11 Epidemiology, Etiopathogenesis, Diagnosis, and Treatment of Postoperative Paralytic Ileus in Intensive Care

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A recent paper has proposed a score for the assessment of the inadequacy of the digestive tract [1]. It might be, at first sight, the umpteenth rating scale to be inserted in the staging of how critical is a patient in Intensive Care: actually, for the first time, this yardstick puts the digestive tract and its function among the elements that affect the outcome of the hospital stay.

We now know how much the SOFA score (Simplified Organ Failure Assessment) underscores the hepatic, renal, circulatory, respiratory, as well as the neurological, and hemostatic failures: it is since 10 years that an expert Consensus [2] stated that the intestinal function is a primary determinant in the outcome of critically ill patients, and is therefore necessary to pay great attention to the dysfunctions of this apparatus.

The parameters that enter in the evaluation of the Gastrointestinal Failure(GIF) () score are: the truly administered percentage of the prescribed enteral nutrition, the duration of fasting, and the ileum or the diarrhea (as intolerance to nutrition), the abdominal hypertension, and the abdominal compartment syndrome.

It is well known how intolerance to nutrition is expressed as high gastric stagnation, vomiting, bowel distension, and altered transit time. The GIF score measured in the first 3 days after admission to intensive care shows a strong prognostic value.

The aim of the critical care nutrition is to minimize the malnutrition associated with the acute illness: it considers the influence of the current illness, the therapeutic interventions, the organ dysfunctions with the nutritional care, and measures risks and benefits of the nutritional care itself.

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In a recent report on "nutritional risk in critical area" [3] the weight loss related to hospitalization reaches prevalence between 35 and 41 % [4]. The loss of lean body mass is related to the functional state prior to the acute episode, to the severity of the injury/illness, to the intensity of the inflammatory response, to the restoration of physiologic enteral nutrition, and the balance between loss and protein synthesis.

Any patient who remains in Intensive Area for more than 2 days in the absence of a close to normal oral intake can be considered at risk of malnutrition.

The motility disorders of the digestive tract play a central role in reducing or delaying the "normal" nutrient intake.

The postoperative ileus (POI or PI is, unfortunately, very common after major abdominal surgery (but even in other or minor surgical procedures).

An acceptable definition may be "transient cessation of coordinated motility of the digestive tract, following an abdominal surgical procedure, which effectively prevents the transit of intraluminal content and tolerance to food intake."

There are clear implications of an abnormal postoperative ileus on the poor quality of hospital stay for the patient, the increase in costs and occupation of beds in acute care areas due to increase of length of stay(LOS). In a recent review of patients undergoing colectomy, a postoperative ileus lengthened hospital stay of 8 days on average, with an additional cost of approximately $15,000 per patient [5].

The set of symptoms is variable: some patients remain largely asymptomatic, while others complain of cramps, nausea, vomiting and pain from distension. Occasionally, gaseous distension and biliary vomiting occur.

Anorexia is evident, the flatus almost always absent.

At the physical exam abdominal distention and tympanism are typically found: the tenderness is not specific and is more often correlated to wound or underlying disease.

The absence of bowel sounds typically defines paralytic ileus, which is specific and necessary to define the syndrome: on the contrary the recovery of a normal GI motility is heralded by bowel sounds reappearance.

A modern clinical approach cannot find a close link between gastrointestinal function and audible noise: the clinical decisions cannot be entrusted based on this finding.

Not even the imaging helps to establish with certainty the diagnosis of post-operative ileus: an anteroposterior or tangential X ray of the abdomen, an abdominal ultrasound or CT scan only help to deepen a causal diagnosis when the ileum does not resolve after five or 6 days (search for abdominal abscesses or anastomotic dehiscence, evidence of adhesions, volvulus, and other).

Moreover, using the resumption of bowel sounds or passage of air as the criterion to define the functional recovery of the gastrointestinal tract (GI) is irrespective of the GI physiology.

Experimental measurements of the motility of the GI show that the activity in the small intestine is reestablished in 12–24 h, after 24–48 h in the stomach and after 3–5 days in the colon.

Waiting for proofs of colon motility (flatus and noise) to restart feeding means underestimate the ability of the stomach to tolerate feeding and of the small intestine to perform the functions of digestion and absorption.

Another questionable indicator of the end of ileum is the amount of gastric residual volume, based on the assumption that a normal function of GI allows the distal transit of a higher amount of secretions. Clinical evidences show the unreliability of this parameter: more usefully, the shift of color of nasogastric secretion from green to almost colorless can be employed. It is good to remember that the nasogastric drainage should be removed as soon as possible to make room for an early feeding.

The best proof for the end of ileus is the patient's ability to tolerate oral feeding without pain, gaseous distention, bloating, or vomiting, with appropriate caution, small meal testing should be performed as soon as possible, that must be promptly increased as soon as the tolerance of the patient is demonstrated.

In the discussion that follows, the specific motility disorders of the postsurgical phase (postoperative ileus per se) will often intersect with chronic disorders of transit. Similarly, considerations of gastroparesis (limitation of the proximal portions of the GI disorders), and disorders of the ileal and colonic transit will overlie.

The discussion of remedies has been intentionally kept in its totality, leaving to the reader the placement of the various concepts in a sectorial scheme.

11.1 Anatomy and Physiology of the Digestive Tract Motility

To fulfill its task of digesting food and to promote the absorption of nutritive substance in blood, the gastrointestinal (GI) tract performs three distinct activities:

- motility;
- secretion;
- digestion and absorption.

For the purposes of our discussion, we will examine as first item the anatomical structure of the gastrointestinal tract, and then the physiology of motility.

