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Gastroparesis: New insights into an old disease

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Abstract

Gastroparesis (Gp) is a chronic disease characterized by a delayed gastric emptying in the absence of mechanical obstruction. Although this condition has been reported in the literature since the mid-1900s, only recently has there been renewed clinical and scientific interest in this disease, which has a potentially great impact on the quality of life. The aim of this review is to explore the pathophysiological, diagnostic and therapeutic aspects of Gp according to the most recent evidence. A comprehensive online search for Gp was carried out using MEDLINE and EMBASE. Gp is the result of neuromuscular abnormalities of the gastric motor function. There is evidence that patients with idiopathic and diabetic Gp may display a reduction in nitrergic inhibitory neurons and in interstitial cells of Cajal and/or telocytes. As regards diagnostic approach, 99mTc-Technetium scintigraphy is currently considered to be the gold standard for Gp. Its limits are a lack of standardization and a mild risk of radiation exposure. The ¹³C breath testing is a valid and safe alternative method. ¹³C acid octanoic and the ¹³C Spirulina platensis recently approved by the Food and Drug Administration are the most commonly used diagnostic kits. The wireless motility capsule is a promising technique, but its use is limited by costs and scarce availability in many countries. Finally, therapeutic strategies are related to the clinical severity of Gp. In mild and moderate Gp, dietary modification and prokinetic agents are generally sufficient. Metoclopramide is the only drug approved by the Food and Drug Administration for Gp. However, other older and new prokinetics and antiemetics can be considered. As a second-line therapy, tricyclic antidepressants and cannabinoids have been proposed. In severe cases the normal nutritional approach can be compromised and artificial nutrition may be needed. In drug-unresponsive Gp patients some alternative strategies (endoscopic, electric stimulation or surgery) are available.

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Key words: Gastroparesis; Delayed gastric emptying; Gastric Scintigraphy; ^{13}C breath testing; Wireless motility capsule; Prokinetics; Antiemetic drugs; Gastric-per-oral endoscopic myotomy; Gastric electrical stimulation

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Core tip: Gastroparesis has a great impact on the quality of life and a heavy economic burden. Our objective was to consolidate current knowledge on its pathophysiology, diagnosis and therapy. Recent evidence has shown that gastroparesis may be due to intrinsic neuropathy. Diagnostic tests that are validated and available are 99-Tc^{99m} scintigraphy, the ^{13}C breath test and the wireless motility capsule. The therapy is varied and related to the severity of the disease. After dietary modification, old and new prokinetics and antiemetics are available. In drug-refractory patients, endoscopic or surgical procedure may be indicated.

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INTRODUCTION

Gastroparesis (literally “gastric palsy”) (Gp) is a pathological condition characterized by objectively demonstrated delayed or absent emptying of the stomach in the absence of mechanical obstruction^[1,2]. Although this condition and some of its various subtypes (idiopathic, diabetic, post-surgery, post-infective) have been reported in the literature since the mid-1900s^[3-6], only in recent years has there been a renewed interest in a better knowledge of its pathophysiological mechanisms and in a more targeted therapeutic approach^[7,8]. Indeed, in addition to the above reported causes, other causes of Gp have been described (*e.g.*, secondary to the use of drugs, to neurological disorders, to connective tissue disorders, to renal insufficiency)^[7]. These efforts have led to new suggestions in terms of the definition of this disorder, aimed at framing Gp within the context of a wider spectrum of gastric neuromuscular abnormalities^[9-11], in a manner similar to that proposed for other neurogastroenterological disorders^[12,13].

Gp is still a relatively unexplored disorder^[14], since there is a significant overlap between some symptoms complained of by these patients (such as bloating, early satiety, belching, upper abdominal discomfort or pain) and those complained of by patients with functional dyspepsia^[15]. In addition, a large number of Gp patients are represented by both insulin-dependent and non-insulin dependent diabetes mellitus^[16], which accounts for most epidemiological studies. However, there is substantial agreement on the fact that many patients with diabetic Gp are actually underdiagnosed^[7]. Therefore, the actual prevalence of “gastroparesis”, which features heterogeneous subgroups of patients, is still unknown^[18].

