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Gastroparesis in the intensive care unit

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Abstract

Gastroparesis is a common problem in the intensive care unit. Impaired gastric motility in critically ill patients is associated with an increased risk of enteral feeding intolerance, gastric bacterial colonization, pulmonary aspiration and progressive malnutrition leading to adverse outcomes. It is estimated that at least 60% of intensive care patients are affected by some form of gastrointestinal tract failure and that in 30% of critically ill patients in whom enteral feeding is attempted the feeding route needs to be modified because of feeding intolerance. The article highlights the physiology of normal gastric motor function and mechanisms of abnormal gastric motility as well as the current approach to detecting and treating feeding intolerance in intensive care.

Key words: intensive care, nutrition, gastric emptying, enteral nutrition, gastroparesis.

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INTRODUCTION

Upper gastrointestinal (GI) motility disorders are a common problem in the intensive care unit (ICU). Delayed gastric emptying in critically ill patients is associated with the risk of intolerance to GI (enteral) feeding, aspiration of food into the airway, pathogenic colonization of the stomach, and progressive undernutrition.

Gastrointestinal dysfunction is estimated to affect at least 60% of ICU patients [1]; in 30% of critically ill patients in whom enteral feeding was attempted, the route of nutrition has to be changed due to feeding intolerance [2].

THE CONCEPT OF GASTROPARESIS

Gastroparesis (literally – stomach paralysis) is a disorder of gastric emptying in the absence of any noticeable mechanical cause. In the United States, the number of hospitalised patients with the diagnosis of gastroparesis increased by more than 136% between 1995 and 2004 [3].

In outpatients, gastroparesis may manifest as postprandial fullness and early satiety after eating small amounts of food, flatulence, nausea, vomiting, or epigastric pain [4].

The diagnosis of gastroparesis is made based on the demonstration of delayed gastric emptying in a patient with typical symptoms in the absence of mechanical obstruction. Disorders of gastric motility in gastroparesis do not always correlate with the severity of symptoms, although this seems to depend on the quality of the diagnostic method used [5–8].

The most common clinical symptom is nausea, which occurs in more than 90% of patients [4]. Abdominal pain develops in half of patients and is predominant in 20% of them [9].

The risk factors include diabetes, vagus nerve injury associated with surgery, especially anti-reflux and bariatric procedures, in the past also with surgical treatment of peptic ulcers, and the use of drugs that inhibit GI peristalsis, including opioids. In the general population, however, idiopathic gastroparesis is observed most frequently; in nearly half of patients, the exact cause of complaints cannot be determined [4, 10]. In some patients, idiopathic gastroparesis is preceded by GI or respiratory tract infections. The implicated mechanism of this phenomenon is damage to the autonomic neurons in the gastric wall or gastric pacemaker cells during infection. In patients with post-infectious gastroparesis, the prognosis is better, and the severity of symptoms is lower; in many cases, the condition improves spontaneously [11, 12].

As the incidence of diabetes and the number of procedures performed to treat obesity and reflux disease are increasing, the incidence of gastroparesis can be expected to become increasingly high in hospitalised patients.

NORMAL MOTOR FUNCTION OF THE STOMACH

The normal motor function of the stomach includes:

- active relaxation of the smooth muscles of the proximal stomach after a meal,

- peristaltic contractions in the body and antrum for maximum griding of food and its mixing with the gastric juice,
- gradual emptying of the antrum via the pylorus and release of small portions of thoroughly crushed food into the duodenum.

The fundal smooth muscle cells exhibit a constant tone while at rest. Distending the stomach with food triggers vagus nerve reflexes, which actively decrease the tone of the gastric wall muscles in the proximal part and increase the stomach capacity; therefore, despite its increased volume, the pressure in the stomach does not undergo major changes [13, 14].