Despite the peculiar structural changes in the different sections of the GI tract, there are common characteristics in all segments (stomach, small intestine, colon).

From the lumen to the outside we always find the mucosa, consisting of:

- the epithelium, single layer of specialized cells, characteristic of the GI tract in question;
- the lamina propria, layer of loose connective tissue containing capillaries, lymphatic cells, and glands;
- the muscularis mucosae, where the innermost layer of the smooth muscle of the GI tract is structured in two thin muscular foils, the circular one innermost and the longitudinal one outermost;
- the submucosa layer of connective, crossed by nervous trunks and blood vessels of greater dimensions;

- the muscularis externa, muscular layer consisting of smooth muscle, with internal circular fibers and external longitudinal ones. These muscle fibers are responsible for the actions of mixing and propulsion of the contents of the GI tract;
- the serosa (adventitia), a connective tissue one.

The rich innervation of the wall of the GI tract, very interconnected, is called the enteric nervous system: within its scope two plexiform structures are particularly relevant:

- the submucosal plexus of Meissner;
- the myenteric plexus of Auerbach, localized in the muscularis externa, between the two circular and longitudinal layers.

The importance of the enteric nervous system (ENS), which together with the sympathetic and parasympathetic innervation constitutes the autonomic nervous system (ANS), is proven by the large number of neurons that are involved, about 100 million, same as all the remaining ANS or the entire spinal cord.

The peculiarity of the ENS is to be able to operate entirely within the GI tract, without the involvement of the spinal cord or central nervous system (CNS). This function is strongly independent and led the English to create the term "GI minibrain", assuming that the ENS possesses a set of preprogrammed responses to afferent stimuli which can lead to similar efferent answers. For example, the mechanical distension during fasting and the presence in the same site of bacterial enterotoxin elicit both the stimulation of a profuse secretion of fluids and electrolytes, along with coordinate, propulsive, and propagating muscle contraction.

Across the whole GI tract the action of parasympathetic NS is activatory and excitatory, while the one of the sympathetic NS is inhibitory. Moreover, it is intuitive that in all stages of stress activity sympathicotonic digestive processes are downregulated and, at the same time, are dysfunctional: furthermore, isn't it common to say, "I have everything left on the stomach…" when you are subjected to stress or tension?

In effect, despite the ability of the GI tract to work with "local" reflections, which take place entirely in the ENS, nervous control of the digestive system is also a function of extrinsic nerves, parasympathetic extrinsic pathways, and to a lesser extent, sympathetic, under the control of brainstem and autonomic centers.

Acetylcholine (ACh) is the main neurotransmitter that regulates the secretory and contractile activity of smooth muscle in the GI tract while the vasoactive intestinal peptide (VIP), has an important muscular and prosecretive inhibitory role. The field of neurotransmitters of the ENS is under heavy development: in addition to enkephalin, somatostatin, substance P, serotonin, and nitric oxide (NO), the list of agonists is growing, along with new developments in the understanding of their functions.

In addition to local control and the activity carried out by the sympathetic NS and parasympathetic NS, the upper control is present, localized in the central brain structures (for example, the response of "flight or fight" which drastically reduces the blood flow to the GI tract, or the response "sight and smell" for food, which increases the gastric secretion).

This communication is bidirectional, so even local secretions send signals to the center: it's the case of cholecystokinin (CCK) that, in part, mediates the feeling of satiety.

Thus, a real "cerebro-neuro-intestinal" axis is created, that acts as a bidirectional system of functional control through the autonomic nervous system, hormones, gastrointestinal peptides, and the immune system.

The latter is, in fact, an essential component of "neuro-digestive" communication, in particular thanks to the neuroimmune regulatory action of the mast cells of the intestinal lamina propria: sensitive to neurotransmitters, they process the information from the CNS to the ENS and respond to interneurons of ENS itself; they send sensory input from the intestinal lumen when in contact with antigens, and regulate the activity of smooth muscle by their chemical mediators.

The motor activity of the GI tract, which is regulated by the ENS and the activity of smooth muscle, complies with three main functions:

- segmental contractions associated with non-propulsive movements of the intraluminal content: their effect is the mixing and blending of content and secretion, to promote digestion and absorption of nutrients;
- contractions generating propulsion: the movements that with their propagation transport the food and the products of digestion in the caudal direction, toward the disposal sites;
- in some hollow organs (stomach and intestines in particular) an activity of "reservoir" is present, to contain and hold a temporary luminal contents: this function is achieved through the coordination of motor function of other structures—the sphincters—that separate the different structures of the GI tract [6].

In all these activities we recognize a central role to the coordinated GI smooth muscle activities.

The meccano electric properties of intestinal smooth muscle necessary for this purpose are of two types:

(1) tonic contractions (sustained);
(2) rhythmic contractions (alternance of contraction and relaxation).

The smooth muscle cells of the gastrointestinal tract are long (about 500 μm) and narrow (5–20 μm), organized in bundles, separated, and defined by connective tissue.

The intrinsic rhythmic contractility is a function of membrane voltage (V_m) of the single myocell.

V_m can swing in two ways:

- in a low frequency range below the threshold, many times in a minute, known as slow-wave activity (slow-wave activity, or Basic electric rhythm);
- reaching the threshold of generation of a real action potential.

The integrated effect of slow waves and action potentials determines the muscular activity of the GI tract.

On the contrary to what happens in most excitable tissues, the membrane potential at rest of the smooth muscle cell of the GI tract varies significantly over time, giving rise to slow waves, in measure of 3 (stomach) to 12 (duodenum) per minute.

These waves, thanks to the "gap junctions" between adjacent muscle cells, propagate rapidly along entire sections of the intestine.