This paper will review the pathophysiologic, clinical, diagnostic, and therapeutic aspects of patients affected by the various forms of Gp.

LITERATURE SEARCH

A comprehensive online search of MEDLINE and the EMBASE was made using the keywords “gastroparesis”, “delayed gastric emptying”, “gastric”, “stomach”, “emptying” and “delay” in various combinations with the Boolean operators “and”, “or”, and “not”. The search generally included articles related to human studies, but some animal studies were retrieved when judged to be of importance. We performed manual cross-referencing, and selected articles published in English between January 2000 and November 2019, but a search in non-English languages and among journals older than 2000 was also carried out in our library.

PATHOPHYSIOLOGY

As stated above, the relatively wide heterogeneity of Gp patients largely accounts for the fact that, notwithstanding the recent advances in knowledge, the pathophysiological basis of this disorder still displays striking gaps to be filled^[7].

One main point is that Gp is the result of neuromuscular abnormalities of the gastric motor function^[19]. The food that reaches the gastric cavity is fragmented and liquefied through the synergic mechanisms of acid secretion and antral contraction, until it is homogenated to 0.5-2 mm diameter particles that can empty into the duodenum^[20]. Before emptying into the duodenum, the food is stored in the gastric fundus by means of gastric accommodation^[21], modulated by vagal innervation. Gastric antral contractions are also modulated by vagal fibres, as well as by intrinsic cholinergic neurons, whereas nitrergic neurons modulate relaxation of the pyloric sphincter and gastric peristaltic activity^[7]. The pacemaker effects on excitatory and inhibitory impulses are mediated by the interstitial cells of Cajal and by other fibroblast-like cells (positive for platelet-derived growth factor receptor alpha) that also have a pacemaker function^[22]. The latter, also known as telocytes, were initially known to be confined to the digestive system, but there is present evidence that these cells are present in the genital tract, lung, heart, skin, meninges, and urinary system, and are thought to participate in the pathogenesis of several diseases^[23].

Pacemaker cells direct the gastric smooth cells to act as a syncytium and coordinate contractions that start in the proximal stomach to propagate aborally toward the pylorus^[7]. Abnormalities involving these mechanisms cause Gp by bringing about antral hypomotility and (less frequently) pyloric dysfunction.

As regarding pathophysiological mechanisms, there is evidence that patients with Gp may display an intrinsic neuropathy. Analysis of full-thickness biopsy samples from patients with idiopathic and diabetic Gp revealed reduction in nitrergic inhibitory neurons (more pronounced in idiopathic gastroparesis) compared to controls^[24], as well as in interstitial cells of Cajal^[25,26]. The latter has been also associated with a decrease in anti-inflammatory M2 macrophages, protecting neural tissues from the effects of inflammation^[26]. All these abnormalities may cause impairment of gastric emptying through a decreased coordination of peristaltic activity, of paramount importance to triturate food in the antrum. In addition, delayed gastric emptying may be due to abnormal small bowel motility^[27,28].

Of course, other factors are likely to play a pathophysiological role, even though there is still uncertainty as to exactly how they might do this. For example, although the induction of acute hyperglycemia in humans inhibits antral contractility, delays gastric emptying, and induces gastric dysrhythmias^[29-31], controlled studies have shown no change in gastric emptying in patients with type 1 and type 2 diabetes and delayed emptying following improved glycemic control^[32,33]. Gastric emptying may be delayed by drugs, in particular by opioids^[34]; the latter are frequently responsible for high symptom severity and high hospitalization rates and a decrease in working hours and employment rate^[35]. In addition, abnormal gastric emptying with Gp may be observed rarely after an acute self-limited viral infection, especially in middle-aged women^[36]. However, literature data are quite limited and it is likely that this condition is frequently underestimated. Other rare and miscellaneous cases of Gp may be secondary to systemic scleroderma, mitochondrial degenerative disease, amyloidosis and visceral myopathies^[7].

