutrition (TEN). Hadfield *et al*., [109], studied the effect of enteral nutrition (EN) and parenteral nutrition (PN) on gut mucosal permeability in human critically ill patients. They found that compared to a control group, gastrointestinal tract dysfunction (reduced absorption and increased permeability) are evident in critically ill patients. The introduction of an EN is followed by a significant decrease in gastrointestinal (GI) permeability, whereas the use of TPN results in the perpetuation of the loss of

mucosal integrity. A significant difference between both methods of nutrition is seen after 9 days of stay in the ICU.

7.1 Parenteral nutrition

With intravenous TPN, nutrients do not directly reach the liver; they have to pass through the lung and the systemic capillaries before they reach the hepatocytes. That is probably why the parenteral way of nutrition, although it is relatively practical to manage, is associated with numerous complications. A non-exhaustive list of the latter includes:

- Dysfunctions of the gut (alteration of the gut mucosa, bacterial translocation)
- Immune effects (impaired immune function, immunosuppressive effect)
- Catheter related problems (infections, thrombosis, arterial puncture, pneumothorax)
- Metabolic effects (secondary bone disease, hepatic and renal dysfunction, hyperglycemia, hyperinsulinemia, elevated lipogenesis, biological acute pancreatitis)

Relevant complications for this study are developed below.

7.1.1: Morphologic changes in the intestinal mucosa related to parenteral nutrition

It is the presence or absence of nutrients in the intestinal lumen, which affects gut structure and function. If adequate nutrients are provided by intravenous route, bypassing the intestine, the intestine still atrophies (review of animal and human studies [110], human case-report [111, 112]). Intestinal adaptation (increasing intestinal length and weight) occurs rapidly if EN is added to PN. Intestinal morphologic and functional changes in humans are substantially less significant than observed in animal models. But the loss of mucosal structure may be sufficient in these patients to cause increased intestinal permeability (intracellular edema develop during TPN and resolve with enteral refeeding) [113]. TPN in itself does not influence the overall mortality rate of surgical or critically ill patients when compared to an oral diet associated with the administration of intravenous dextrose. However, when the studies including only critically ill patients are analyzed, Heyland *et al*. demonstrate a significant increase in complication and mortality rates in comparison to the studies of surgical patients [114].

7.1.2: Bacterial translocation related to TPN

Several studies on animals have investigated the fact that TPN is associated with bacterial translocation and increase in morbidity and mortality.

The initial study evaluating the route of nutrient administration on bacterial translocation was by Alverdy *et al*. (administration of a TPN to rats [115]). They hypothesized that bacterial translocation results from different factors including: hypotension, blood loss, impaired host immune defenses and disruption of the ecological balance of the normal microflora of the gut (happens in case of parenteral feeding [116]).

Other studies on animal models show that:

- TPN or a single amino acid –based formula administered IV increase mortality in animals after hemorrhage (secondary hypotension with subsequent reduced intestinal blood flow) but on the other hand, the administration of EN is associated with zero mortality and a protection of liver functions under the same conditions [117]. Bacteria, and/or toxin, induce release of cytokines (i.e. tumor necrosis factor, interleukins) from hepatic

macrophages and complement activation, which is thought to initiate progressive multiple organ failure and death after hemorrhage.

- The induced bacterial translocation, following the administration of the same TPN solution via oral and intravenous route, can be reversed by dietary fiber [83]. The protective effects of cellulose fiber seemed to be related to its ability to stimulate trophic gut hormones. Even a small amount of oral nutrition in combination with a parenteral nutrition prevents increases in the intestinal permeability and bacterial translocation associated with TPN [113, 118].

Another hypothesis could be that bacterial translocation is the consequence rather than the prime cause of systemic sepsis. Although the strict TPN is associated with gut mucosal atrophy and increased permeability to lactulose, the incidence of bacterial translocation is not significantly different between groups (TPN intra venous; TPN via enteral way; TPN solution administered half enteral, half parenteral; normal EN) in the study of Illig *et al.* on a rat model [119]. A septic state, occurring in association with TPN or trauma and apparently originating from the gut, may be initiated by macromolecules (cytokines, other inflammatory mediators) arising from the gut itself rather than from bacteria within the lumen.

7.1.3: Modifications of the GALT (Gut Associated Lymphoid Tissue) related to TPN

Alverdy *et al*., who studied the effect of TPN on the gastrointestinal immunity of rats, found that in parenteral nutrition groups, a diminution of the S-IgA is observed which returns to normal levels after resumption of enteral feeding [12]. Wu *et al*. [11] made the hypothesis that GALT is modified in case of TPN to explain the increased susceptibility to pneumonia and other complications associated with this nutritional support in critically ill and critically injured patients, compared with enteral feeding. They demonstrated in their first work that intra venous TPN significantly reduces GALT mass by depleting Peyer's patches, lamina propria and the intraepithelial space of T and/or B cells and decreasing the CD4+/CD8+ ratio within the lamina propria [120]. Reduction in GALT cell population occurred simultaneously with drops in both intestinal and respiratory IgA levels.

7.1.4: Septic complications

Catheter sepsis rates related to TPN are variable and depend on several patient-specific factors. These factors include the presence of immunosuppression or critical illness, the use of multiple intravascular catheters, bacterial translocation and the insertion at femoral vein site [121, 122]. If the duration of catheterisation increase [122] or not [123] the rate of catheter related sepsis remains controversial. Nevertheless, a prevention strategy targeted on the insertion and maintenance of vascular access [124], use of ionic silver (anticoagulant/antimicrobial flush solution) and antimicrobial impregnation of catheter and dressings [125] in order to decrease catheter-related sepsis, are the only way to diminish the incidence of such acquired infections

7.1.5: Metabolic complications

The frequency rate of hyperglycemia and other complications are not related to the quantity of intra venous delivery of glucose. Indeed, McCowen *et al*. found in patients receiving 5 days of normal (standard weight-based regimen) versus hypocaloric (1 L containing 70 g protein and 1000 kcal) TPN, that the average level of glycemia was similar. The control group (normocaloric) showed a trend toward a higher insulin requirement than hypocaloric group. Furthermore, the numbers and types of infections were also similar [126].

The most frequent hepatobiliary complications associated with TPN include hepatic steatosis, intrahepatic cholestasis and biliary sludge. Cholestasis predominates in infants, steatosis in adults, and biliary sludge in both. Other less frequent complications are steato-hepatitis and gallstones. All hepatobiliary complications are more likely to occur after extended periods of TPN, and are prevented by the concomitant consumption of nutrients by the enteral route. The pathogenic causes are multiple and only partially known. They include lack of gastrointestinal stimuli for biliary secretion and gall-bladder motility, abnormalities in bile acid metabolism, the presence of sepsis, and the potentially unfavourable effects of individual components in the TPN formulae, including an excess of calories [127].

TPN has also been reported to increase sympathetic nervous activity [128].

7.1.6 Immunosuppressive effects of intravenous fat

Immunosuppressive effects of intravenous fat are well known. Intravenous long-chain triglycerides reduce the functions of the reticulo-endothelial system [129], neutrophils [130] and the ratio of T helper to T suppressor cells [131]. This is illustrated by the fact that TPN-fed animals and human patients undergoing skin grafting or solid organ transplantation have better graft survival [132].

7.2 : Enteral nutrition (EN)

The enteral way of nutrition is more physiological, as it preserves the hepato-splanchnic axis, and seems to be superior to parenteral nutrition by reducing infectious morbidity and maintaining gastrointestinal immunological function [101, 102, 133].

There are several advantages associated with EN:

- Maintenance of mucosal gut and blood flow
- Avoidance of translocation with maintenance of the barrier function
- Maintenance of the enteral bacterial flora [106]
- Prevention of stress ulceration
- Maintenance of the immune function of the gut with the persistence of secretion of the S-IgA
- Lower cost

The enteral nutritional support seems to be more efficient than the parenteral route, if administered very early. But it has to be maintained during at least four days to have a sufficient caloric and nutritional support that is similar to the nutritional support provided via the parenteral route, without associated complications. Nevertheless, several technical problems including the lack of reliable access and their related complications limit the use of this technique. Contraindications to its administration are: ileus, eso-gastric surgery, gastro-intestinal bleeding, pancreatitis and inflammatory bowel disease.

7.2.1: Complications related to enteral nutrition

Relevant complications are regurgitation or vomiting of the gastric content, gastro-esophageal reflux, gastrointestinal intolerance (high gastric residue, diarrhea, constipation), abdominal distension and aspiration pneumonia [134]. Clinical and biological surveillance techniques can generally prevent these complications, and actually only sterile, commercially prepared solutions are administered. In addition, Heyland *et al*. [135] showed that there are also other barriers in the application of enteral nutrition research to daily clinical practice, because of physician practice

patterns. Management protocols, that include every situations or complications, are necessary for the application of enteral nutrition, and to avoid early withdrawal.

Gastrointestinal complications
In the multicenter cohort study of Montejo *et al.* [134], more than 60% patients present gastrointestinal complications during their feeding course, high gastric residue (define as more than 200ml) being the more frequent and appearing earlier. The naso-gastric tube is also associated with oesophagitis attributed to gastro-esophageal reflux, which can be observed within 24 to 36 hours and more commonly after a week or more of naso-gastric intubation [136]. The frequency of diarrhea is highly variable, from 14,7% [134] up to 50% [137], but definition and reporting varies considerably between studies.

Pulmonary complications
Aspiration pneumonia is the most frequent encountered complication. The reported incidence of nosocomial pneumonia in the ICU, related to mechanical ventilation, varies between 10 to 65% [138-140]. If associated with EN, the incidence is of 2,4 per 1000 tube-feeding days [141]. This incidence correlates directly with the rate of gastric colonization by Gram-negative bacilli [138]. It is estimated that at least 50% of the pneumonia case are due to gastro-esophageal reflux, while the remaining cases are caused by oro-pharyngeal aspirations and/or are of atelectatic origin [1]. Hypothesis to explain secondary colonization of the lung is that bacteria coming from the stomach colonize the naso-gastric feeding tube and then the oro-tracheal tube (89% of patients), in patients that are mechanically ventilated and that cannot expectorate; some microorganisms also come from the oropharynx [139, 140].

The restoration of an acid gastric pH, which prevents gastric colonization, associated with normal gastro-duodenal motility might help prevent pneumonia in mechanically ventilated patients. Lee *et al*. [142] confirmed this theory with an intermittent feeding protocol (reduced gastric pH during fasting time). They observed a lower incidence of pneumonia in the intermittent feeding group (12%, 3/26) compared to a group of continuously feed patients (54%, 13/24) observed in a previous study [139]. They also found a correlation between high morning gastric pH (> 3.5, persistently) and the occurrence of pneumonia. This is in agreement with other studies, suggesting that reduced gastric acid production or artificial elevation of the gastric pH (via antacid or cimetidine) is a contributory factor in gastric bacterial overgrowth and subsequent pulmonary colonization and that acidified enteral feeds are effective in reducing gastric colonization [133, 143]. A trend to a lower incidence of pneumonia and lower mortality rate is observed in patients whose gastric pH is not altered [144]. Stress ulcer prophylaxis can be done either with sucralfate (antibacterial properties, no clinically relevant gastric pH modifications) which seems better than ranitidine in reducing the risk of late onset pneumonia [145] or with ranitidine which seems better than sucralfate for the prevention of upper gastrointestinal bleeding [146].

Impaired gastric and small intestine motility promotes bacterial overgrowth in the duodenum. In case of duodenal reflux, gastric colonization and subsequent retrograde bacterial colonization of the lower respiratory tract can occur in mechanically ventilated patients [147].

Pulmonary aspiration of gastric content is partially prevented by a semi-recumbent position (45° angle) and elevating the head [148, 149], but is favored by a naso-gastric tube (double the likelihood of gastro-esophageal reflux [150]) and an oro-tracheal intubation, as mentioned at the beginning of chapter #4. Positive gastric pressure

during ventilation may increase the esophageal reflux of gastric content [149]. The cuff of the tracheal tube may also compromise function of the upper esophageal sphincter, increasing micro aspiration into the lower respiratory tract [148, 149].