The width and frequency of slow waves can be modulated by neuronal intrinsic and extrinsic activity (e.g., sympathetic activity decreases in the amplitude or abolishes the waves) or by hormones.

At the exceeding of the threshold of the cell excitability, slow wave generate one or more action potentials (1–10/s).

While the slow waves in the absence of action potentials lead to weak contractions of the gastrointestinal tract, bursts of action potentials, grouped at the peak of slow waves, produce vigorous contractions: the higher the frequency of action potentials, the greater is the force of the smooth muscle cell contraction, with the individual contractions of each potential that add up to produce global and progressive tension increase.

During the interval between discharges, the voltage level never drops to zero even in case of considerable reduction: this tension is the basal tone, modulated by drugs, hormones, and neuroeffectors.

For the understanding of the subject we are dealing with, it is necessary to deepen the physiology of the motility in stomach and intestines, leaving at separate in-depth analysis the esophageal motility, the swallowing, vomiting, and defecation, as well as the important activities reflected between distant segments of tract digestion (e.g., the gastrocolic reflex).

11.2 The Stomach

The basic functions of gastric motility are:

- to allow the function of container for even large amounts of food that can be ingested in a meal;
- to fragment the food and mix the particles obtained with gastric secretions;
- to empty the stomach contents into the duodenum.

It all starts when, as a result of esophageal peristaltic wave, the lower esophageal sphincter is released, which corresponds to the relaxation—so-called receptive—of the fundus and body of the stomach. The latter allows increases in volume of more than 1.5 l without inducing significant increases of intragastric pressure (reservoir function): very weak contractions occur, which induce a negligible mixing of the food in this location.

The antrum instead, produces vigorous contractions that effectively mix chyme and gastric juice, as well as divide the antral content in smaller particles. These "jet" contractions push the gastric contents into the duodenum, with a speed finely regulated by multiple mechanisms that should prevent the chyme to be sent to the duodenum in an amount greater than its boarding capacity.

Because of the scarcity of strength of the contractions of the bottom of the gastric body, the content of the stomach tends to be arranged in layers of different density, and this arrangement does not undergo stratiform remixing for periods of 1 h.

The oily layer of food fats goes on the surface, and is transferred to the duodenum at last; liquids flowing around the solid mass are rapidly emptied into the duodenum. Particles of large volume or not digestible remain in the stomach for longer time.

The stomach contracts at a rate of about 3/min: the contractions start in the middle of the body and, heading toward the pylorus, progressively increase of strength and speed: therefore in the antrum there is the highest intensity of fragmentation and remixing.

Obviously, this description is valid for the phase during which the stomach takes food from swallowing and esophageal peristalsis: different story for fasting stomach motility (consistent with such an attitude of the intestine).

In a subject having a fasting, the antrum is dormant for a period of 75–90 min, which is followed by a phase of intense electrical and motor activity lasting about 10 min, in which the antrum contracts vigorously, and pylorus releases: in this way the stomach expels caudal parts of food or other material left over from the previous meal, followed by a new period of quiescence of 75–90 min.

This cyclic alternation of contractions and quiescence is part of a more complex transverse mechanism, called migrating myoelectric complex (MMC).

Antrum and duodenum are well coordinated with each other, so when the antrum shrinks the duodenal bulb is released. The gastroduodenal junction, in whom the pylorus functions as a true sphincter, must:

- enable the tightly regulated emptying of gastric contents, with a speed that commensurate with the ability of the duodenum to digest the chyme;
- prevent the reflux of duodenal contents into the stomach.

The stomach has a rich innervation (parasympathetic from vagus nerve and sympathetic from the celiac plexus) which presides over the activation or inhibition of motility and secretion (shared with hormones and neuropeptides) in the same way the pylorus receives stimulus to contract from sympathetic fibers and by hormones such as gastrin, CCK, secretin, and gastroinhibitory peptide (but also by vagal fibers employing ACh), while induction of relaxation is given by the parasympathetic that uses the VIP as a neurotransmitter.

11.2.1 The Small Intestine

The mucosa of the duodenum and jejunum is equipped with receptors and sensors for osmolarity, pH, some lipids, amino acids, and peptides.

Taking advantage of a complex physical and neurohormonal signaling:

- the fats do not empty into the duodenum at a speed higher than that of emulsion of bile acids and lecithin;

- the hydrochloric acid (HCl) passes into the duodenum at a speed lower than that necessary to pancreatic and duodenal secretions for buffering it;
- the speed with which the other components of the chyme are transferred from the stomach into the duodenum never exceeds the capacity of the latter to digest them;

(…in summary… the presence of fats, acidic pH and hypertonicity/hyperosmolarity in the duodenum, all slow the gastric emptying, through a decrease in the contractile force of the antrum and an increase in the contractile power of the smooth duodenal muscle).

Almost 5 m of small intestine are traversed by the chyme in a time ranging from 2 to 4 h.

It is in the 25 cm of the duodenum and in about the 2 m of the jejunum—the two proximal portions—that most of the digestion and absorption of nutrients occurs, and it is here, therefore, that the motility assumes preponderant significance, to enhance the functions of mixing chyme and secretions, contact with the microvillus and propulsion toward the colon.

The most represented movement is the segmentation, close contractions of contiguous segments of the circular muscle layer of the small intestine: the alternating contractions and relaxations of the circular wall optimizes mixing and contact with the mucosa.

Short peristaltic waves, and long ones to a lesser extent, promote the contraction of successive segments of the intestine with peristaltic progression toward aboral direction (or orocaudal).

As in most proximal segments of the stomach and duodenum, also in the small intestine there are slow waves with a progressively smaller frequency, from 11–13 of the duodenum to 8–9 in the distal ileum. The release of action potentials that are inscribed on the tonic phenomena activate contractions of the circular muscle, limited to short bowel tracts, so performing an highly localized activity.