In the further part of the stomach, food is mixed and ground by peristaltic contractions of the body and antrum. In the pacemaker region of the stomach, located in the upper part of the body from the side of the greater curvature, the slow waves are generated with the frequency of about 3 cycles per minute in a healthy individual. The cells responsible for the generation and conduction of slow waves in the stomach wall are interstitial Cajal cells and fibroblast-like cells (FLC), described quite recently. Both types of cells form numerous gap junctions with the smooth muscle cells of the gastric wall and are themselves innervated by the processes of neurons of the autonomic nervous system [15]. The interstitial Cajal cells form a dense network of fibres of the gastric muscular layer (about 5 interstitial cells in the visual field at high magnification), extending from the upper part of the body to the pylorus [16].

The depolarisation wave triggers a coordinated wall contraction followed by its relaxation, resulting in a peristaltic wave. The peristaltic waves spread distally and circularly every 20 seconds, reaching the highest amplitude in the distal part of the antrum. The constant tone of the pyloric sphincter muscle prevents uncontrolled entry of food into the duodenum. During the contraction of the gastric wall, most of the pulp remains in the stomach, and only a small amount (about 3–4 mL) moves through the pyloric sphincter to the duodenum, which promotes thorough crushing and mixing of the contents with gastric juice and prevents simultaneous loading of the duodenum with large volumes of food. In the duodenum, the slow waves have a frequency of 12–13 cycles per minute [13, 14]. The rate of gastric emptying depends on the volume and type of food. Carbohydrates leave the stomach most quickly, while fats stay in it the longest. Stretching of the duodenal wall and exposure of membrane receptors to hydrogen ions and fatty acids lead to reflex inhibition of peristaltic contractions and an increase in the pyloric sphincter tone, which slows down gastric emptying [14].

In the interprandial period, the stomach exhibits a cyclical activity called the migrating motor complex (MMC). The resting period (phase I of MMC) is followed by the phase of initially uncoordinated (phase II) and then rhythmic (phase III) contractions of the muscles of the gastric wall, which enables gastric emptying of undigested food residues. Any disorder or absence of phase III can result in the formation of gastric bezoars [17].

The motor function of the stomach is regulated at various levels – by the central nervous system, the sympathetic and parasympathetic autonomic system, neurotransmitters, as well as locally by the gastric wall cells themselves [13].

The stomach is innervated by neurons of the parasympathetic system (reaching the stomach via the vagus nerves) and the sympathetic system (originating in the visceral plexus). The mucous membrane and smooth muscular layer contain numerous sensory receptors, from which the stimuli reach the brain stem through the vagus nerve and sympathetic nerves.

The sympathetic and parasympathetic systems exert opposite effects on gastric motility. Parasympathetic fibers increase while sympathetic ones inhibit gastric motility. Acetylcholine, one of the locally released neurotransmitters, stimulates the contractile action, while nitric oxide, neurotensin, substance P, and somatostatin slow it down [14].

Gastrin and motilin, the hormones released from the GI endocrine cells, increase gastric motility. Somatostatin, secretin, and gastric inhibitory peptide (GIP) inhibit gastric contractile function [14].

Loss of vagus nerve tone in diabetic neuropathy or following iatrogenic intraoperative damage and relative predominance of the sympathetic system impair the migrating motor complex, both directly and due to impaired release of motilin.

PATHOPHYSIOLOGY OF GASTROPARESIS

The pathomechanism of gastroparesis is complex. Disorders of gastric emptying may result from impaired relaxation of the gastric fundus in response to the food bolus, disorders of the contractile function of the body and antrum caused by atrophy of the stimulogenic (triggering) cells and the smooth muscular layer of the gastric wall, disorders of neuromuscular coordination or spastic pylorospasm (in some patients).

Histological abnormalities of the gastric wall are found in most patients with gastroparesis and include a decrease in the number of interstitial Cajal cells, atrophy of the nerve ganglia, inflammatory infiltrations of macrophages and lymphocytes, an increase of the fibrous connective tissue. Moreover, the ratio of pro-inflammatory (M1) and anti-inflammatory

(M2) macrophages has been found to be altered in gastroparesis [18–20].