7.2.2: Surveillance techniques

The surveillance techniques include a close monitoring of the position of the gastric tube and its functionality, a monitoring of the gastrointestinal emptying with measurement of the gastric residual volumes several times a day. The abdominal distension and the emission of stools are to be evaluated every day. Blood glucose, transaminases and albumin are checked from time to time and white cell count is monitored if an infection is suspected [150, 151]. Radiography can be done to ensure the position of the gastric tube, and need to be done if aspiration pneumonia is suspected.

7.2.3: Difficulty with the delivery

High gastric residual volume is a frequent cause for cessation of enteral nutrition. The question is how to judge if the residual volume observed corresponds to tolerance or not to the enteral feeding. Number of values has been advocated as the designated level indicating tolerance or intolerance, ranging from 75 to 150mL of gastric aspirate [33]. McClave *et al*. [152] made a blind comparison between measure of gastric residual volume, physical examination and radiographic findings to establish the validity, range and limitation of this parameter. First, they found that in critically ill patients, a residual volume of up to 400ml does not necessarily indicate intolerance, but nevertheless residual volume should be checked regularly after initiation of enteral feeding. According to their protocol, if the residual volume is over 200ml in patients with naso-gastric tube, or over 100mL in those with gastrostomy tubes, the patient should be observed closely but feeding need not to be stopped. Low residual volume does not seem to guarantee tolerance and adequate gut motility, because abnormality still appeared on physical examination and radiography. They found that there is no difference in residual volume obtained from the supine or the right lateral decubitus position. They make several recommendations:

- Residual volumes are more easily obtained with a large 60mL syringe
- Residual volumes should be checked frequently at the initiation of enteral feeding (every two hours), and less frequently if good tolerance is observed
- Content of the aspiration should be returned to the patient
- Residual volume does not need to be checked if the tube is positioned below the pylorus

Jejunal tube feeding seems to be superior to gastric feeding in the study of Montecalvo *et al*. [153] with a higher caloric intake (target intake of 61 versus 47%) and a lower rate of pneumonia (with only two case are observed in the gastric group). But other studies in non-ventilated patients [154] or head injured patients [155] show that transpyloric passage of feeding tube is followed by a same complication rate as gastric feeding. Moreover, the position of the jejunal tube is difficult to achieve (frequent use of an endoscopic placement), and the tube moves frequently back into the stomach.

7.2.4: Time to initiation of enteral feeding and rate

EN should be preferred where possible and be started as early as possible, to stimulate gut immunological function and maintain gut mucosa as soon as possible.

In animal studies, early enteral feeding has shown benefits. Zaloga *et al*. [156], compared rats receiving no EN or delayed EN (>72h), with rats receiving early feedings (within 24 hours of injury). They found that early EN promotes greater

wound strength after abdominal surgery. After burn injury, early EN can prevent hypermetabolism via preservation of gut mucosal integrity [157] and diminish catabolic phase [158], lower the rate of translocation [159] and prevent increased secretion of catabolic hormones [157].

In human patients with major abdominal trauma and burn patients, those patients receiving early EN within 12 to 18hrs of injury have a lower infection rate than control patients [160, 161]. Immediate EN compared to gradual reintroduction of EN after bowel resection is also feasible and results in improved wound healing response and less bowel obstruction [162]. The results of a meta-analysis comparing early EN to TPN done by Moore *et al*. [102], on postoperative septic complications, show that early EN is feasible even in high-risk surgical patients. Septic morbidity rates observed in case of EN are lower than in case of TPN, as mentioned at the end of chapter #5 and as illustrated below.

Postoperative septic complications (Phase II)

(See Fig #10)

Adapted from [102]

But initiation of enteral feeding, achieving tolerance and nutritional requirement goals is difficult. Heyland *et al.* [163] evaluated a protocol of administration of early enteral feeding on critically ill mechanically ventilated patient. EN started within 24 hours of admission (16,4 ± 7,9 hours) and tolerance was assessed. Intragastric feeding was initiated at 10mL/hr rate and gastric residues were checked every 4 hours. Every 12 hours, the rate was increased by 25mL/hr if the gastric residual volume was less than 200mL. If the residual volume was over 200mL and accompanied by feeding intolerance signs, feeds were discontinued for 4 hours then reassessed every 4 hours. Initiation of EN took time (62% of patients received less than 100mL of feed the first day; by day two, 94% of patients had received some gastric feed). The average time from admission to ICU to tolerance of EN was 3,8 ± 1,6 days, 42% of patients achieved tolerance at that time. In their study, high gastric residue was the limiting fact to the success of early feeding.

In order to diminish gastric residue and achieve better tolerance to early enteral feeding, prokinetic drugs can be used.

AIM OF THE STUDY

Critically ill patients suffer from protein and caloric loss during their stay in the intensive care unit (ICU). It is now admitted that they are in a catabolic state at their arrival in the ICU and that they need a nutritional support. The intuitive concept of an early nutritional support to maintain host defense and preserve organ function has been well studied for many years and is admitted, but scientific evidence are still missing. The enteral route should be preferred if possible (maintenance of gut mucosal, avoidance of complications associated with TPN). As mentioned in the introduction, critically ill patients generally have delayed gastric emptying for multiple reasons (mechanical ventilation; circulatory failure; medications including opiates and dopamine; post-surgical ileus, neurological trauma and underlying disease such as diabetes mellitus).

We designed a study to investigate the effect of adding cisapride to an early enteral feeding protocol, and how it would improve the tolerance to enteral nutrition in sedated critically ill mechanically ventilated patients. The design was a prospective double blind randomized controlled trial. The main endpoint of the study was to estimate the tolerance to early enteral feeding measured by gastric aspirate and daily quantity of enteral support

MATERIAL AND METHOD

Patients protocol was submitted and approved by the ethical committee of Geneva University Hospital in January 1997 and by the ethical committee of the Hôpital des Cadolles, Neuchâtel, by mutual recognition of local commissions and by Dr Damke, at the OICM (Office Intercantonal des Médicaments). The drugs: cisapride and the identical matched placebo were donated by Janssen-Cilag, which provided them in randomly numbered bottles. The randomization key was maintained undisclosed by the pharmacy of the Hôpital des Cadolles. A physician involved in the study obtained written consent from each patient or his nearest family member.

Inclusion criteria:

From Mai 1997 until March 1999, patients were recruited in the ICU of the Hôpital des Cadolles, Neuchâtel, Switzerland and in the surgical ICU of the Geneva University Hospital, Geneva, Switzerland. All patients admitted in the above mentioned units and meeting the following criteria were included in the study:

- Mechanical ventilation lasting for less than 24 hours
- Expected length of enteral feeding of five or more days

Exclusion criteria:

- History of recent upper digestive surgery (oesophagus, stomach, duodenum)
- Upper gastrointestinal bleeding
- Intestinal inflammatory bowel disease
- Liver failure, or cirrhosis confirmed by biopsy
- Recent abdominal trauma
- All conditions known to be a contra-indication to enteral feeding (mechanical ileus, paralytic ileus)
- Concomitant administration of the following drugs (mainly drug metabolized via cytochrome P450 3A4):
    - Azolated antimycotics drugs such as fluconazole, itraconazole, ketoconazole and miconazole
    - Macrolides antibiotics such as erythromycin and clarithromycin
    - Protease inhibitors such as ritonavir, indinavir
    - Nefazodone
    - Drugs known to promote long QT syndrome such as class Ia anti-arrhythmic and class III anti-arrhythmic
    - Tricyclic and tetracyclic antidepressant drugs
    - Some anti psychotics and anti histaminics whose contra-indications appeared in the drug information
- Concomitant administration of parenteral nutrition
- Inclusion of previously screened and excluded patients (after re-intubation for example) was not allowed

Design of the study

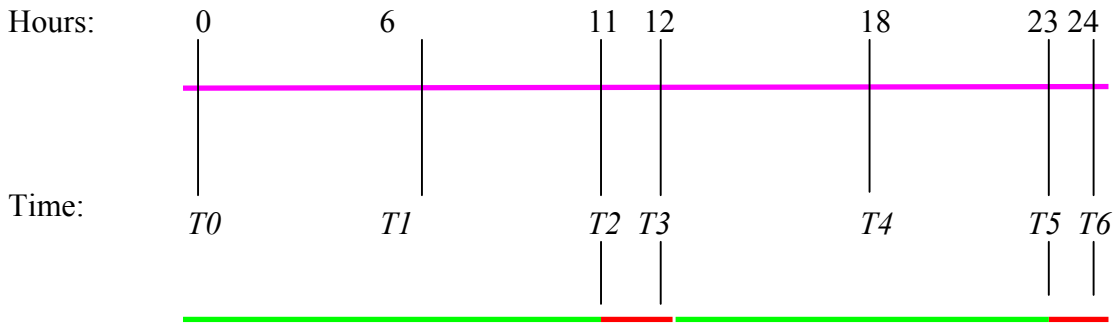
The time of initiation of the enteral nutritional support was planned to be during the first 24 hours following the beginning of the mechanical ventilation. Enteral nutrition (EN) was administered through a naso-gastric tube (Salem 14Fr or 16Fr). The correct position of the tube in the stomach was assessed initially by chest x-ray and

subsequently by air inflation through a 60mL-syringe and auscultation of a gastric sound. The correct position of the naso-gastric tube was assessed twice a day.
EN composition were:

	Type of formula	Protein content (g/100ml)	Calories (kcal/100ml)
Neuchatel	Fresubin ® normal	3.8	100
	Fresubin ® plus	3.8	100
	Fresubin ® MCT	7.5	150
Geneva	Osmolite fibre ®	4.2	100
	Novasource energie ®	5.6	150

The protocol consisted in the blinded administration of either cisapride or its matched placebo via the naso-gastric tube four times daily in patients receiving enteral nutrition 22h/24h. The protocol was established on a 24-hours scale for each patient. Nutrition was continuously administered during 11 hours followed by 1 hour fast. Gastric aspirate was then measured. Depending on the result of the gastric residue, EN was continued or stopped. After 24 hours tolerance to the rate of administration of nutrition, the administration rate was increased following the protocol. Cisapride or its matched placebo was administered after the measurement of the gastric residue and 6 hours later.

Feeding protocol on 24 hours



T0 to T6 24 hours interval
T0 to T2: eleven hours of continuous enteral feeding
T0: administration of 10 ml of cisapride or his placebo (cisapride/placebo)
T1: administration of 10 ml of cisapride/placebo
T2 to T3: 1 hour fast
T3: measurement of the gastric residue and administration of 10 ml of cisapride/placebo
T3 to T5: eleven hours of continuous enteral feeding
T4: administration of 10 ml of cisapride/placebo
T5 to T6: 1 hour fast
T6: measurement of the gastric residue and administration of 10 ml of cisapride/placebo

Based on data reported in the literature [152] and clinical experience as explained in the discussion part, we defined a gastric aspirate equal to or lower than 250mL as normal and the patient was qualified as tolerant to enteral nutrition. The procedure to be followed in case of normal or larger gastric aspirate was described in the protocol and explained to the nurse in charge of the patient.

Description of the procedure to follow in case of normal or larger gastric aspirate:

- *Normal gastric aspirate **(≤to 250mL)**:*

The rate of enteral feeding is progressively increased, from 500mL (250mL/11 h) on **day** #**1**, to 1000mL (500mL/11h) on **day** #**2** and 1500mL (750mL/11h) on **day** #**3**. The rate of enteral feeding is then adjusted to give 25 to 30 kcal/kg/day per patient.

- *Larger gastric aspirate **(>250mL)**:*

The entire gastric aspirate is reintroduced in the stomach and the enteral nutrition discontinued during 4 hours.
Following 4 hours of fasting, gastric aspiration is repeated:

- If the aspiration is ***≤250mL,*** it is given back to the patient and enteral nutrition is reintroduced at the same rate as before being discontinued.
- If the aspiration is ***>250mL***, the total gastric aspirate is given back to the patient, and 10 ml of cisapride/placebo is given 2 hours later. Fast is maintained during 4 additional hours. The gastric aspirate is then measured again:
    - At this time, if the aspiration is ***≤250mL,*** it is given back to the patient and enteral nutrition is reintroduced at a rate at which tolerance has already been observed; if tolerance was not previously observed, enteral feeding is reintroduced at a rate of 250mL/11 hours.
    - If the aspiration is ***>250mL***, only 250mL are given back to the patient, and fast is maintained during 4 additional hours. The gastric aspirate is then measured again:
        - At this time, if the aspiration is ***≤250mL,*** it is given back to the patient and enteral nutrition is reintroduced at a rate at which tolerance has already been observed; if tolerance was not previously observed, enteral feeding is reintroduced at a rate of 250mL/11 hours.
        - If the aspiration is ***>250mL***, the study is stopped and a total parenteral nutrition is introduced. Gastric aspirate are still measured at the same time points.