As elsewhere, the basic electrical rhythm originates in the intrinsic innervation (ENS), while frequency and intensity of bursts of action potentials are influenced by ANS and neurohormones.

Anyway, the motion of a bolus of chyme within the intestine, result of an upstream contraction and a downstream relaxation, follows the "law of the intestine", that fix the movement direction in the aboral sense.

Compared to what happens after the ingestion of food and the production of a bolus of chyme, intestinal motility of a fasting individual is completely different, characterized by discharges of intense electrical and contractile activity, separated by long periods of quiescence: in analogy as what described for the stomach, this activity is called migrating myoelectric complex (MMC).

The MMC has the periodicity of about 75–90 min, and only when a complex reaches the terminal portion of the ileum the next complex is generated in the stomach, with contractions of greater intensity than those recorded in an intestine containing chyme: it is an activity of cleaning and emptying toward the distal portions (colic).

Another type of intestinal motility is that of the muscularis mucosae, which contract irregularly, about three times per minute: the profile of ridges and folds of the mucous membrane is modified to increase contact of the continuously stirred nutrients with secretions and their absorption. Similarly, the villous contract probably optimizing the lymphatic flow.

11.2.2 The Colon

The role of the colon is to transform 500–1,500 ml of chyme into feces containing the equivalent of only 50–100 ml of water: this action of reabsorption takes place thanks to a mixing movement, slowly progressing (5–10 cm/h), of the chyme that gradually becomes more and more solid. In fact caecum and colon work primarily as mixing machines, with little segmental propulsive movements, in reverse peristalsis, all aimed at promoting the reabsorption of water and salts. It is only with a frequency of one/three times per day that in the colon a peristaltic wave of contraction is produced, in which the segments involved remain contracted a long time: it is the peristaltic wave of mass, which has the function of advancing the semi-solid mass in a long section of the colon, in the direction of the evacuation tract. Because of the greater consistency of the luminal contents, the need for a greater contractile developed force is guaranteed by teniae coli (specialized external muscle layer), and by greater vigor contractile layers concentrated in the rectum and in the anal canal. The complex system of neural and hormonal control of gastrointestinal motility operates in the state of fasting and food intake by managing physical and secretive activities.

Talking about the "perioperative motility disorders" of the gastrointestinal tract, we talk about a system (digestive) artificially inactivated: the digestive tract is in fact structured to deal with boluses of ingested nutrients, and during fasting only plays auto cleansing activity. You must therefore remind the concept of the migrating motor complex(MMC).

During fasting, MMC characterizes the contractile pattern of the GI tract, in its entirety [7]. In men the contraction frequency is every 1/2 h, and this "house-cleaning" is developed in four phases.

The first (lasting about 60 min) is characterized by oscillatory potentials of the membrane of the smooth muscle without development of contractions, which instead appear in the transition to phase II.

In stage III there is an increase of frequency of contractions up to the maximum allowed by the slow underlying wave (3/min in the stomach and 11/min in the duodenum). In this stage the contraction migrates from the stomach to the ileo-caecal (thanks to "gap junctions" between myocytes), moving distally the entire luminal residual.

Phase IV sees the cessation of contractions, with the return to the quiescent phase of the GI tract.

Typically, the introduction of food (fed state) interrupts the MMC, and gives rise to the characteristic phasic pattern.

11.3 The Reasons of Postoperative Ileus

The pathogenesis of any transit disorder is multifactorial, with direct, indirect, local, and systemic factors, and its arbitrary establish a priority order among these mechanisms [8]. The description of the different contributions, proven or hypothetical, studied in humans and in animals, will be useful in understanding how to approach the postoperative ileus and other motility disorders.

11.3.1 Surgical Manipulation

The surgical manipulation of the abdominal organs makes the dysmotility of the digestive tract inevitable, with a relative contribution of local inflammatory reaction, loss of mucosal integrity and translocation of luminal contents, and alteration of the neural and neurohumoral signaling [9].

11.3.2 Intestinal Injury

The intestinal mucosa is particularly susceptible to any proinflammatory stimulus, of traumatic, postischemic reperfusive type, or infectious, and each of these can produce organic damage and dysmotility. The transition outward the lumen of the intestinal contents inevitably activates all paths of systemic inflammation. The direct surgical trauma is directly involved in this process.

11.3.3 Inflammation

The intestine is a really peculiar site for the immune response: it is a powerful interface with the external world, which interacts with food, toxins, living ecosystems. The villi are extremely sensible to exogenous stimuli, the muscularis externa is covered by leukocytes and in particular macrophages: any proinflammatory stimulus combines these defensive positions to release interleukins, prostaglandins, nitric oxide, and reactive oxygen species. Sepsis and surgery trauma on the digestive tract are described in the literature as typical inducers of gastrointestinal dysmotility [10, 11].

11.3.4 Hypoperfusive Damage

The gastrointestinal tract is particularly susceptible to decrease of cardiac output: while the macrohemodynamics (systemic arterial pressure and heart rate) does not change for bleeding up to 30 % of the blood volume, the gastrointestinal splanchnic is already suffering at 10–15 % [12].

The hypoperfusive damage is easily revealed by the organ dysfunction that ensues, mostly the gastroparesis and the increase of intra-abdominal pressure. The hypoperfusive damage is easily revealed by the organ dysfunction that ensues, mostly the gastroparesis and the increase of intra-abdominal pressure.

11.3.5 Systemic Hypoxia and Hypercapnia

Hypoxia—in animal models—induces mucosal acidosis in the intestine, even with maintained perfusion [13]. Respiratory acidosis alters, in an inhibitory mode, the gastropyloric motility.