DIAGNOSIS OF GASTROPARESIS

Gp has a great impact on the quality of life and is highly relevant in terms of mortality and morbidity. Therefore, it is necessary to carry out an accurate diagnostic workup aimed also at reducing economic impact (hospitalization, diagnostic tests and therapeutical interventions), which is still widely underestimated^[14].

CLINICAL HISTORY

The characteristic symptoms which should be carefully investigated are nausea, vomiting, loss of appetite, early satiety and post-prandial fullness, bloating, upper abdominal distention and pain^[37]. A delayed gastric emptying can be also suspected in the absence of characteristic symptoms because of the presence of food in the stomach during endoscopic or imaging procedures carried out for other reasons. However, in this case the term "delayed gastric emptying" seems more appropriate than "gastroparesis"^[37-41]. An accurate clinical history should rule out organic diseases such

as diabetes mellitus, connective tissue diseases (*e.g.* scleroderma and Sjogren's syndrome), myopathies and the outcome of abdominal or thoracic surgery causing damage to the vagus nerve^[16,38,42-44]. The most frequent conditions able to provoke Gp are reported in [Table 1](#).

Furthermore, some procedures such as cardiac ablation for atrial fibrillation, mesenteric revascularization, and celiac plexus blockage should be carefully considered. The presence of constipation and defecation disorders^[38,45-47] and autonomic neurological symptoms (orthostatic hypotension, sexual dysfunction and bladder emptying disorders, anhidrosis or hyperhidrosis) should also be investigated^[16,38,42-44].

Careful medication history should be collected concerning the use of medications potentially interfering with gastrointestinal motility, such as opioid analgesics, anticholinergic medications (especially second-generation antipsychotics), and the abuse of cannabinoids such as marijuana, which can delay gastric emptying ([Table 2](#))^[38,48].

Opioid-induced Gp is typical of patients using opioid μ receptor agonists such as oxycodone or tapentadol. These drugs interfere with gastric and intestinal motility, slowing gastric transit, and they can also induce vomiting by a central mechanism, acting on the chemoreceptor trigger zone in the area postrema^[38,49,50].

Reported unintentional loss in body weight, in the absence of important voluntary dietary changes, is useful to assess the severity of the disorder^[38,51].

DIFFERENTIAL DIAGNOSIS

Several conditions can mimic Gp. Due to the limited repertoire of symptoms arising from the upper gastrointestinal tract and the frequent overlap between symptoms of Gp and other disorders, the differential diagnosis can be very difficult ([Table 3](#))^[10,37,38,52]. For example, in patients using angiotensin-converting enzyme inhibitors (especially in diabetics) it is important to rule out the diagnostic hypothesis of visceral angioedema as a cause of vomiting^[37,38,52,53].

Vomiting can also be induced by the use of second-generation antipsychotics; due to their anticholinergic effect they can provoke a severe delay in gastric emptying, even an intestinal pseudo-obstruction, especially if used in combination with other anticholinergic drugs^[38,54].

Cannabinoid hyperemesis syndrome is characterized by cyclic vomiting episodes in patients chronically using marijuana and who have normal gastric emptying between the episodes^[38,55].

The hypothesis of cyclic vomiting syndrome, characterized by non-self-induced vomiting and nausea present at least one day a week for about 3 mo, in a patient in which other causes of vomiting have been excluded, must be taken into account in patients with nausea and vomiting^[38,56].

Moreover, some psychiatric/psychological disorders such as depression, anxiety and eating disorders, can manifest themselves with dyspeptic symptoms similar to those of Gp^[37,38,57].

Furthermore, patients with gastroesophageal reflux disease or affected by functional dyspepsia, characterized by postprandial fullness and/or early satiation, and those who are non-responders to pharmacological therapy, should be carefully investigated^[37,52]. The same is for subjects referring symptoms compatible with the diagnosis of rumination syndrome, which is characterized by the presence of effortless postprandial regurgitation in the absence of vomiting preceded by nausea^[38,58].