(See Fig #11 for an algorithm)

In case of intolerance to the rate of enteral nutrition (defined as a gastric aspirate greater than 250mL), the cisapride/placebo solution was still administered at the planned time. If enteral nutrition is restarted with a new time scale, the time of administrations of the cisapride/placebo solution are adapted.

Patient fulfilling one of the following predefined criteria were considered as intolerant to EN:

- More than three consecutive gastric aspirates > 250mL following the protocol explained above.
- Vomiting more than once a day

If patient in either group met criteria for intolerance to enteral nutrition, a trial was attempted with the administration of 10 mg of cisapride in an open label fashion, while maintaining the same time scale as planned for cisapride/placebo. If this test was inconclusive, the patient was considered intolerant to enteral nutrition.

Clinically significant nosocomial respiratory infection was defined when criteria originally developed by Johanson *et al* [164] and adapted by Cook *et al* [165] were met (chest X-ray, clinical and chemical changes):

- Definite infection: radiographic appearance or progression of pulmonary infiltrate; fever; leucocytosis; and purulent tracheal secretions.
- Probable respiratory infection: fever; leukocytosis; and either a new or a progressive radiographic infiltrate, or the presence of purulent secretions.

Investigations were done as previously reported by Pingelton *et al* [140].

The study was terminated when the patient discontinued enteral nutrition support, initiated concurrent oral nutrition, or was discharged from the ICU.

Clinical collected data

1. Patients' demographics characteristics:
   - Age, Gender,
   - Admission date in the ICU, date of randomisation, number of hours between tracheal intubation and beginning of EN. Duration of tracheal intubation, enteral and/or parenteral nutrition, ICU and hospital length of stay and ICU and hospital outcome.
   - Severity scores at the ICU admission: SAPS II (Simplified Acute Physiology Score [166]), multiple organ failure: SOFA (Sequential Organ Failure Assessment [167])
   - Primary admission diagnosis and co-morbidities
2. Repeated data collected longitudinally
   - Severity scores: SAPS II, SOFA
   - Concomitant medications
   - Laboratory tests:
     - Urea, amylase, lipase, ASAT, ALAT, albumin, potassium, and calcium: on day #1 and #6
     - Arterial blood gazes, platelets, bilirubin, and creatinine, daily
   - Nitrogen balance: on day #3. UUN is the urinary urea nitrogen excretion (in grams) in 24 hours, total protein intake (in grams) in the same 24 hours [168]:

     nitrogen balance (g)=(protein intake (g)/6.25) – (UUN+4)
   - Caloric and protein intake was calculated daily
   - Gastric aspirate every 12 hours
   - Presence of nausea, vomiting or diarrhoea were recorded
   - Gastroscopy between day #3 and #5 to confirm the absence of gastric residue after gastric aspiration through the naso-gastric tube and validate the results of gastric aspiration. (See Fig #12 for the procedure)
   - Chest X-ray to confirm the correct position of the oro-tracheal tube and the naso-gastric tube on day #1 and repeated as necessary (in case of suspicion of aspiration pneumonia)

3. Nutritional support
    - Time and reason for cessation of EN
    - Duration of enteral support
    - Time to reach target nutrition rate
    - Time and reason for initiation of parenteral nutrition (PN)

<u>The main results are:</u>

- Daily caloric intake
- Tolerance to EN (gastric residue every 12 hours, nausea, vomiting or diarrhoea)
- Length of ICU and hospital stay as well as ICU and hospital vital status

STATISTICAL ANALYSIS

Power calculation: In order to reach a 50% difference in the gastric residue between both groups with a two-sided alpha level of 0.05 and a power of .8, 20 patients were required in each arm, for a total sample size of 40 patients. After the enrolment of 32 patients in the study protocol, an interim analysis was performed. Since significance was reached at this point, the study was stopped early.

Confirmatory data analysis: We evaluated the distribution of baseline characteristics using t-test or frequency tables, as appropriate. For variables that were measured repeatedly, summary measures were calculated by averaging over all time points, so that each individual only contributed one observation. A two-tailed t-test was used to compare mean values of gastric residue, caloric and protein intake between patients assigned to the cisapride and the placebo groups. Because of the longitudinal nature of the data and the large inter-individual variability, we used generalized linear mixed models with random effects to analyze the effect on treatment on the amount of gastric residue, on the daily caloric intake, as well as on the daily protein intake.

The generalized linear mixed model for normal data is a linear repeated measure analysis. Our model is a repeated measure analysis. Fitting this model is equivalent to the model requested by reviewer. In addition, this model is more flexible in that it better handles missing data, i.e. subjects without complete data are not excluded from the analysis, whereas the traditional repeated measure ANOVA excludes subjects without complete data.

All values are expressed as mean ± standard deviation (SD). A $p<0.05$ was considered statistically significant. The STATA statistical software, version 7.0 (Stata Corporation, TX) was used for all analyses.

RESULTS

1. Demographic data

Thirty-two patients pooled together (28 admitted to Neuchâtel Hospital and 4 to Geneva University Hospital) were screened and randomized to receive either cisapride (n=16) or placebo (n=16). The patient characteristics are shown in *Table #1*.

Table #1 : Patients' demographic characteristics

Parameter	Cisapride group	Placebo group
Number of patients	16	16
Age, yrs, mean ± SD	64 ± 14	67 ± 10
Gender (male/female)	11/5	10/6
SAPS II score at ICU admission, mean ± SD	37.8 ± 12.2	37.9 ± 12.6
Total SOFA score at ICU admission, mean ± SD	8.5 ± 4.0	7.4 ± 2.0
Primary diagnosis (n°)		
Cardiogenic shock	2	2
Cardio respiratory arrest	1	3
Liver disease/GIT illness	0	2
Multiple trauma	3	0
Neurological disease	1	2
Pneumonia/acute respiratory failure	5	7
Septic shock/multiple organ failure	4	0
ICU mortality rate (%)	7 (43%)	7 (43%)
Duration of ICU stay, days, mean ± SD	9.9 ± 5.2	11.6 ± 7.0
Time from ICU admission to start of EN (hours, mean ± SD)	13.0 ± 14.6	13.4 ± 6.4
Duration of enteral nutrition support, days, mean ± SD	5.6 ± 3.1	5.4 ± 2.2
Duration of oro-tracheal intubation, days, mean ± SD	6.2 ± 4.0	6.8 ± 4.9

SAPS II: Simplified Acute Physiology Score [166]
SOFA: Sequential Organ Failure Assessment [167]
ICU: Intensive Care Unit
GIT: Gastro-Intestinal Tract
EN: enteral nutrition

2. Trial profile and tolerance to enteral nutrition

The trial profile is summarized in *Table #2.* Six patients (three in each randomization groups) were declared intolerant to enteral feeding and received parenteral nutrition. The clinical course of the patients that did not tolerate enteral feeding is detailed below (^{d}: known diabetic patient)

Cisapride group (c patients thereafter):

- Patient #2, #3^{d} and #27 were declared intolerant to enteral nutrition (EN) after 48h due to high volume gastric aspirates at repeated intervals. In patient #2 the gastric residues did not return to normal for a long period of time after discontinuation of EN but cisapride was never given in an open labeled fashion. In patients #3 cisapride was given in an open labeled fashion on day # 3 and gastric residue normalized on day #5. Finally, concerning patient #27, the gastric residue normalized on day #3 and cisapride was never given in an open labeled fashion.

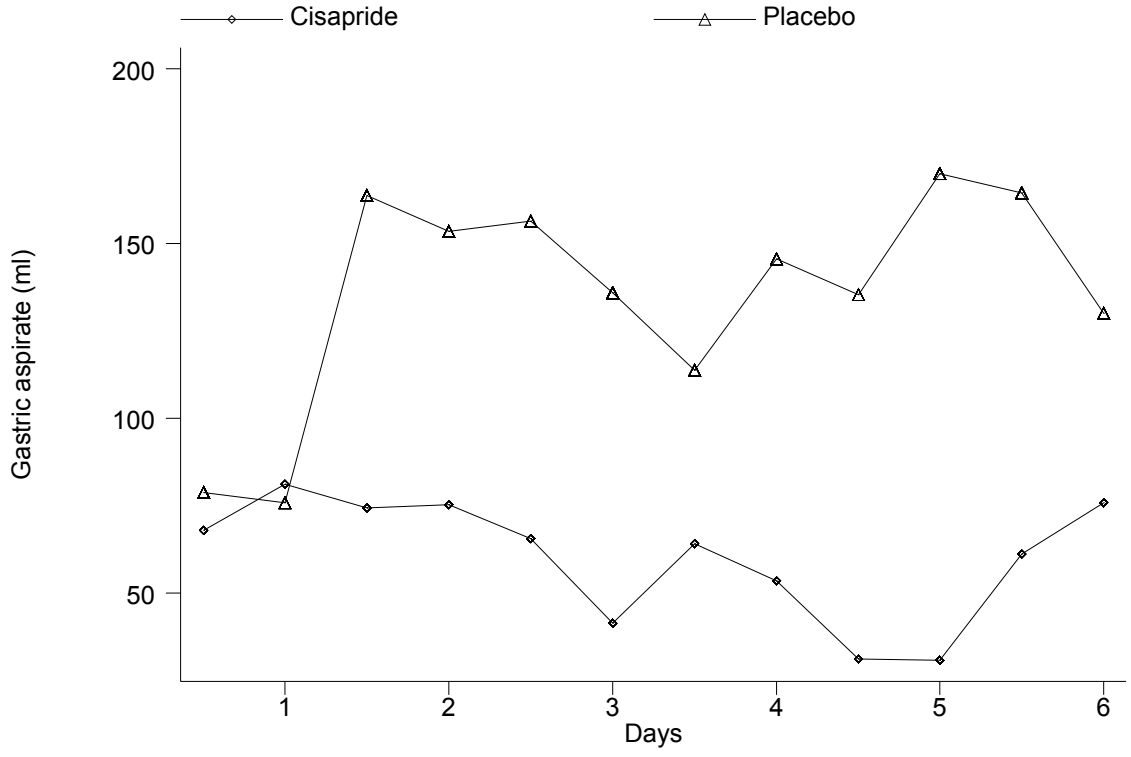
Placebo group (p patients thereafter)**:**

- Patient #21[d], #22[d] and #24 were declared intolerant to EN after 48h due to high volume gastric aspirates at repeated intervals. In patients #21 cisapride was given unsuccessfully in an open labeled fashion on day #3. Indeed, gastric residue normalized only temporarily on day #4. In patients #22, the treating physician tapered down the rate of EN and concomitantly started TPN. EN was discontinued on day #3 for persistent high gastric residue. Finally, for patient #24, the gastric residue normalized on day #4 and cisapride was never given in an open labeled fashion.

3.Effect of cisapride administration on daily gastric aspirates

The mean and median daily gastric (Graphic #1 and Graphic #2-see APPENDIX I) aspirates were 71mL ±23mL and 76mL (min-max range: 33-99mL) respectively in the cisapride group and were 132mL ±36mL and 136mL (min-max range: 70mL-181mL) respectively in the placebo group ($p<0.005$). The output of the statistical analysis is displayed in APPENDIX II.