11.3.6 Neurogenic Inferences

Surgical manipulation of the intestine can alter the neuronal and neurohormonal balance in different ways, all explored only in form of hypotheses. One of these involves the release of hypothalamic corticotropin releasing factor(CRF) useful to activate inhibitory adrenergic efferent pathways destined to intestinal smooth muscle [14]. Another hypothesis invokes a local release, following hypoxia and hypoperfusion, of 5-hydroxytryptamine three with a close link between induction of vomiting and disturbance of motility.

Other inhibitory neurotransmitters locally released include nitric oxide (NO), VIP, substance P, and prostaglandins.

11.3.7 Metabolic Disorders

The altered motility of the GI may be motivated by any disorder of acid-base balance, blood glucose, and electrolyte homeostasis, particularly by hypokalemia, by hypomagnesemia and hyponatremia.

Hyperglycemia and metabolic acidosis both slow emptying of the stomach [15].

11.3.8 Fluid Balance

We will discuss when treating the postoperative ileus the importance of intraoperative fluid restriction. Like any parenchyma or tissue, even the intestinal wall may experience edema, as stressed in a fundamental work on Lobo about salt and water balance during the intraoperative period of colonic surgery [16].

11.3.9 Hypothermia

Hyperthermia and hypothermia are both associated with dysfunction of GI motility. It is not clear whether the redistribution of blood flow, especially in the context of hypothermia, plays a primary role, nor if the delays in recovery of motility of cardiac surgery patients can only be attributed to the role of induced hypothermia.

11.4 Anesthetic Drugs and Ileum

Virtually any anesthetic drug has an effect on motility of the GI tract.

The action of anesthetic drugs is exercised mainly on the intestinal tracts which is directly regulated by neuronal integration. In particular the colon, where the tight junctions between myocells (gap junctions) are under-represented, is particularly sensitive to the inhibitory action of anesthetic drugs.

The effects of gastroparesis are dangerous in the context of anesthesia since they may lead to regurgitation and subsequent inhalation, and are also critical in the induction of PONV (post operative nausea and vomiting) and interference with the absorption of per os drugs.

11.4.1 Propofol

Numerous reports are available in literature on the effects of propofol on gastrointestinal motility. At intravenous subhypnotic doses (0.5 mcg/ml) and hypnotic (sleepy but arousable on command) propofol slows mildly orocecal transit [17].

At high doses, even the fat emulsion of the drug (Intralipid) may adversely affect gastric emptying.

The mechanisms of the inhibitory effect of propofol (and midazolam) on the alterations of motility are not yet clarified. It is possible (but not proven) an activation of GABAa receptors, widely present in the CNS, and therefore also in the dorsal vagal nuclei, which send cholinergic fibers in the GI tract [18].

At ENS level the answer is bivalent, activating and inhibiting motility, and it is supposed that the one induced by propofol (and midazolam) is inhibitory.

11.4.2 Nitrous Oxide

Despite being an anesthetic gas in disuse, like enflurane and halothane, the characteristic of nitrous oxide to be delivered electively in the structures containing gas (such as the gastrointestinal tract) remains well known, with the result of an expansion of these spaces many times the initial volume. This has led to contraindicate the use of nitrous in all situations of intestinal surgery in which a volvulus or occlusion with gaseous distension are proven.

Nitrous oxide, however, does not disturb by "itself" the gastrointestinal motility, with negligible effects compared to other inducers of postoperative ileus.

11.4.3 Inhalation Anesthetics

The effects on colonic motility of inhaled anesthetics are well highlighted in work on the animal: the administration of enflurane and halothane was known to cause the cessation of the contractile activity in the right and left colon, and the suppression of motor activity lasted for the whole period of administration of the gas, normally recovering at the complete elimination of the same in the expired gas. The recovery of peristaltic activity was earlier in the right colon than the left [19].

11.4.4 Morphine and Opiates

Opioids play a primary role in the genesis of postoperative ileus, because of their depressant effects on motility in the digestive tract.

The pharmacological action involves receptors, locally in the digestive tract, with a minimal contribution of spinal and brain receptors.

Among the classes of receptors for opiates (κ, δ and μ), the one implicated in the effects on the gastrointestinal system is the μ: μ receptor action on the CNS is kind of analgesic.

The action of morphine and derivatives on intestinal motility is ubiquitous, and include inhibition of gastric motility, antrum, and first portion of the duodenum hypertonia. The action of opiates is biphasic, initially causing a contractile stimulus for the ileal activation of MMC, which is subsequently inhibited, with induction of atony and slow transit. At colonic level, morphine reduces the propulsive waves, and increases the tone and amplitude of non-propulsive contractions.

Alongside the action and the effects of opioids administered for therapeutic purposes, in the context of surgical trauma there is an increase in endogenous opiates (endorphins), with obvious relapse and amplification of the effects on transit [20].

The relationship between the analgesic effect and the constipating one is about 4:1, that means that it takes doses $\times 4$ to obtain analgesia compared to the alteration of motility.

Moreover, while it easy to induce tolerance to the analgesic effect for repeated doses of morphine, it is impossible to induce tolerance to the constipating effects.

The antagonism of the effect of μ receptor by administration of naloxone has limited effectiveness, and in any case, it induces partial or complete loss of analgesia [21]. We will discuss later the use of the most modern and selective μ receptor antagonists in the treatment of postoperative ileus.

It is stimulating to reconsider the whole context of the motility disorders of the GI tract as the consequence of a hypersympathetic tone, due to surgical stress and pain, a condition known to induce inhibition of contractile activity.