In cancer patients, gastroparesis may be part of the paraneoplastic syndrome and result from direct infiltration of the visceral plexus or vagus nerve, surgery, chemotherapy and radiotherapy [21].

The paraneoplastic disorders of gastric motility can occur in small-cell lung cancer and various other cancers [22–26]. Some patients have onconeuronal antibodies (anti-Hu, anti-Yo), which are likely to bind to antigens common to both the cancer and elements of the nervous system [24, 28].

Post-surgical gastroparesis can occur after the procedures associated with the risk of damage to the vagus nerve, such as some procedures within the stomach (fundoplication, gastric resection), after surgical treatment of obesity and duodenal resection. Damage to the vagus nerve causes loss of gastric accommodation and inhibition of its contractile function, which impairs gastric emptying of solid particles, in particular [27]. Resection of the duodenum results in a decrease in the plasma concentration of motilin, which plays a certain role in interprandial emptying of the stomach of food residues. Less commonly, post-surgical gastroparesis is caused by damage to gastric innervation during extensive epigastric lymph node resections or damage to the visceral plexus [28].

DIAGNOSIS OF GASTROPARESIS

The diagnosis of gastroparesis made based on the demonstration of delayed gastric emptying in the absence of mechanical obstruction and at least one of the typical symptoms, which include nausea, vomiting, postprandial fullness, early satiety, and abdominal flatulence. To exclude any mechanical obstruction, an upper GI endoscopy is performed.

The gold standard for the diagnosis of gastric emptying disorders is gastric emptying scintigraphy (GES), which assesses the extend of gastric emptying 4 hours after ingesting a standardized technetium-labelled meal. The result is considered abnormal when retention of more than 10% of food is observed 4 hours after ingestion [29]. Although many patients with symptoms suggestive of gastroparesis may have normal or even accelerated gastric emptying [30], scintigraphy performed optimally shows a good correlation with the presence of symptoms [8].

An alternative method for assessing gastric emptying is the gastric emptying breath test (GEBT) with a test meal containing carbon-13 (^{13}C) [31]. The test is initiated with sampling of exhaled air; later the patient receives a standardized meal containing a substrate labelled with a stable carbon isotope ^{13}C (usually octanoic acid or spirulina). Over the next 4 hours, the samples of the patient's exhaled air are taken at regular intervals. As the stomach empties, the substrate molecules are absorbed in the duodenum and metabolized to carbon dioxide; the rate of gastric emptying is measured based on the amount of isotope in the exhaled air. The advantage of this test is that it can be performed at the patient's bedside and that both a solid and a liquid test meal can be used; moreover, the test can also be performed in the ICU setting. The breath test is reproducible and comparable to scintigraphy [32], yet may not be reliable in patients with malabsorption, exocrine pancreatic insufficiency, and respiratory diseases [13].

The wireless motility capsule assessing pH, pressure and temperature in the GI lumen allows to determine the transit time through individual GI sections and to evaluate the time of gastric emptying. Delayed gastric emptying is diagnosed when the capsule passage into the duodenum is observed after more than 5 hours. The results of endoscopic capsule testing correlate well with the scintigraphy findings in both healthy individuals and patients with gastroparesis. The test detects a higher number of cases of delayed gastric emptying in patients with suspected gastroparesis, as compared to scintigraphy [33]. The asset of this method is the possibility of simultaneous assessment of the motility of other GI sections. On the other hand, since the capsule is not digested, the capsule passage time may not reflect the actual time of gastric emptying, given that undigested solid particles are removed from the stomach later than the chyme, in phase III of the migrating motor complex [34].

GASTROPARESIS IN THE INTENSIVE CARE UNIT

Many factors can impair normal GI motility in critically ill patients. On the one hand, such factors include the disorders of GI wall perfusion, effects of cytokines released during sepsis, oedema of the intestinal wall caused by capillary leak, hyperglycaemia, electrolyte disorders and impaired secretion of hormones responsible for the regulation of motility; on the other hand, the effects of sedatives, analgesics and vasoactive drugs should be mentioned [35]. The above factors impair both the motility of the proximal and distal stomach and lead to dissociation of the activity of these two regions described in ICU patients.