SYMPTOM SEVERITY EVALUATION

Patients can complain of a differing severity of symptoms. According to the severity of symptoms, Waseem *et al.*^[59] identified three different clinical forms: (1) Mild Gp: Easily manageable symptoms and no body weight loss; (2) Moderate Gp: More frequent, but not daily, symptoms treatable with antiemetics, prokinetics, dietary modifications and glucose control; and (3) Severe Gp: Symptoms occurring every day despite medical treatment, in addition to the presence of malnutrition and weight loss; the patient needs frequent medical examinations and hospitalizations^[52].

An easily usable tool to assess symptom severity is the Gastroparesis Cardinal Symptom Index (GCSI)^[52,60]. This consists of 9 items, grouped into three subscales: Nausea/vomiting, postprandial fullness/early satiety, and bloating, evaluated in the previous two weeks. A score from 0 to 5 for each item (where 0: "none or absent" and

Table 1 Conditions able to provoke gastroparesis

Conditions able to provoke gastroparesis
Diabetes mellitus
Post-surgical conditions (vagotomy or vagus nerve damage after fundoplication, esophagectomy, gastrectomy, pancreatectomy, Roux-en-Y gastric bypass, heart or lung transplant)
Connective tissue disease (including scleroderma, amyloidosis, Sjogren's syndrome, LES, polymyositis/dermatomyositis)
Eosinophilic gastroenteritis; infiltrative enteritis
Eating disorders (anorexia nervosa or bulimia)
End-stage renal disease
Hypothyroidism
Infectious diseases (recent viral infection by CMV, EBV, VZV; Chagas disease)
Malignancy (pancreas, lymphoma, paraneoplastic syndrome)
Mesenteric ischemia
Myopathies and muscular dystrophies (myotonic dystrophy, Duchenne muscular dystrophy)
Nervous system disorders (myasthenia gravis, Parkinson's disease, Guillain Barre syndrome, multiple sclerosis, dysautonomia)
Stroke

LES: Low esophageal sphincter; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; VZV: Varicella zoster virus.

5: "very severe") is assigned by the patient. The total score is calculated as the average of the scores of the each subscale and a higher score corresponds to a higher severity of the clinical manifestations.

In Gp a strong correlation between the severity of symptoms and the degree of the delay of gastric emptying and the level of psychological distress has been observed^[60].

PHYSICAL EXAMINATION

This includes the recording of vital parameters, weight, height, and calculation of the Body Mass Index. In order to assess the state of hydration and nutrition, attention should be paid to the skin and mucosae. Skin examination could also detect the presence of characteristic features of connective tissue diseases (microstomia, telangiectasias and sclerodactyly). Any abdominal surgical scars should be evaluated. The presence and the degree of abdominal distension and tenderness must be evaluated^[38].

LABORATORY TESTS

The initial assessment consists of basic laboratory tests: *i.e.* complete blood count, electrolytes, glucose, thyroid stimulating hormone, creatinine and urea. In the case of diabetes the assessment of hemoglobin A1c values is mandatory. The evaluation of serological nutritional markers are relevant in underweight and malnourished patients. The assessment of specific antibodies are necessary if there is suspicion of autoimmune diseases^[38].

INSTRUMENTAL TESTS

These are mandatory in order to rule out organic causes and/or to detect the presence of a gastric emptying delay and its severity. It is important to underline that before undergoing an evaluation of gastric emptying drugs able to slow down (*e.g.* opioids and anticholinergics) or accelerate (*e.g.*, prokinetics and erythromycin) gastric emptying should be discontinued at least 48-72 h in advance. In diabetic patients, special attention should be paid to the control of blood glucose levels, as hypoglycaemia and hyperglycaemia are associated with accelerated and delayed emptying, respectively. Current guidelines suggest that the patient should not be tested if blood sugar levels are greater than 275 mg/dL^[37,51,61,62].