Experiments on animal models have demonstrated an increase in serum levels of catecholamines after laparotomy and manipulation of the intestinal loops and, in mice, the depletion of the intestinal deposits of norepinephrine after laparotomy [22].

The blockade of sympathetic reflexes by resection of the splanchnic innervation or by chemical sympathectomy reduces postoperative ileus significantly [23]. The change of priorities in the homeostatic control systems regarding the digestive apparatus is well demonstrated by changes in perfusion and redistribution of cardiac output in the states of stress and hyperdynamics: it is not surprising that the loss of parasympathetic dominance modulating digestion and absorption amplifies the motility disturbances seen at the bedside.

11.5 The Therapeutic Approach

The strategies for the prevention and treatment of gastrointestinal dysmotility include the use of prokinetic molecules stimulating motility.

Among these there are the central and peripheral antagonist's dopamine-2 receptors, the motilin agonists and the agonists of serotonin-4 and -3 receptors.

It is clear that improvements in understanding the mechanisms of neurohumoral control of gastrointestinal motility will enable the development of new molecules, and their application in critical and non-critical patients.

As already mentioned in the section devoted to the physiology of gastrointestinal motility, there is a complex receptor activity spread throughout the ENS in and out of the myenteric plexus and intestinal smooth muscle: the beginning and propagation of the contractile activity of GI are mostly based on this activity [24].

The main excitatory neurotransmitters are acetylcholine and tachykinins released by motor neurons in the myenteric plexus, active on M2 and M3 muscarinic receptors for tachykinins of the smooth muscle.

Dopamine inhibits the release of acetylcholine from these neurons by binding to D2 receptors, with a reductive effect on gastric emptying and intestinal peristalsis.

The motilin, a peptide secreted by enteroendocrine cells of the GI tract, amplifies and induces phase III of the MMC.

The serotonin (5-hydroxytryptamine or 5-HT) is located all along the GI tract, regulating motility, secretion of the electrolytes, and the visceral perception of intestinal distension and pain. Of particular interest is the pharmacological modulation of 5HT3 receptors (contraction and relaxation of smooth muscle) and 5HT4 (chloride secretion and increase of ileal and colonic transit).

The cholecystokinin (CCK) is secreted from the duodenal mucosa in response to the presence of free fatty acids in its lumen: the effect is a slowing of gastric emptying and colonic transit mediated by CCK-1 receptors distributed throughout the GI tract.

We mentioned above the control of motility mediated by opiates receptors, and we will see the therapeutic implications in the next section.

11.5.1 Targeted Drug Therapy

The depressant effect of the hypersympathetic tone on the GI motility has justified the use of antagonists or blockers of the sympathetic activity to reduce the duration of postoperative ileus.

The results of the administration of **propranolol** (4 or 10 mg twice per day) showed significant effects only in some studies [25] but not in others [26].

The role of the **postoperative epidural analgesia** finds an excellent explanation in the decrease of hypersympathetic tone associated to pain.

The many benefits of postoperative epidural analgesia are:

- greater pain control and more space for mobilization;
- dose reduction of opioid analgesia, with secondary reduction of side effects;
- blockade of nociceptive afferents from the wound with reduction of the effects induced by surgical stress.

The shortening of ileus duration after thoracic epidural analgesia, compared to intravenous treatment with opiates, is well documented and proven [27].

Epidural analgesia with local anesthetics and of opiates may modestly lengthen postoperative recovery of motility.

The reason for the shortening of ileus must be found in the block of sympathetic inhibitory reflexes, originating from the viscera and surgical wound: this explains why a thoracic but not a lumbar block leads to the favorable effects in colon surgery.

The role of pain itself in the genesis of postoperative ileus has not been fully clarified, and the pain level of Visual Analogic Score (VAS) is not directly related to the intensity of ileus when studied in multimodal programs of postoperative intervention [28].

The same results are seen during balanced anesthesia in protocols of opioids restriction, in which paracetamol and NSAIDs were included (in some studies paracetamol and NSAID seem to reduce per se the time of ileus through effects on inhibitory prostaglandin synthesis) [29].

In an extensive meta-analysis of 2008 [30], the effect of continuous intravenous infusion of **lidocaine** significantly correlated with the shortening of postoperative ileus.

Since the first report in the literature in 1954 [31], lidocaine was used as intraoperative analgesia to cover the first postoperative phase. Almost the total absence of PONV did suggest a positive action on the GI transit, which later addressed some targeted research protocols.

In these studies (8 RCT, randomized controlled studies) a bolus of lidocaine (1.5–2 mg/kg) was administered before surgical incision, followed by continuous infusion (in one study the infusion was started without bolus). In the eight studies the infusion lasted for the entire surgery and up to 24 h postoperatively.

The meta-analysis showed Forrest plots in favor of lidocaine versus placebo for reduction of postoperative ileus duration, pain, nausea, and vomiting after surgery, as well as for hospital LOS.

Evidence supports that lidocaine suppresses some neural inhibitory activity of ENS.

Known the simplicity and the low cost of the technique, this results support a wider diffusion of lidocaine.

Neostigmine is an acetylcholinesterase inhibitor: its administration causes an increase in cholinergic activity (for reduced esterification of ACh) in the wall of the intestine, with a resulting increase in motility.

Despite proofs of a significant increase in activity of the colon in the early postoperative ileus (colorectal surgery) [32], the clinical utility of neostigmine in the postoperative phase may be limited by frequent side effects such as cramping, salivation, vomiting, and bradycardia. Particularly feared by the surgeon is the possibility of stress exerted on the anastomosis by a perking up of contractile activity.

Among the most studied and diffuse prokinetics, **metoclopramide** acts as a cholinergic agonist and dopaminergic antagonist (central and peripheral D2 receptor). It starts the phase III of the MMC antagonizing the action of endogenous dopamine.