The motility disorders may cause feeding intolerance, which is usually defined as an inability to obtain a sufficient supply of calories due to excessive food retention in the stomach or the presence of symptoms such as increased abdominal circumference, bowel distension, vomiting or abdominal pain [36]. The incidence of feeding intolerance

depends on the definition adopted; nevertheless, it occurs in more than 30% of ICU patients, on average [2, 36]. Feeding intolerance is associated with longer ICU stays and higher mortality [37]. The most serious consequence of gastric emptying disorders is the aspiration of food contents and aspiration pneumonia, especially in patients undergoing mechanical ventilation. In some cases, the excessively distended stomach can cause the abdominal compartment syndrome.

The incidence of gastroparesis in critically ill patients is difficult to be explicitly assessed due to the lack of an unambiguous definition and criteria differentiating the mechanism causing feeding intolerance. In a systematic review by Blaser *et al*. [36], 43 definitions are listed, most of which are based on the assessment of gastric residual volumes (GRVs) with different values of this parameter considered significant, the presence of various 'gastrointestinal symptoms' and the inability to provide the normal volume of nutrition. Given the above discrepancies, it is difficult to conclusively estimate the incidence of gastroparesis in this group of patients [38].

In ICUs, the most common method of assessing gastric emptying is the measurement of GRV by aspiration or passive gravity drainage. According to some authors, the values above 150 ml within 24 hours may indicate gastric emptying disorders requiring intervention [39]; in clinical practice, however, the range of values is wide – from 75 mL to 500 mL. The usefulness of this parameter is controversial due to the lack of proper measurement standardisation and the impact of confounding factors. The size of the gastric residual volume depends, inter alia, on the diameter of the tube used, aspiration technique, density of the food administered, and even on patient's body position [40].

Scintigraphy, which is the gold standard for the diagnosis of gastroparesis in outpatients, can be performed in the ICU setting; as the method is time-consuming, it is not widely used in practice.

A potentially useful method for assessing gastric emptying is to evaluate the absorption of paracetamol after its oral administration. Since paracetamol is not absorbed in the stomach but in the small intestine, an increase in serum paracetamol concentration after administration into the stomach reflects the rate of gastric emptying. This method is also time-consuming and lacks standardisation; therefore, it is rarely used in practice [41].

MANAGEMENT, INCLUDING PHARMACOTHERAPY

The guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) on nutrition therapy in ICUs contain the recommendations for the management of enteral nutrition intolerance caused by gastroparesis [42, 43]. In both guidelines, enteral nutrition is the preferred route of nutritional support that should be initiated as soon as possible – within 48 hours after ICU admission [42, 43]. According to the guidelines, the assessment of the risk of gastrointestinal motility disorders is fully justifiable. However, the mere presence of risk factors should not be the reason for abandoning enteral nutrition; moreover, audible peristalsis is not a prerequisite for enteral feeding [43]. Although the GRV measurement is the basic method for assessing nutritional tolerance, it is essential that only values above 500 ml within 6 hours are an indication to withhold the supply of a nutritional mixture (according to ESPEN) [42]. In cases of significantly impaired motility of the upper GI tract, pharmacotherapy or nutritional supply below the pylorus is used.

At present, two drugs are used for the treatment of gastroparesis in the ICU, i.e. erythromycin, whose action results from the activation of motilin receptors, and metoclopramide, which is an agonist of dopamine receptors of the Auerbach's plexus, a partial antagonist of $5HT_3$ receptors, a partial agonist of $5HT_4$ receptors and a weak cholinesterase inhibitor [44, 45]. Both drugs accelerate gastric emptying in critically ill patients. Due to its postulated higher effectiveness, erythromycin is recommended as a first-line drug (ESPEN) [42], which can be used together with metoclopramide. Hersh and colleagues [46] have demonstrated a synergistic mechanism of action of the above-mentioned drugs.