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy rules out organic diseases and may detect the presence

Table 2 Medications and drugs able to delay gastric emptying

Medications and drugs able to delay gastric emptying
Alcohol
Aluminum hydroxide antacids
Anticholinergics
Antipsychotics
Beta-adrenergic receptor agonists (beta-agonists)
Calcitonin
Calcium channel blockers
Cyclosporine
Dexfenfluramine
Diphenhydramine
Glucagon hydrochloride and glucagon-like peptide-1 analogs
H ₂ -receptor antagonists
Octreotide acetate
Opioids
Peginterferon alfa (interferon alfa)
Progesterone
Proton pump inhibitors
Sucralfate
Tobacco
Tricyclic antidepressants

of food in the stomach, suggesting ineffective antral motility. However, finding retained food in the stomach should not be considered as an automatic diagnosis of Gp, but simply suggesting a delayed gastric emptying because some of these patients may have normal gastric emptying when scintigraphy is performed: This finding seems to be related to a pattern of preserved postprandial antral motility with an abnormal interdigestive antral motility, which delays gastric emptying between meals^[38,51,52,61].

Double-contrast upper gastrointestinal radiography

This can be considered alternative or complementary to esophagogastroduodenoscopy and can more accurately demonstrate the presence of a hiatal hernia and/or an obstruction of the small intestine. The radiographic features that may suggest a diagnosis of Gp are: Reduced or absent peristalsis, gastric dilatation, retention of gastric content and delayed gastric emptying of barium. However, it cannot replace scintigraphy (see below) in evaluating gastric emptying because barium is an inert material and it does not have the same physical-chemical features of food. The main information provided is approximately how long the barium takes to leave the stomach, but at present there are no reference values for healthy subjects and it is not possible to calculate the exact fraction of barium leaving the stomach per unit of time^[38].

Gastric emptying scintigraphy

Gastric emptying scintigraphy (GES) provides a reliable assessment of gastric emptying. It is currently considered the “gold standard” to establish the diagnosis of Gp. A technetium 99 m-labeled meal is offered to the patients and serial gamma camera scans are taken to evaluate the transit of the meal through the upper gastrointestinal tract. A low-fat, solid-phase meal consisting of egg whites, jam, toast, and water is recommended by the Society of Nuclear Medicine and by the American Neurogastroenterology and Motility Society. The meal is ingested after an overnight fast and scans are performed at 0, 1, 2, and 4 h. Results are reported as retention percentage at 2 h and 4 h^[37]. Alternatively, results may be reported as 50% emptying (T1/2)^[61]. It is generally accepted that > 60% gastric retention at 2 h and/or > 10% at 4 h is considered abnormal^[37,62]. Even though GES is considered the gold standard for Gp^[30], differences are reported regarding the suggested meal contents, the variability of the image timing, and the differences of the parameters used for the assessment of gastric emptying. These differences have inevitably provoked some conflicting results and/or difficulties in interpreting and comparing data coming from different

Table 3 Diseases and conditions to be considered in the differential diagnosis

Diseases and conditions to be considered in the differential diagnosis
Angiotensin-converting enzyme inhibitor-related visceral angioedema
Antipsychotic-induced dysmotility
Cannabinoid hyperemesis syndrome
Chronic pancreatitis
Cyclic vomiting syndrome
Dumping syndrome
Eating disorders, such as anorexia nervosa and bulimia nervosa
Functional dyspepsia
Gastric tumors or other malignancies
Gastric outlet or small-bowel obstruction
Gastroesophageal reflux disease
Helicobacter pylori infection
Median arcuate ligament syndrome
Peptic ulcer disease
Rumination syndrome
Small intestinal bacterial overgrowth syndrome
Superior mesenteric artery syndrome

centres^[61]. The evaluation of the emptying of only liquids is associated with a reduction in diagnostic sensitivity because liquids may empty the stomach normally in patients with solid food retention (false negatives). Moreover, liquid retention does not seem to be correlated with the presence or severity of Gp^[62], whereas the simultaneous measurement of gastric emptying of liquids and solids confers a greater sensitivity in the diagnosis (increase of sensitivity: 25%-36% in non-diabetic patients). Finally, a mild risk of radiation exposure has to be highlighted and consequently some caution should be used in carrying out scintigraphy in paediatric age and in pregnancy^[62].