Graphic #1 **Mean daily gastric aspirate at baseline, and for the following 6 days in patients randomized to receive enteral cisapride (n=16) or enteral placebo (n=16)**



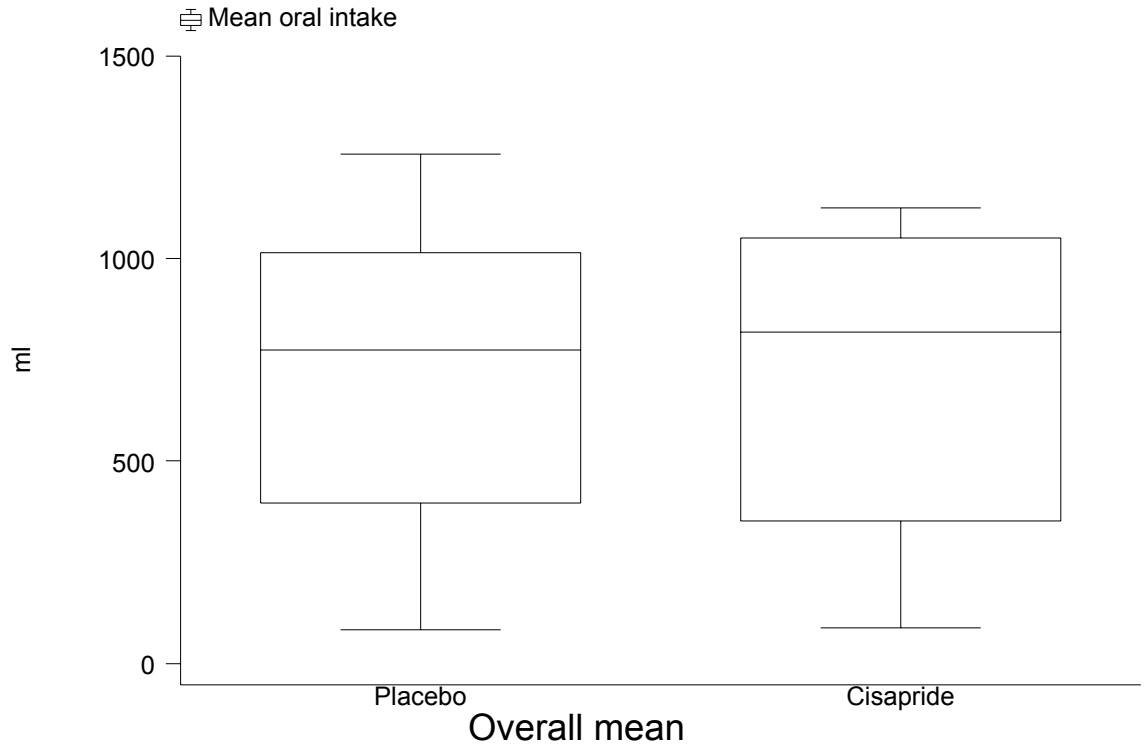
4. Effect of cisapride administration on daily enteral nutrition, caloric and protein intakes

Since gastric aspirates were always reinjected in the nasogastric tube except if superior to 250 ml, oral intake takes into account the amount prescribed plus the gastric residues reinjected.

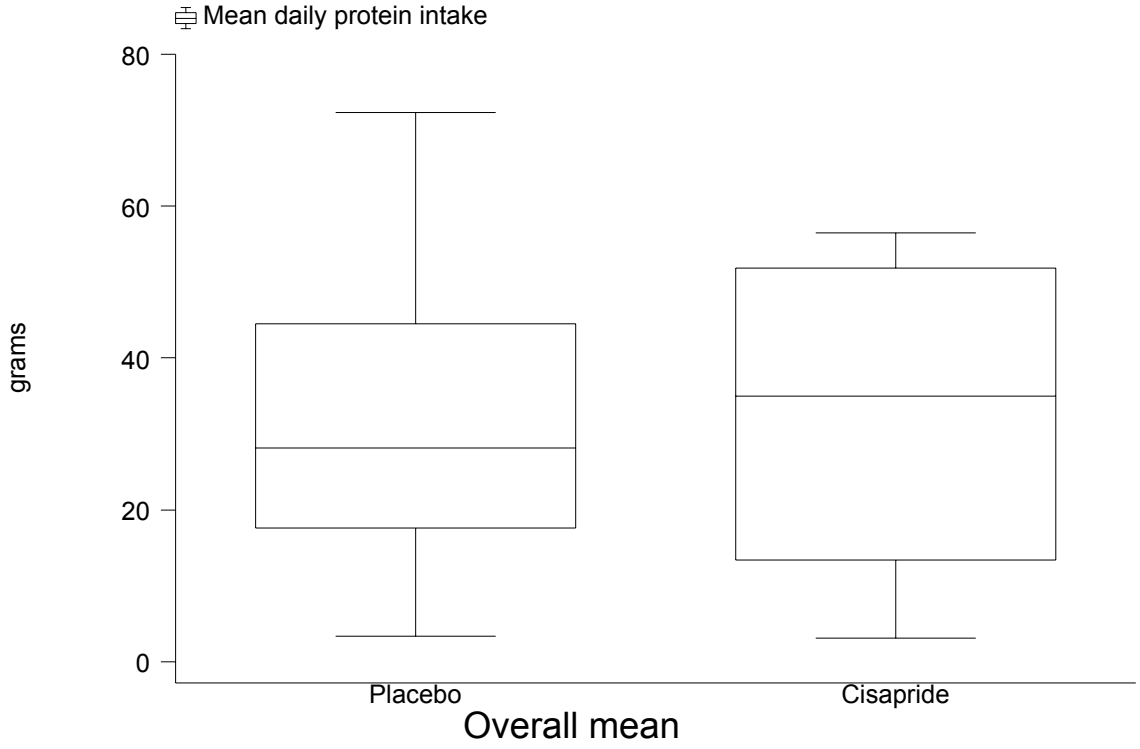
Data for protein and caloric intake are derived from total oral intake and type of enteral nutrition used for the patients.

The three following graphics shows the overall mean on the six days of the study protocol of the daily enteral intake in each randomization group, with the amount of EN, protein and caloric intake:

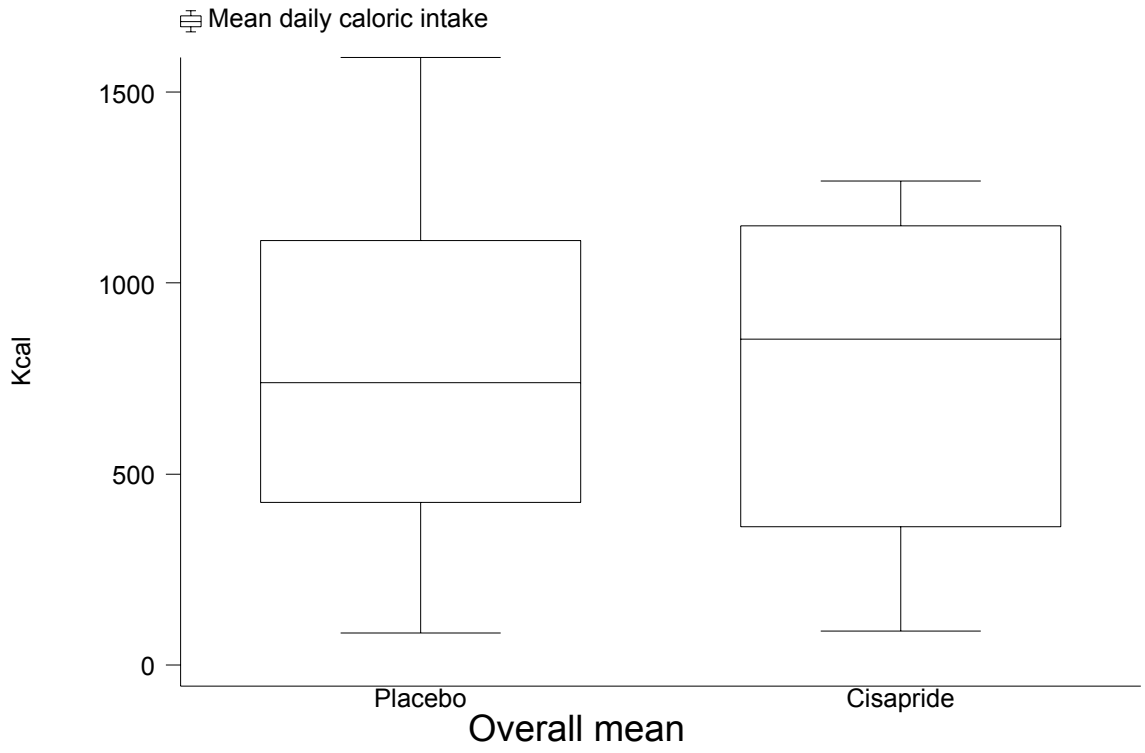
Graphic #3 **Box and whiskers display of the mean and interquartile range of total daily EN intake (=mean oral intake), in patients randomzied to received cisapride (n=16) or placebo (n=16)**



Graphic #4 **Box and whiskers display of the mean and interquartile range of daily protein intake, in patients randomized to received cisapride (n=16) or placebo (n=16)**



Graphic #5 **Box and whiskers display of the mean and interquartile range of daily caloric intake, in patients randomized to received cisapride (n=16) or placebo (n=16)**



Neither total EN volume, daily protein nor caloric intake were statistically significantly different comparing patients receiving cisapride and patients receiving placebo.

5. Effect of cisapride administration on biological markers of metabolic activity

- The nitrogen balance

  Nitrogen balance was measured in 22 patients (11 in each group) on day #3. The mean and median values were **–7.27** ± 6.1 and **–8** (min-max range: –18, +1) respectively, in the cisapride group and were **-9.91** ±14.7 and **–8** (min-max range: –51, +4) respectively, in the placebo group. The nitrogen balance was not statistically different between patients in the cisapride group and patients in the placebo group (P=0.59, two-sample t-test).

  .

- Proportion of patients and time to achieve the minimally required caloric intake based on anthropometric measures

  Minimal caloric intake was defined as 25 kcal/kg/day per patient. It was calculated when exact body weight was available (26 out of 32 patients). Mean body weight and mean BMI (body mass index) values were 74.9 ± 14.5 and 26.5 ± 3.8, respectively in the cisapride group and values were 71.3 ± 16.9 and 23.4 ± 4.3, respectively in the placebo group. Minimal caloric intake was reached only in a small percentage of patients: 35% after a mean time of 3.8

days respectively in the cisapride group and 25% after a mean time of 4 days respectively in the placebo group. The difference in the proportion of patients achieving the minimal caloric intake was not different between the two groups (P= 0.55, Log-rank test).

6. Complications attributed to enteral nutrition

No clinically relevant aspiration pneumonia cases were diagnosed during the study.

Patients #2^{c} (day #1-2-3 and #5), #12^{p} (day #6), #22^{p} (day #3) and #25^{p} (day #5) experienced vomiting. All of them were nursed with oscillating beds without semi-recumbent position and had high volume gastric residues. Only 2 of these patients were declared intolerant to EN (patients #2^{c} and 22^{p}).

We did not observe diarrhea, and stools were rarely present during the study period.

7. Agreement between quantification of residue by blind gastric suction and by suction performed under gastroscopic control

Gastroscopy was planned between day #3 and day #5 according to the study protocol. It was performed only in 9 patients. The endoscopic examination confirmed the blind quantification of gastric aspirate in 6 cases (67% agreement). In the last 3 patients, gastric aspirate measured under gastroscopic control were 400mL (patient #5^{c}), 100mL (patient #15^{c}) and 50mL (patient #18^{p}) respectively.

The clinical course of the three divergent results patient is detailed below:

- Patient #5^{c}: the gastric residue was not measured before the endoscopic examination. During the latter a gastric residue was measured and found 400 ml. This residue is expected. Indeed, the EN was delivered at a rate of 65mL/h during 4 hours (260 ml) adding 300mL normal gastric secretion (2000ml/24h, around 300ml/4h). Then more than 500 mL could have been found if an ileus was present.

- Patient #15^{c}: the endoscopic examination revealed solid residue (around 100ml), which could not be aspirated though the feeding tube.

- Patient #18^{p}: the endoscopic examination revealed a gastric aspirate of about a 50mL.

DISCUSSION

The present double blind randomized study indicates that the mean daily gastric residues over 6 days were lower in patients treated with cisapride compared with placebo. Overall mean oral, caloric and protein intake are similar in both groups, because the feeding protocol implicated to re-inject the gastric aspirate. If gastric residue had not been re-used, oral intake would have been lower in the placebo group. These findings are in accordance with the study conducted by Spapen *et al* [80], which demonstrated that patient treated with cisapride have a decrease gastric residue.