This drug has been the subject of numerous prospective randomized and placebo-controlled studies. Although some of these have demonstrated an earlier tolerance to solid foods, in general they did not show advantages compared to placebo regarding the transit of gas or of bowel movements.

Although with different end points, at least six controlled clinical trials of abdominal surgery have not been able to demonstrate the advantages of metoclopramide in the treatment of postoperative ileus [33].

Like **domperidone** (a peripheral dopamine D2 receptor antagonist) metoclopramide is associated with adverse arrhythmic effects (torsades de pointe, ventricular arrhythmias and cardiac arrest) correlated with prolongation of QTc (corrected QT): moreover metoclopramide inhibits dopaminergic transmission in the basal ganglia and causes significant extrapyramidal disorders, including dystonic reactions and tardive dyskinesia [34]. The short-term administration of metoclopramide (10 mg 4 times daily) is certainly more effective than the placebo in promoting the transit [35], but the desired prokinetic effects decrease rapidly after 3 days, opposite to the risk of irreversible tardive dyskinesias, which are related to the duration and the amount of the drug administered, and the presence or absence of previous extrapyramidal disorders .

Erythromycin exerts its prokinetic effect through a motilin agonist action: the stimulation occurs only at ileal level, where the action of motilin itself is maximum. The lack of influence of the drug on the duration of the ileus (highlighted in the majority of studies) can be explained by the paucity of effects on colonic tract, whose inertia is more relevant to the duration of the postoperative ileus [36].

Azithromycin stimulates the activity of the gastric antrum in a way similar to erythromycin, and presents a more lasting effect (104 vs. 136 min) [37].

In addition, unlike erythromycin, interactions with other drugs are fewer and less significant.

Cisapride has played an important role among the prokinetics until it has been withdrawn from the commerce because of the severity of cardiac side effects.

It is a serotonin 5-HT4 receptor agonist.

The **N-methylnaltrexone** is a quaternary derivative of the opioid antagonist naltrexone.

Similar to its precursor, peripherally blocks the effect of morphine and similar compounds, but being unable to cross the blood–brain barrier, does not affect the central analgesic effect of it.

It is mainly used in oncology and algology to combat constipation from opiates: numerous studies demonstrate its usefulness in the treatment of postoperative ileus.

The **almivopan** is a powerful μ receptor antagonist, acting purely at the periphery. Intended for oral administration, it is available for the treatment of morphine-induced bowel dysfunction (oncology!) and postoperative ileus.

Its exclusive peripheral action, absolutely localized in the intestine, is due to almost zero penetration through the brain–blood barrier [38]. The duration of its action is greater than that of already available μ antagonists (naloxone, *n*-methylnaltrexone), thanks to the kinetics of receptor binding of the drug (high affinity but slow dissociation).

The drug has an overall positive effect in restoring motility in the context of postoperative ileus, meanwhile leaving some doubt because of an increased need of opiates to maintain the analgesic effect.

Tegaserod is a 5-HT4 partial receptor agonist, acting peripherally, and at the same time a strong 5-HT2B receptor antagonist.

Many clinical studies have demonstrated the effect of tegaserod on GI motility: the series were of 24 cases of irritable bowel syndrome [39], 12 [40], and 40 [41] healthy subjects.

The effects on gastric emptying and ileal and colonic transit were significant and mainly localized in the upper GI tract.

Diarrhea and headache are not rare side effects with the use of this medication, and 1 of 250 patients has severe forms of hypotension, hypovolemia, and syncope, with recourse to hospitalization and infusion therapy [42].

Especially when used in critically ill patients, tegaserod exposes to the potential risk of ischemic colitis, particularly if there is a preexisting defect of mesenteric flow.

Loxiglumide and **dexloxiglumide** are two isomeric molecules with a strong, effective and specific antagonism of receptors for cholecystokinin 1.

They are drugs studied for irritable bowel syndrome, non-ulcer dyspepsia, disorders of delayed gastric emptying.

In human studies [43], infusion of loxiglumide increased gastric motility by shortening the time of stomach emptying in comparison to placebo.

The accelerated emptying was associated with increased amplitude and frequency of contractions, toward the distal stomach (antrum).

Nowadays, no studies on critically ill patients are available.

Among other drugs that have been proposed or experimentally used in treating motility disorders of the GI tract—and in particular the postoperative ileus—we must also mention:

- **dihydroergotamine**
- **vasopressin**
- **prucalopride** (5-HT4 receptor agonist]
- **bisacodyl** (magnesium salt)
- **prostaglandins**
- **edrophonium** (inhibition of adrenergic and cholinergic activation)
- b**ethanechol** (inhibition of adrenergic and cholinergic activation)
- **NSAIDs**
- **ceruletide** (antagonist cholecystokinin)
- **Octreotide** (somatostatin analogue)
- **atilmotina** (analogue of motilin)
- **lubiprostone** (bicyclic fat acid, the active secretion of intestinal water).

To shed light on such a vast number of proposals and studies, was published in 2009 a number of the Cochrane Library entitled "Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults" (Review).