Gastric emptying breath test

A possible alternative test to GES is the ¹³C-octanoic acid gastric emptying breath test (GEBT), a simple and low cost test which is increasingly widespread due to the availability of the equipment used also for the detection of *Helicobacter pylori* infection. First developed by Ghoo and colleagues in 1993^[63], the diagnostic kit approved by the Food and Drug Administration (FDA) is made up of a 238-kcal meal (41% fat) consisting of ¹³C-*Spirulina platensis* (a pharmaceutical grade, edible blue-green alga enriched with the stable 13-carbon isotope), scrambled egg, 6 saltine crackers and 180 mL of water^[38]. The patient ingests the meal after at least 8 h of fasting and then samples of exhaled air are collected on which the ratio of ¹²C to ¹³C is calculated by mass spectrometry at baseline and at 45, 90, 120, 150, 180, and 240 min^[33-35]. This ratio is used to calculate the percent dose excreted multiplied by 1000, also termed kPCD. The amount of ¹³C in the exhaled air is proportional to the gastric emptying rate. Gp is diagnosed if the kPCD values are below the cut off points at 90, 120, or 150 min, and the maximum excretion rate is shifted toward the 240-min time point compared to reference values. GEBT is easy to use and does not involve radiation exposure. The main disadvantage is that it indirectly estimates gastric emptying because the values of excreted ¹³C also depend on the rate of digestion and intestinal absorption of the meal and on gaseous lung exchanges. Therefore, it is considered unreliable in patients with pancreatic insufficiency, malabsorption and chronic obstructive pulmonary disease^[38,61,64-68].

Wireless motility capsule

The wireless motility capsule (WMC) is an FDA-approved device for studying gastric emptying, consisting of a 2.6 mm diameter ingestible capsule. It is able to record temperature, pH and pressure, which are transmitted to a wireless receiver worn by the patient. The capsule is evacuated after 2-5 d and the recorded data are then analyzed. The time of persistence in the stomach, also defined "retention time", is obtained by evaluating when the pH changes passing from the gastric antrum to the duodenum. A gastric retention time of more than 5 h is used to define delayed gastric emptying^[69]. To avoid false positive and false negative results the patient must strictly

follow a preparation protocol before undergoing the test: Gastric acid secretion inhibitors should be discontinued (proton pump inhibitors one week before and H₂ blockers three days before); drugs affecting gastric motility should be discontinued three days before; tobacco and alcohol should be avoided 8 and 24 h before the test, respectively^[58]. The patient, in a fasting state, eats a 260 kcal nutrient bar (2% fat) immediately before the capsule^[69].

Although gastric emptying measured by the WMC and GES are highly correlated ($r = 0.73$), a higher proportion of severe gastric emptying was reported by using WMC than GES with a higher diagnostic yield compared to GES in non-diabetic patients^[38]. This is probably due to the fact that these two techniques do not measure identical parameters. Although both depend on the rate of meal emptying, the WMC uses an indigestible object, whose gastric emptying is facilitated by the return of phase III activity of the migrating motor complex (MMC)^[70]. Hence, the WMC could have an increased sensitivity for detecting Gp because it measures gastric emptying time, impaired MMC, and dyscoordination of gastric and small bowel motility, whereas GES evaluates only meal emptying^[66]. The WMC does not involve any radiation exposure and it has the ability to detect a delayed transit of the small and large bowel, unlike GES. However, at present, it cannot be considered as the first choice in studying Gp due to its cost and scarce availability in many countries. The main contraindications are the presence of gastrointestinal strictures and of electrical devices such as a cardiac pacemaker or gastric stimulator^[37,38,69].

Gastric emptying of radiopaque markers

Gastric emptying of radiopaque markers measures gastric emptying using multiple small indigestible solid particles. This procedure is economical and widely available, but it has a low diagnostic reliability compared to GES and the GEBT^[68].