Nitrogen balance was not statistically different between the two-randomization groups, even if the nitrogen balance was less negative in the cisapride group. Finally, no complication either related to enteral nutrition was observed except a few cases of vomiting, or related to cisapride administration in particular no arrhythmia was diagnosed. ECG monitoring was continuous and we were aware to avoid drug interaction with imidazole components and all other drugs concerned as mentioned in the methodology.

Patient's demographic characteristics were similar indicating that the two groups were comparable. In particular there are no significant differences in age, sex, SAPS II score, SOFA score, primary diagnosis, duration of ICU stay and outcome, even if a trend to a shorter ICU stay in the cisapride group is present. Time to initiation of enteral nutrition support, duration of enteral support and duration of oro-tracheal intubation are also similar. Furthermore, the interval time between ICU arrival and initiation of enteral feeding is 13 hours for both groups. In six patients out of nine, gastroscopy confirmed the gastric aspirate, which validates the result in 67% of cases.

Review of the literature

Relevant prospective studies about cisapride or other prokinetic drug administration and their effects on gastro-intestinal transit (**GIT**) and feeding tolerance (**FT**) on critically ill patients are listed below:

Investigator (reference)	Prokinetic drug	Design	Duration of the study	GIT studied	FT studied	Endpoints
Spapen [80]	C	RC, no placebo	7 days	Yes	Yes	Acetaminophen absorption, Labeled test meal absorption, Volume of gastric aspirate
Williams [169]	C	RPC	5 days	No	Yes	Ability to absorb 80% of a gastric feed on the 5th day
Goldhill [26]	C	DBRPC	2 days	Yes	No	Acetaminophen absorption, Volume of gastric aspirate, Presence of bowel sounds
Heyland [81]	C	DBRPC	2 days	Yes	No	Acetaminophen absorption, Volume of gastric aspirate
Mc Laren [50]	M, C, E	RPC; crossover	2 days	Yes	No	Acetaminophen absorption, Volume of gastric aspirate
Mc Laren [170]	M, C	DBRPC	2 days	Yes	Yes	Acetaminophen absorption, Volume of gastric aspirate
Present study	C	DBRPC	6 days	No	Yes	Volume of gastric aspirate

C: cisapride, **M**: metoclopramide, **E**: erythromycin
DBRPC: double blind randomized placebo controlled; **RPC**: randomized placebo controlled;

Two studies observe the effect of cisapride on gastrointestinal transit and feeding tolerance in ICU patients. The first one, by Spapen *et al* [80], was an open prospective randomized control trial studying the benefit of adding cisapride to enteral nutrition on gastric tolerance in 21 patients. Patients were not feed before their inclusion in the study. The results showed that patients treated with cisapride (compared to no cisapride) had an accelerated gastric emptying time (measured by bedside scintigraphy) and a significantly lower mean gastric residue after 5 to 7 days of treatment. The second study, by Williams *et al* [169] recruited 27 ICU intolerant to EN patients, and administered 10 mg of cisapride or placebo in the nasogastric tube for 5 days in a randomized manner. Treatment was declared effective when patients were able to absorb 80% or more of a nasogastric feed by day 5. There was no significant difference in tolerance to enteral feeding between the two groups by day 5, but the amount of EN and the daily amount of cisapride prescribed or received were not described in the paper. Methodological description is unfocused, which precludes reproducibility.

Two other studies observed the effect of cisapride on gastrointestinal transit only. Goldhill *et al* [26] investigate during 2 days the rate of absorption of rectally administered cisapride (60mg-30mg-30mg) *versus* placebo, on 27 randomized patients unfed before their recruitment. Enteral feeding was not permitted until the end of the study. Their study showed that rectal absorption of cisapride is similar between ICU patients and healthy subjects and that gastric emptying does not correlate with the volume of gastric aspirate or the presence of bowel sounds. Heyland *et al* [81] demonstrated that cisapride improves gastric emptying as measured by acetaminophen absorption model in a randomized, double blind, placebo-controlled study. Seventy-two patients were studied. No feeding was allowed during the study protocol, to allow measuring the difference in the absorption of acetaminophen between the two groups (cisapride or placebo). The acetaminophen test absorption was performed before and after the administration of 20 mg of cisapride suspension or an identical placebo. As acetaminophen absorption was enhanced after cisapride administration, they concluded that cisapride enhances gastric emptying.

Mc Laren *et al* [50, 170], performed studies comparing cisapride with other prokinetic drugs in critically ill, mechanically ventilated patients. In a first study [50], they compared sequential doses of prokinetic drugs (cisapride, erythromycin and metoclopramide), versus placebo, administered to 10 patients intolerant to EN (any measure of gastric residue > 150 ml) during a 48h study period. Gastric residual volume and plasma acetaminophen absorption were measured. All the three-prokinetic drugs were effective in promoting gastric emptying. A second study was performed on 14 patients receiving either enteral cisapride 10 mg or metoclopramide 10 mg every 6 hours with a total of 7 doses. EN was continued throughout the study if possible. Both cisapride and metoclopramide were effective to enhance gastric motility and improve tolerance to EN, but the study period was, as for the first study, of only 48 hours.

The study of Spapen *et al.* is the only ones demonstrating long-term (>48h) improvement of gastro intestinal intolerance.

Comparison with the literature

The current double blind-randomized study was performed during a 6 days period and focussed on tolerance, as gastroparesis is often the limiting factor to achieve sufficient EN in critically ill mechanically ventilated patients. To note the absence of bowel sounds did not prevent delivering EN because it has no correlation with gastrointestinal and colonic transit [26, 61]. We defined high gastric aspirate by an gastric aspirate >250mL. Most studies use either 100 to 150mL [50, 170] up to 200mL [97, 134, 169] or 250mL [171] as the designated level to indicate intolerance. But a well-performed study conducted by Mc Clave *et al* [152] has demonstrated that residual volume in normal healthy volunteers receiving total EN may exceed 150mL in as many as 15% of subjects. In critically ill patients receiving naso-gastric feedings, a wide range of residual volume (even up to 400mL) may be measured with no obvious intolerance. High gastric aspirate usually appears after 24 hours of feeding [27, 152, 172] and resolves after the introduction of a prokinetic agent.

Time to initiation of EN, which corresponds to the time between admission and study inclusion, was short in the present study with a mean of 13 hours (± 14.6 hours-c group; ± 6.4-p group) in comparison to the other studies (varying between 24 and 72 hours) [33, 81, 97, 101, 134, 135, 171, 173] Other studies did not mention the interval without EN [26, 50, 80, 170, 174]. Moreover, the majority of the studies also include patients in whom tolerance to EN is difficult to achieve [50, 81, 170].

We observed a rate of intolerance of 18% (6/32 patients), which is comparable to other studies on critically ill patients. Montejo *et al* [134] in their multicenter study, had an intolerance rate of 15.2% (EN withdrawal as a consequence of incontrollable gastrointestinal complications), and Heyland *et al* [97] had an intolerance rate of 24%. No prokinetic drugs were administered in both studies. In the current study, the 6 EN intolerant patients received a parenteral nutrition, which was begun on day #3 (4 patients) to #5 and EN was discontinued. A delay to achieve tolerance for the remaining 26 patients, as observed by Heyland *et al* in two different prospective cohort studies, was not observed in our patients. Indeed, in Heyland *et al*. first study on 99 patients [135], 74% patients were started on enteral feeding after an average 3.1 days after ICU admission. Forty three percent of them achieved tolerance (received 90% of daily estimated energy requirement for > 48h without gastro-intestinal dysfunction) after an average time of 5.8 days (range 1 to 14) from admission. In the

second study [163], on 73 patients suspect of intolerance to EN, 24 % patients failed early EN, and 42% achieved tolerance at 3.8 ±1.6 days (same definition as in the first study).

A negative nitrogen balance was measured on day # 3. Retrospectively, it would have been more useful to collect this information at 2 different times. Indeed at day #3 steady state EN was not achieved in many patients. Thus, it is not surprising that a negative nitrogen balance is found. In Moore *et al* [102] meta-analysis the nitrogen balance and nitrogen intake was measured at baseline (day #0 or #1), mid-study (day #4, #5 or #6) and end of study (day #7, #8 or #9). Although the difference in nitrogen balance between the two groups narrowed over time, it was always negative in the enteraly feed group: -11 at baseline, -3 at mid-study and -6 at the end of the study. Despite these negative results, total enteral feeding was proved more efficient than parenteral nutrition on septic post-operative complications. We found similar results (-7.3-c group, respectively –9.9-p group) on day #3, assuming that minimal caloric were not reached for the majority of patients. The principal reasons usually given to explain the relative low protein intake have been well described and explain the present results. Indeed, medical staff does not insist to increase caloric intake and in some cases patients did not benefit from normal EN intake because they were extubated recently. In case of enteral feeding, gastric tolerance seems always to be the major problem as high gastric residue, vomiting and pulmonary aspiration are not well tolerated by nurses and medical staff. Enteral nutrition is also stopped for other reasons such as exams, transportation, surgery, nursing work over load etc. [172, 173]. If we compare to recent studies, it is only when strict protocols are implemented that the percent of calories ordered/required can be raised from 78% to 100%, and ultimately the percent of calories delivered/required can be raised from 66% to 87% [172].

Finally, only critically ill mechanically ventilated patients were included in the study. Most of them received analgesia (morphine or sufentanyl in low quantity) and sedation (propofol, midazolam), and some time needed vasoactive support. In comparison to placebo administration, the administration of cisapride was able to normalize gastric residue particularly when morphine or insulin administration were co administrated.

Future investigations should evaluate the long-term benefit of early enteral nutrition associated with prokinetic administration in terms of ICU length stay, outcome and cost effectiveness. New prokinetic drug similar to cisapride or erythromycin but without the secondary effects (drug interactions for cisapride, anti- microbial activity and low therapeutic window) should be investigate. Cefazolin was recently tested [175] but without success in critically ill patients.

CONCLUSIONS

This double-blind randomized study allows drawing the following conclusions:

In critically ill, mechanically ventilated patients, gastric emptying is reduced by fifty percent if cisapride is added to a standard enteral feeding protocol. Tolerance to enteral nutrition is enhanced by the administration of cisapride if one considers the gastric aspirate as the reflection of tolerance. The strict observance of an enteral feeding protocol is the clue to promote efficiently oral intake and can compensate in terms of caloric intake for the delayed gastric emptying. Moreover, time to initiation of enteral nutrition can be very short if a strict protocol is applied.