The authors' conclusions are the following:

> Drugs are commonly used to reduce the impact of postoperative ileus. The evidence for the majority of these drugs is based on small trials of limited methodological quality, which jeopardizes the interpretation of the provided data.
>
> ….. are necessary greater statistical power trials and greater methodological quality…
>
> Limited evidences from a few small trials of medium-low quality indicate that the use of intravenous lidocaine and neostigmine can provide favorable effects on postoperative ileum recovery time….
>
> For drugs acting like cholecystokinin, for cisapride, for dopamine antagonists, for pantothenic acid, for vasopressin and for propranolol the evidences are insufficient to recommend their use in the postoperative ileus. For all these agents, the effects are inconsistent when addressed to different outcomes, the sample size is insufficient for final assessments, or the methodological quality of eligible trials to test is poor.
>
> Cisapride has been withdrawn from commerce; erythromycin has no effect on postoperative recovery of intestinal motility.
>
> It is possible that the almivopan could reduce the recovery time of motor function of the GI tract after major abdominal surgery: the current evidence is based on six trials of reasonable size, but whose lack of adherence to reporting standards prevents to exclude potential biases…

11.5.2 Non-Pharmacological Measures

11.5.2.1 Chewing Gum

It is a simple, economic and potentially effective approach, based on the concept of "sham feeding". The sham feeding is a procedure for the study of the psychic phase of gastric secretion: in experimental animals, ingested food is brought out by

a cervical esophageal fistula: the effect on gastric secretion given by chewing and swallowing is studied. The cephalic-vagal stimulation, exerted by only chew, gives rise to hormonal and propulsive activity similar to that produced by the normal power supply.

A recent meta-analysis [44] on the use of chewing gum in the postoperative abdominal shows significant results in terms of first passage of flatus, the appearance of appreciable auscultatory bowel movement, and the LOS of these surgical patients.

The use in the early postoperative phase of chewing gum (in the various studies administered in a variable manner: from 5 to 30 min 3 or 4 times a day) has the advantage of availability, absence of costs, and tolerability.

11.5.2.2 Laxatives

The use of laxatives in the treatment of constipation is widespread and supported by evidence. Broadly speaking, they are divided into osmotic (lactulose, sorbitol, polyethylene glycol) and non-osmotic (salt: magnesium salts; bulking: methylcellulose, psyllium, agar agar, etc.; irritants: senna, sodium pyrosulfate, bisacodyl). They all may be usefully and successfully employed even in critically ill patients, where the transit of fecal material and bowel cleansing are often crucial.

Numerous protocols in the field of intensive care provide at the entrance, or at the most within 72 h, defecation, in particular with laxative action to increase the intestinal water content and soften the stool consistency.

It is clear that these principles do not apply in the narrow context of postoperative ileus.

11.5.2.3 Acupuncture

There are numerous studies that approach the effects of Chinese acupuncture on the gastrointestinal tract.

The stimulation of the Neiguan point (volar forearm) significantly inhibits the frequency of the rhythmic relaxation of the lower esophageal sphincter, frequent cause of delay in the beginning of enteral nutrition in critically ill patients and/or discontinuation of mechanical ventilation [45]. Even in neurosurgery patients the Neiguan point shows a prokinetic gastric effect superior to pharmacological treatment [46].

11.5.2.4 Minimally Invasive Surgery

Laparoscopic surgery and minimally invasive surgery have been proposed to reduce local inflammation at the site of surgical trauma, which finally leads to postoperative ileus.

There is a body of literature supporting this approach, in at least four randomized clinical trials: the lack of perioperative protocols exposes these studies to the risk of bias in the evaluation of the most favorable outcomes.

11.5.3 The Multimodal Approach

A systematic view of the causes and remedies of the postoperative ileus inevitably leads to confusion and uncertainty.

Which is the best of all available treatments?

Nowadays the best treatment is a multimodal regimen.

It has been evaluated [47] a multimodal rehabilitation regimen for postoperative ileus built up with continuous epidural analgesia, early enteral nutrition and mobilization, (cisapride) and laxative treatment with magnesium salts. The authors observed a shorter transit recovery (48 h), compared with the control group.

Another protocol—enrolling patients undergoing segmental colectomy—included thoracic epidural analgesia for 48 postoperative hours, early removal of nasogastric tube or other drains, 1 l of fluids orally on the surgery day, mobilization within 8 h of surgery, the modification of the incision line from longitudinal to transverse (to reduce pain and respiratory dysfunction) and the use of magnesium laxatives [48]. 95 of 100 patients resumed intestinal activities in 48–72 h of postoperative time.

Preliminary results about the multimodal approaches suggests that programs that incorporate continuous epidural analgesia with local anesthetics, early enteral nutrition and early mobilization may reduce the postoperative ileus duration to 24–48 h in the context of colorectal surgery.

Probably these encouraging results should be limited to situations in which there is a limited inflammatory component [49].

All the contribution of the early 2000 about multimodal postoperative rehabilitation programs were reviewed in recent years by the so-called ERAS (Enhanced Recovery After Surgery) protocol.

It consists of 20 elements that strongly influence the duration of treatment and hospital stay, and incidence of complications. It is easy to see how many of the topics covered in this session are reflected in several steps of ERAS in the postoperative ileum.

11.6 Conclusions

The postoperative ileus is still a tangible problem in surgical patients and in particular in the critically ill.

The etiology is certainly multifactorial, with different mechanisms working together or at different times: sympathetic inhibitory input, secretion of hormones and neurotransmitters, inflammatory reaction, effects of opiates, or other drugs. Many different approaches have been used to reduce the impact of postoperative ileus and clinical problems arising therefrom, with variable outcomes.

So far, the best suggestion is to minimize the impact of the factors underlying the phenomenon.

Among these, the reduction of opioids and the use of alternative NSAIDs, acetaminophen, and local anesthetics in epidural analgesia.

The selective use of nasogastric decompression, the correction of electrolyte imbalance, and a cautious policy of restriction of perioperative fluids all play an important role in multimodal management of the ileum.

The promises of the future will be found in laparoscopic and minimally traumatic surgery, in superselective opiate antagonists and in pharmacological manipulation of local factors, neurotransmitters and stress hormones.

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