The disadvantage of both drugs is the risk of side effects – extrapyramidal symptoms in the case of metoclopramide and arrhythmias in the mechanism of QT prolongation. As for erythromycin, slowing down the passage within the small intestine should be emphasised, which may limit its usefulness when the causes of food retention other than gastroparesis coexist [47]. Moreover, there are concerns that erythromycin may induce antibiotic resistance. Due to rapid development of tachyphylaxis, the recommended duration of prokinetic therapy should not exceed 72 hours [48]; moreover, it is suggested to end their supply earlier if the 24-hour tolerance of enteral nutrition is achieved [44]. The basic information on the use of both medicines is presented in Table 1.

Other prokinetics sometimes used in the ICU include domperidone, neostigmine, and opioid antagonists [44]. However, there are no conclusive results of studies confirming their effectiveness; hence no recognized recommendations for their use can be given. In the case of neostigmine, the risk of side

TABLE 1. Drugs used for the treatment of gastroparesis

Drug	Dosage	Contraindications
Metoclopramide	3 × 10 mg, IM or slow IV Minimum interval between doses: 6 h CrCl 15–60 mL min^{-1}: 50% of the dose CrCl ≤ 15 mL min^{-1}: 25% of the dose Severe liver failure: 50% of the dose	Drug hypersensitivity GI bleeding GI mechanical obstruction or perforation Chromaffinoma or its suspicion Epilepsy Parkinson's disease History of tarditive dyskinesis Methemoglobinemia or cytochrome B5 reductase deficiency Use of levodopa or dopaminergic receptor agonists In children below the age of 1 year
Erythromycin	3 mg kg^{-1} every 8 h in a 45-minute intravenous infusion	Drug hypersensitivity History of QT prolongation History of ventricular tachycardia/torsades de pointes Hypokalaemia or hypermagnesemia Use of astemizole, terfenadine, cisapride, domperidone or ergotamine Cautious use in patients with myasthenia gravis

CrCl – creatinine clearance.

effects far outweighing the benefits should also be taken into account.

If enteral feeding intolerance persists despite optimal pharmacotherapy, the ESPEN and ASPEN guidelines recommend the supply of a nutritional mixture below the pylorus [42, 43]. However, it should be remembered that this route is less physiological and potentially unfavourable when the main cause of nutrition intolerance is located below the stomach. In such cases, when in doubt, the previously described diagnostic methods of gastroparesis can be used. Moreover, it is worth emphasizing that in the light of the current guidelines, food intolerance in ICU patients caused by gastroparesis is not in itself an indication for the use of parenteral nutrition in the absence of other concomitant causes of intolerance.

Despite the theoretical usability of the diagnostic methods of gastroparesis described above, in practice their clinical usefulness is disputable. Disorders of the upper GI tract motility are associated with the general problem of gastrointestinal efficiency, which results in an inability to achieve the planned nutritional goals. The problem of gastroparesis in ICUs should be considered in the context of intestinal failure in critically ill patients. In most situations, dysfunction of GI motility will be associated with the severity of symptoms such as shock, visceral hypoperfusion, electrolyte and metabolic disorders, the need to use high doses of sedatives (including opioids) and vasoactive drugs. Thus, it seems that beside symptomatic treatment of gastroparesis in the ICU (administration of prokinetics), optimal compensation of hemodynamic disorders, adequate sedation, and fluid therapy are equally important [49]. As the patient's condition improves, most motility disorders should subside. If they persist, the diagnostic procedures should be deepened; in most cases, such procedures are carried out outside the ICU setting.

CONCLUSIONS

Gastroparesis is a common problem in the ICU. Disorders of gastric emptying are the cause of intolerance to nutrition through the GI tract in a large proportion of critically ill patients. Assessing the actual severity of these disorders can be difficult due to the lack of uniform and reproducible diagnostic criteria available in everyday clinical practice. However, the current guidelines for nutritional therapy in the intensive care unit stress the importance of striving for enteral nutrition in most patients and limiting the use of parenteral nutrition to fully justified cases.

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