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APPENDIX I

Figure #1

Anatomy of the stomach

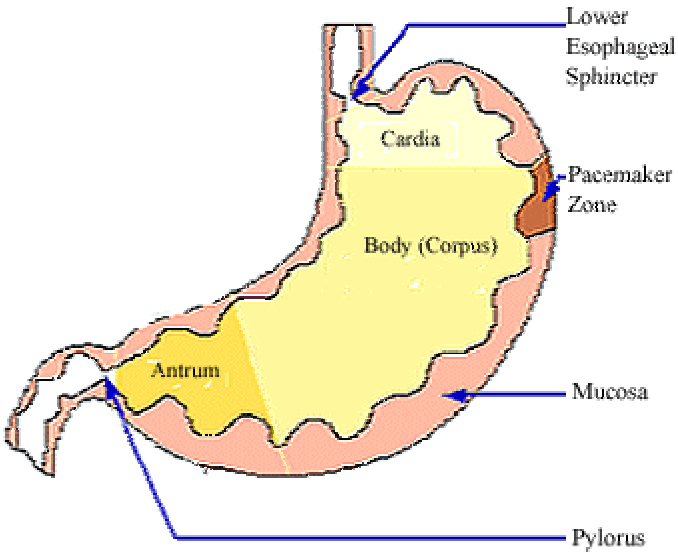


Figure #2

Motor activity of proximal stomach responsible for gastric emptying

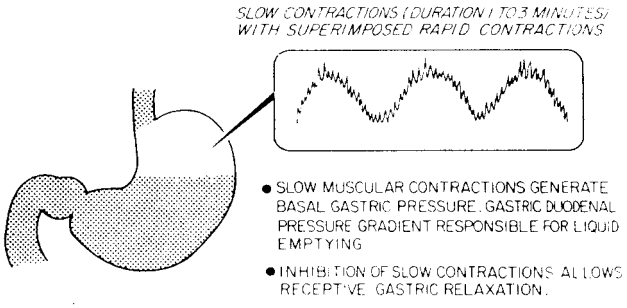
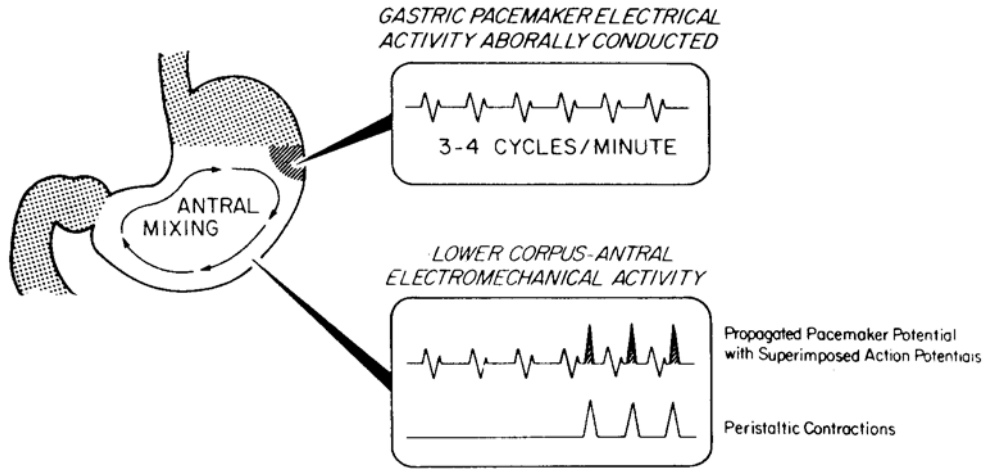


Figure #3

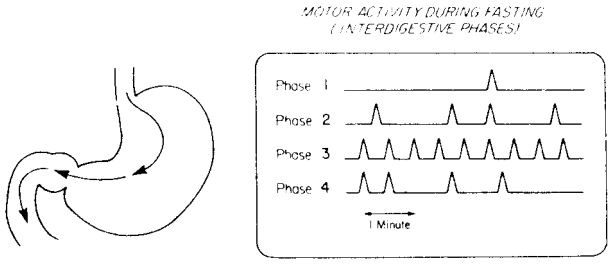
Electrical and motor activity of distal stomach responsible for gastric emptying of digestible solids



PERISTALIC CONTRACTIONS TRITURATE DIGESTIBLE SOLIDS TO NEAR LIQUIFIED FORM

Figure #4

Motor activity responsible for gastric emptying of indigestible solids



MIGRATING MYOELECTRIC COMPLEX (MMC) USUALLY INITIATED AT PROXIMAL STOMACH OR LOWER ESOPHAGEAL SPHINCTER AND CONTRACTIONS DURING PHASE 3 SWEEP INDIGESTIBLE SOLIDS THROUGH OPEN PYLORUS.

Figure #5

Illustration of small intestine cells

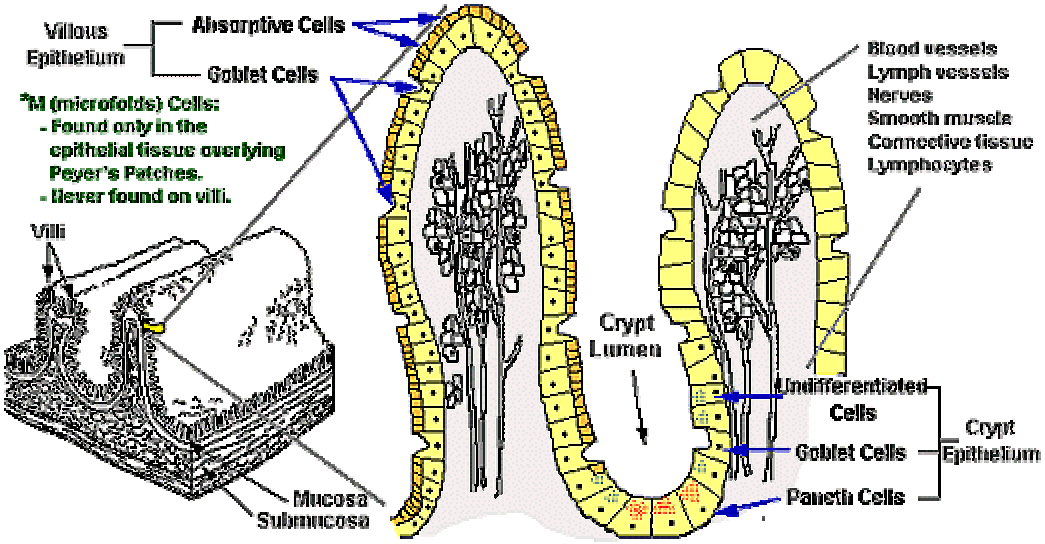
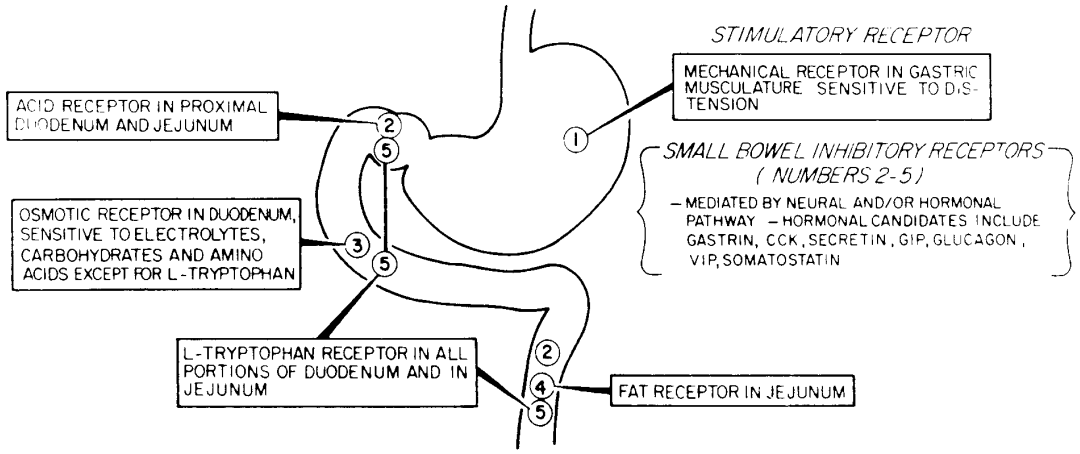


Figure #6

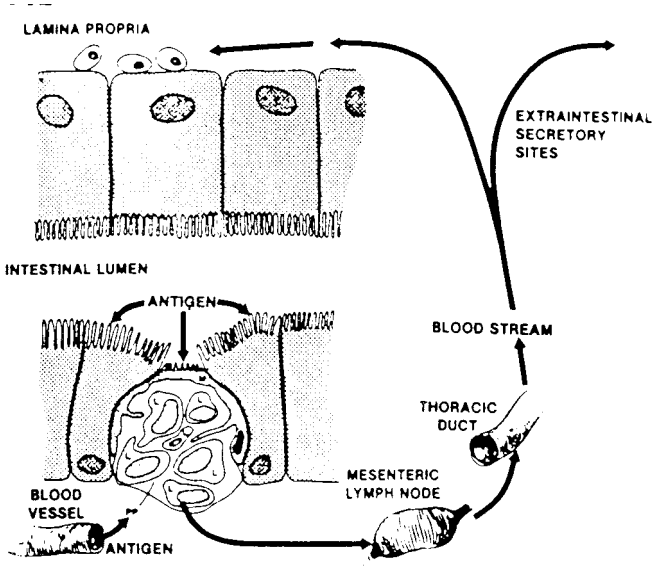
Physiology of gastric and small intestine emptying.



Various factors that influence gastric emptying are depicted. Location of mechanical and osmotic receptors (1 and 3) as determined by human studies. Other receptors localized by studies in dogs. Abbreviations: CCK-cholecystokinine; GIP-gastric inhibitory polypeptide; VIP-vasoactive intestinal polypeptide

Figure #7

Illustration of stimulation and homing of IgA producing plasma cells



IgA is secreted once cells mature in the lamina propria

Figure #8

Diagram of development of multiple organ failure

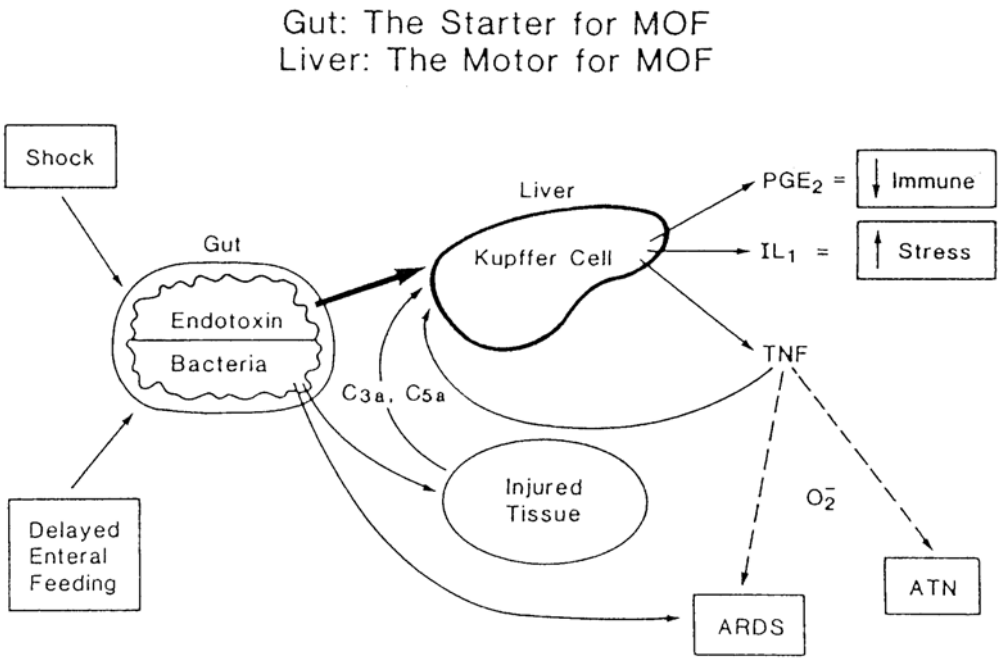


Figure #9

Diagram illustrating the progressive atrophy of the villous height and crypt depth, bacterial proliferation and then translocation through the atrophied epithelial barrier

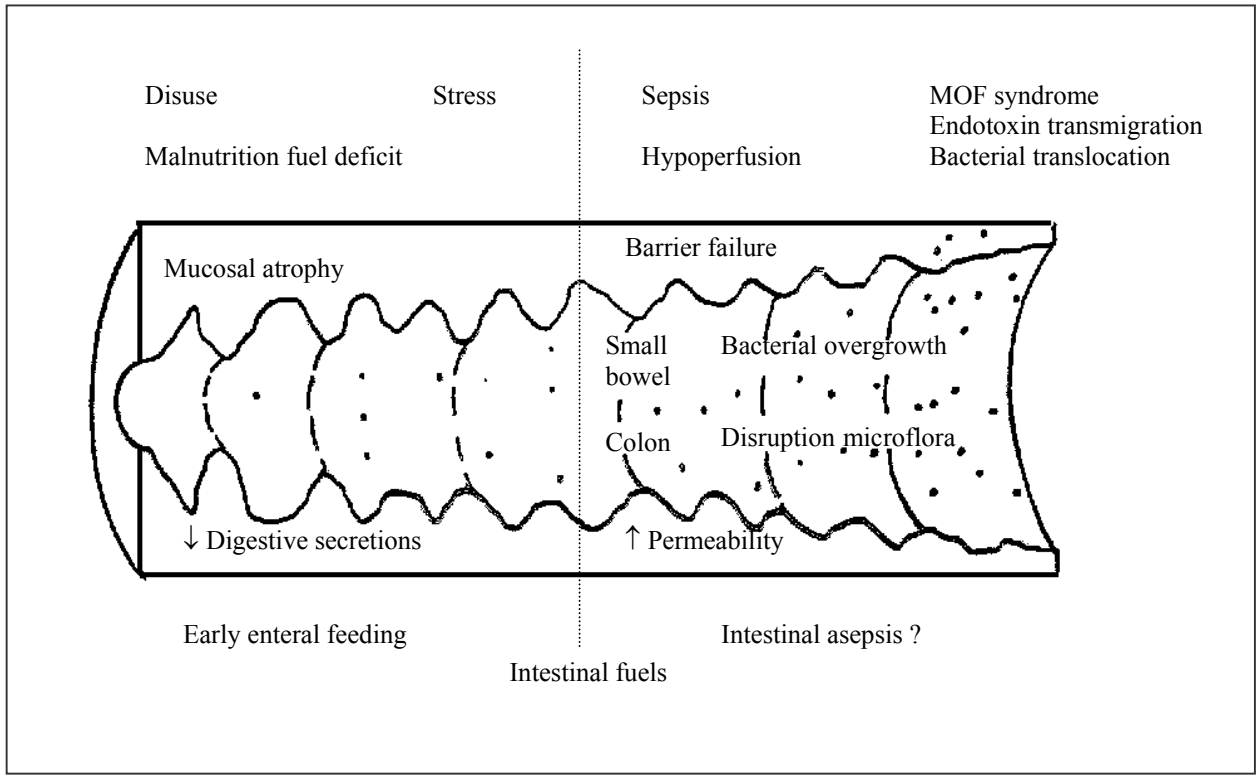
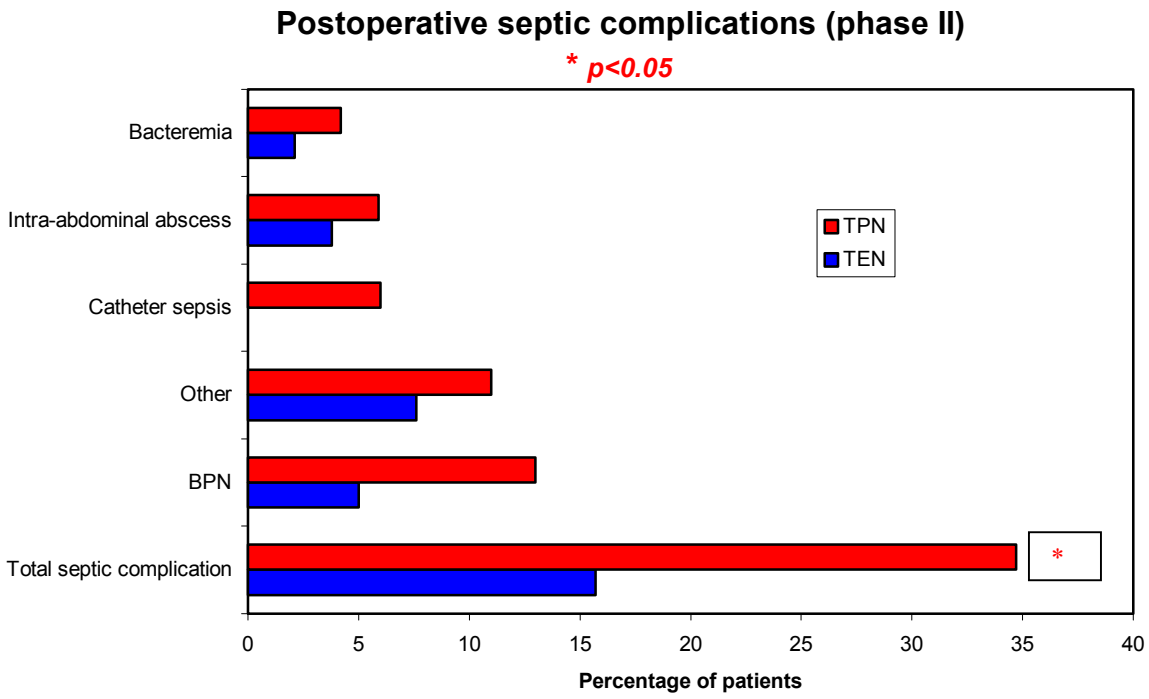


Figure #10

Postoperative septic complications



adapted from Moore et al. [102]

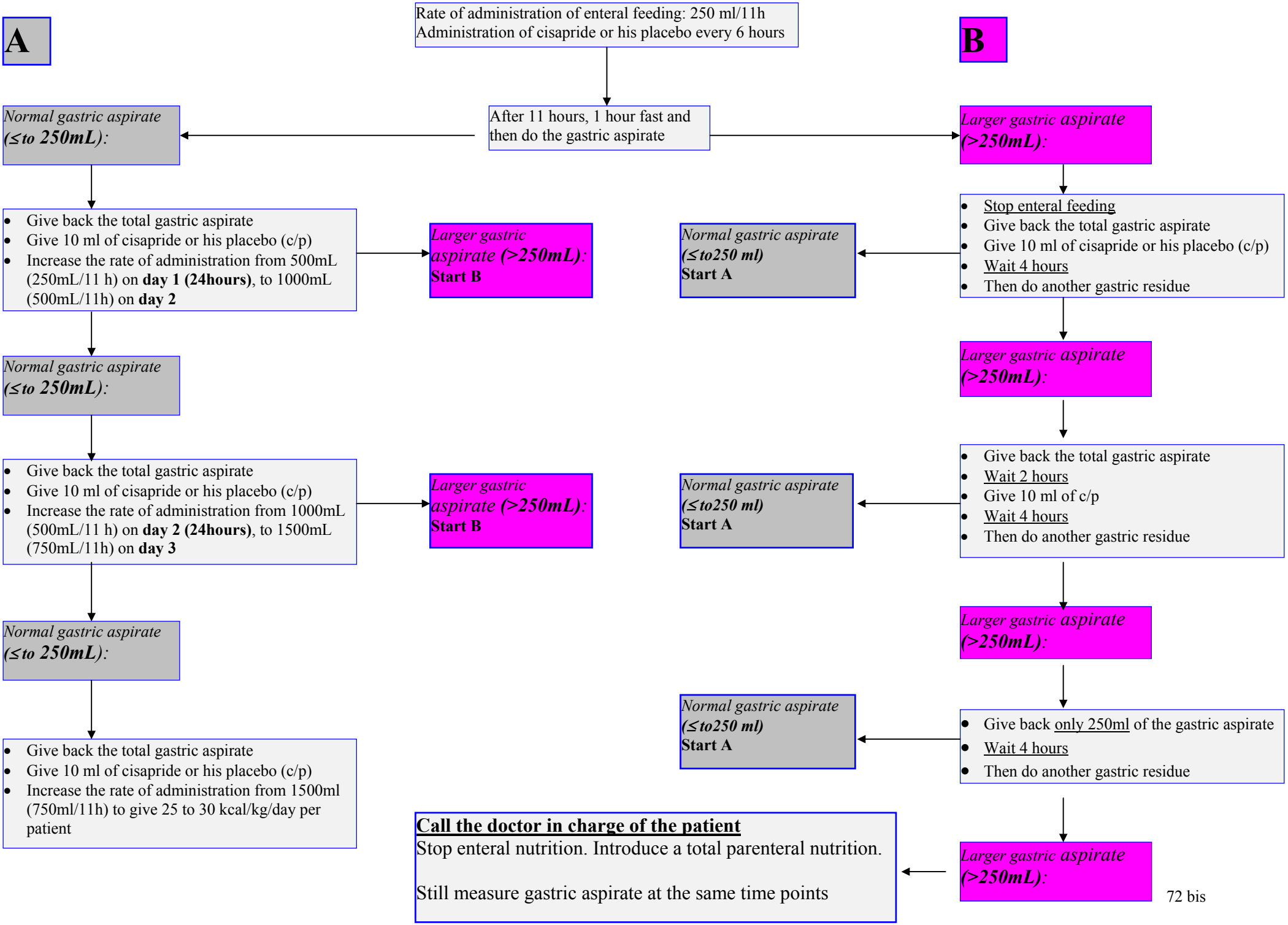

A
Rate of administration of enteral feeding: 250 ml/11h
Administration of cisapride or his placebo every 6 hours
B
Normal gastric aspirate (≤to 250mL):
After 11 hours, 1 hour fast and then do the gastric aspirate
Larger gastric aspirate (>250mL):
Give back the total gastric aspirate
Give 10 ml of cisapride or his placebo (c/p)
Increase the rate of administration from 500mL (250mL/11 h) on day 1 (24hours), to 1000mL (500mL/11h) on day 2
Larger gastric aspirate (>250mL): Start B
Normal gastric aspirate (≤to250 ml) Start A
Stop enteral feeding
Give back the total gastric aspirate
Give 10 ml of cisapride or his placebo (c/p)
Wait 4 hours
Then do another gastric residue
Normal gastric aspirate (≤to 250mL):
Larger gastric aspirate (>250mL):
Give back the total gastric aspirate
Give 10 ml of cisapride or his placebo (c/p)
Increase the rate of administration from 1000mL (500mL/11 h) on day 2 (24hours), to 1500mL (750mL/11h) on day 3
Larger gastric aspirate (>250mL): Start B
Normal gastric aspirate (≤to250 ml) Start A
Give back the total gastric aspirate
Wait 2 hours
Give 10 ml of c/p
Wait 4 hours
Then do another gastric residue
Normal gastric aspirate (≤to 250mL):
Larger gastric aspirate (>250mL):
Give back the total gastric aspirate
Give 10 ml of cisapride or his placebo (c/p)
Increase the rate of administration from 1500ml (750ml/11h) to give 25 to 30 kcal/kg/day per patient
Normal gastric aspirate (≤to250 ml) Start A
Give back only 250ml of the gastric aspirate
Wait 4 hours
Then do another gastric residue
Call the doctor in charge of the patient
Stop enteral nutrition. Introduce a total parenteral nutrition.
Still measure gastric aspirate at the same time points
Larger gastric aspirate (>250mL):

Figure #12

Gastroscopy procedure:

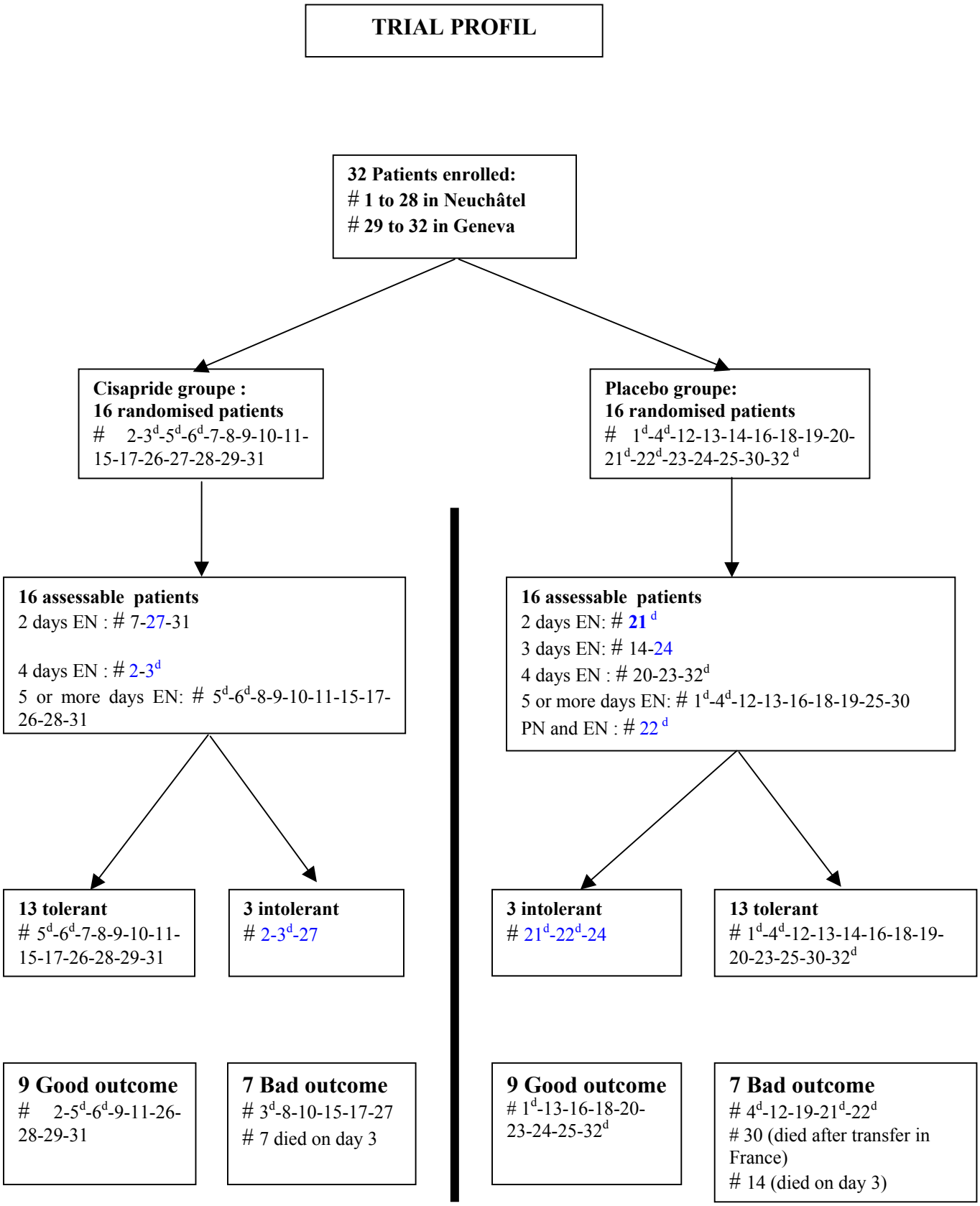
Exact time of the exam known:

- Stop the enteral nutrition one hour before the exam
- Just before the exam to a gastric aspirate
- Note the exact amount of the gastric aspirate in mL
- Do not give that gastric aspirate back to the patient and throw it away
- Remove the naso-gastric tube
- Proceed as soon as possible to the gastroscopy, which should confirm the emptiness of the stomach
- Insert a new naso-gastric tube after the exam and assess its correct position (air inflation through a 60mL syringe and auscultation of a gastric sound). In case of doubt about its correct position, do a chest x-ray.
- Start the enteral nutrition at the rate reached before the exam with a new 24-hours time scale.

Exact time of the exam unknown:

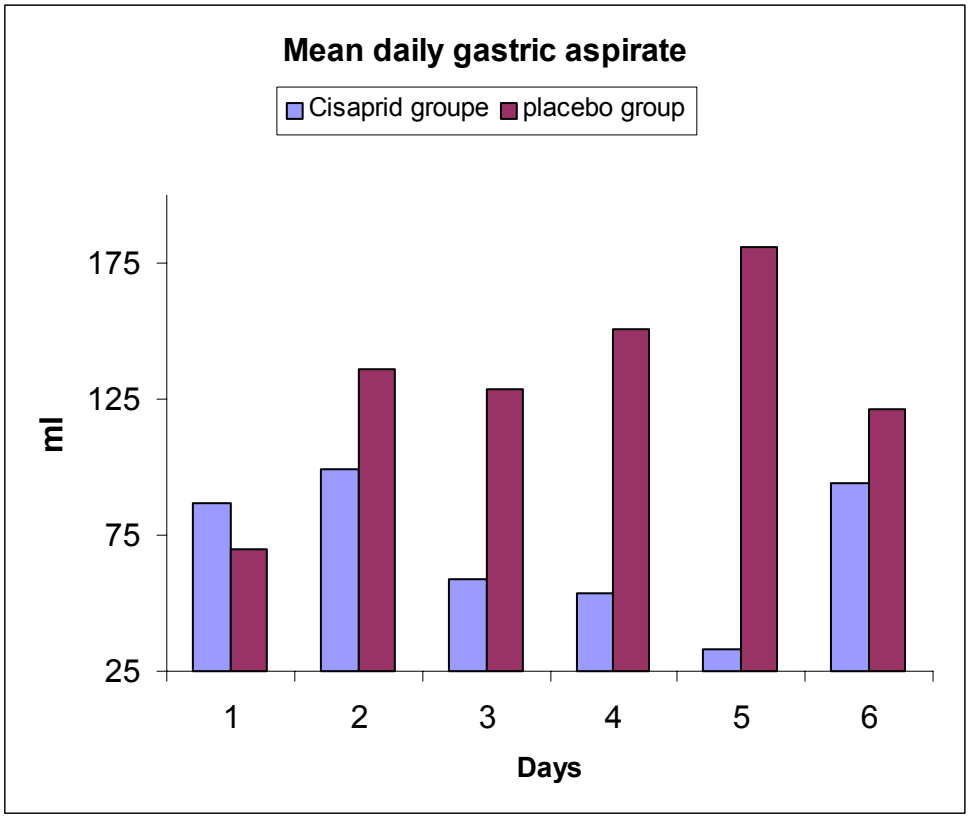
- Stop the enteral nutrition just before the exam and proceed to a gastric aspirate
- Note the exact amount of the gastric aspirate in mL
- Do not give that gastric aspirate back to the patient and throw it away
- Remove the naso-gastric tube
- Proceed to the gastroscopy, which should confirm the emptiness of the stomach
- Insert a new naso-gastric tube after the exam and assess its correct position (air inflation through a 60mL syringe and auscultation of a gastric sound). In case of doubt about its correct position, do a chest x-ray.
- Start the enteral nutrition at the rate reached before the exam with the same 24-hours time scale.

Table #2



d: diabetics patients
#: number

Graphic #2



Mean daily gastric aspirate

Day	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	**Mean** (SD)	Median
Cisapride group (mL)	71	87	83	99	97	59	81	54	33	33	58	94	**71** (+/- 23)	**76**
Placebo group (mL)	74	70	160	136	135	129	101	151	143	181	179	121	**132** (+/- 36)	**136**

APPENDIX II

Results of the statistical analysis

We used a generalized linear mixed model with random effect to analyze gastric aspirate:

```
Generalized linear models                         No. of obs      =       301
Optimization     : ML: Newton-Raphson             Residual df     =       269
                                                  Scale param     =  10235.88
Deviance         =  2753451.129                   (1/df) Deviance =  10235.88
Pearson          =  2753451.129                   (1/df) Pearson  =  10235.88

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]
Standard errors  : Modified Sandwich

Log likelihood   = -1799.849432                   AIC             =  12.17176
BIC              =  2753268.502

                           (standard errors adjusted for clustering on patno)
------------------------------------------------------------------------------
             |               Robust
         res |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |  -33.63636   5.00e-12        .   0.000    -33.63636   -33.63636
   _Ipatno_2 |   214.5455   2.34e-12        .   0.000     214.5455    214.5455
   _Ipatno_3 |    132.197   4.53e-12        .   0.000      132.197     132.197
   _Ipatno_4 |   83.44697   4.46e-12        .   0.000     83.44697    83.44697
   _Ipatno_5 |  -5.416667   2.34e-12        .   0.000    -5.416667   -5.416667
   _Ipatno_6 |        -20   2.34e-12        .   0.000          -20         -20
   _Ipatno_7 |  -11.66667   2.38e-12        .   0.000    -11.66667   -11.66667
   _Ipatno_8 |         10   2.34e-12        .   0.000           10          10
   _Ipatno_9 |   55.90909   2.34e-12        .   0.000     55.90909    55.90909
  _Ipatno_10 |        -24   2.34e-12        .   0.000          -24         -24
  _Ipatno_11 |     -26.25   2.34e-12        .   0.000       -26.25      -26.25
  _Ipatno_12 |   135.5303   4.52e-12        .   0.000     135.5303    135.5303
  _Ipatno_13 |   75.80808   4.47e-12        .   0.000     75.80808    75.80808
  _Ipatno_14 |   88.36364   4.53e-12        .   0.000     88.36364    88.36364
  _Ipatno_15 |   92.85714   2.34e-12        .   0.000     92.85714    92.85714
  _Ipatno_16 |   156.9886   4.45e-12        .   0.000     156.9886    156.9886
  _Ipatno_17 |      21.625   2.34e-12        .   0.000       21.625      21.625
  _Ipatno_18 |  -46.81818   4.43e-12        .   0.000    -46.81818   -46.81818
  _Ipatno_19 |  -32.13636   4.43e-12        .   0.000    -32.13636   -32.13636
  _Ipatno_20 |   82.79221   4.43e-12        .   0.000     82.79221    82.79221
  _Ipatno_21 |   243.3636   4.53e-12        .   0.000     243.3636    243.3636
  _Ipatno_22 |    89.2803   4.46e-12        .   0.000      89.2803     89.2803
  _Ipatno_23 |   24.48864   4.42e-12        .   0.000     24.48864    24.48864
  _Ipatno_24 |   197.7922   4.43e-12        .   0.000     197.7922    197.7922
  _Ipatno_25 |   34.54545   4.43e-12        .   0.000     34.54545    34.54545
  _Ipatno_26 |       -9.5   2.34e-12        .   0.000         -9.5        -9.5
  _Ipatno_28 |         60   2.34e-12        .   0.000           60          60
  _Ipatno_29 |   48.33333   2.37e-12        .   0.000     48.33333    48.33333
  _Ipatno_32 |   79.36364   4.43e-12        .   0.000     79.36364    79.36364
  _Ipatno_33 |      6.625   2.34e-12        .   0.000        6.625       6.625
  _Ipatno_34 |  -58.63636   4.43e-12        .   0.000    -58.63636   -58.63636
       _cons |   63.63636   4.42e-12        .   0.000     63.63636    63.63636
```

We used a random-effect GLS regression to analyse the daily caloric intake:

```
Random-effects GLS regression                   Number of obs      =       172
Group variable (i) : patno                      Number of groups   =        32

R-sq:  within  = 0.0000                         Obs per group: min =         2
       between = 0.0001                                        avg =       5.4
       overall = 0.0001                                        max =         6

Random effects u_i ~ Gaussian                   Wald chi2(1)       =      0.01
corr(u_i, X)       = 0 (assumed)                Prob > chi2        =    0.9396

------------------------------------------------------------------------------
    calories |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |    11.7924     155.74     0.08   0.940    -293.4524    317.0372
       _cons |    781.796   109.9024     7.11   0.000     566.3912    997.2007
-------------+----------------------------------------------------------------
     sigma_u |  378.42789
     sigma_e |  510.70325
         rho |  .35445207   (fraction of variance due to u_i)
```

The daily oral intake in ml:

```
Random-effects GLS regression                   Number of obs      =       172
Group variable (i) : patno                      Number of groups   =        32

R-sq:  within  = 0.0000                         Obs per group: min =         2
       between = 0.0002                                        avg =       5.4
       overall = 0.0000                                        max =         6

Random effects u_i ~ Gaussian                   Wald chi2(1)       =      0.00
corr(u_i, X)       = 0 (assumed)                Prob > chi2        =    0.9818

------------------------------------------------------------------------------
  oralintake |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |  -3.042752   133.1757    -0.02   0.982    -264.0622    257.9767
       _cons |   726.2154   93.97729     7.73   0.000     542.0233    910.4075
-------------+----------------------------------------------------------------
     sigma_u |   321.9862
     sigma_e |  443.40905
         rho |  .34525376   (fraction of variance due to u_i)
```

And the daily protein intake:

```
Random-effects GLS regression                   Number of obs      =       172
Group variable (i) : patno                      Number of groups   =        32

R-sq:  within  =      .                         Obs per group: min =         2
       between = 0.0010                                        avg =       5.4
       overall = 0.0007                                        max =         6

Random effects u_i ~ Gaussian                   Wald chi2(1)       =      0.04
corr(u_i, X)       = 0 (assumed)                Prob > chi2        =    0.8342

------------------------------------------------------------------------------
    proteins |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |   1.463353   6.992691     0.21   0.834    -12.24207    15.16878
       _cons |   32.02748   4.934825     6.49   0.000      22.3554    41.69956
-------------+----------------------------------------------------------------
     sigma_u |  17.171088
     sigma_e |  22.220395
         rho |  .37388939   (fraction of variance due to u_i)
```