Electrogastrography

Electrogastrography (EGG) is the cutaneous recording of gastric electrical activity made by electrodes positioned along the long axis of the stomach^[7]. A 45-60 min preprandial recording is obtained, then the patient eats a 500 Kcal meal followed by a new recording period. EGG evaluates the rhythm of the gastric slow waves, which trigger the antegrade antral peristaltic waves. The normal slow wave frequency is 2.4-3.6 cycles per min. Gastric dysrhythmias include preprandial and/or postprandial tachygastria (3.6-9.9 cycles per min), bradygastria (0.9-2.4 cycles per min) or tachybrady-gastria^[71]. A lower percentage of normal gastric slow waves and a higher percentage of time in which gastric dysrhythmia is recorded are features that may predict delayed gastric emptying^[72-74]. Dysrhythmias have been described in patients with both idiopathic and diabetic Gp and up to 75% of patients with Gp have EGG abnormalities. Usually, those who have EGG alterations complain of more severe symptoms and EGG could be useful to identify subgroups of patients deserving therapies aimed at treating specific rhythm disturbances^[71]. Using abdominal skin electrodes, EGG is subjected to motion artifacts and electrical interferences from other internal organs. Therefore, it is of paramount importance to develop reliable methods to correctly measure gastric myoelectrical activity^[74].

Recently Poscente *et al*^[75] suggested a new method for EGG recording with enhanced patient preparation by swallowing a self-expandable, self-disintegrable pseudobesoar capsule containing a miniature electronic oscillator.

At present the role of EGG in the clinical workup of gastroparesis is still undefined and it is not routinely used, being mainly carried out in patients enrolled in diagnostic and therapeutic research trials.

Antroduodenal manometry

This provides an important overview of gastric and duodenal motility. In normal conditions, during the phase III of the MMC an integrated peristaltic wave is produced, allowing the progression of gastric contents from the stomach to the duodenum.

Food ingestion is the trigger that starts the regular antral and duodenal rhythm inducing antegrade food progression. In the interdigestive phase, the MMC is repeated about every 2 h while in the postprandial phase the stomach shows an activity characterized by three cycles/min contractions and the duodenum displays a 12 cycles/min activity.

Two mechanisms have been mainly identified that contribute to the failure of gastric emptying: Antral hypomotility, and duodenal dysmotility, causing resistance to the gastric emptying. In some cases, the presence of phase III MMC potentials that begin in the duodenum instead of starting in the stomach has been demonstrated. In diabetic patients, antroduodenal manometry showed tonic and phasic pylorospasm and abnormal contractions of the small intestine^[71].

Furthermore, antro-duodenal manometry distinguishes myopathic disorders (such as systemic sclerosis or amyloidosis) from neurological disorders. Myopathic changes are characterized by low amplitude contractile activity, whereas neurological disorders are characterized by regular waves' amplitude, but with abnormalities characterized by the loss of phase III of the MMC and by the onset of random bursts of activity^[71].

The diagnostic work up of a patient with suspected Gp is reported as a flow chart in [Figure 1](#).

TREATMENT OF GASTROPARESIS

The hallmarks of therapeutic management are symptom control, correction of nutritional deficiencies, maintenance of an optimal weight, and identification and treatment of causes of delayed gastric emptying (*e.g.* diabetes, drugs), when possible. Although delayed gastric emptying is, by definition, a unifying finding in all patients with Gp, accelerating or normalizing gastric emptying may not improve symptoms. The therapy of Gp relies on dietary modification, prokinetic drugs, antiemetic agents and, possibly, psychotropic agents able to reduce symptom expression. In case of failure of the pharmacological approach, several alternative strategies (endoscopy, electric stimulation or surgery) are available for the management of unresponsive patients^[1,78]. [Table 4](#) summarizes the therapeutic resources and strategies related to Gp severity.

Nutritional approach

A comprehensive diet history should be obtained and foods that seem to aggravate Gp should be avoided. The dietetic approach usually consists of multiple small meals and should be limited in fat and fiber content, which can delay gastric emptying. In patients with weight loss and malnutrition the use of multivitamin or vitamin supplementation might be needed. Alcohol and smoking should be avoided because they can both modify gastric emptying^[76].

In diabetic Gp, the aim should be directed toward normalization of glycemic control with a diet and hypoglycemic drugs, in order to improve gastric emptying. In fact, poor glycemic control inhibits gastric emptying and even interferes with emptying tests. Especially in type 1 diabetics, blood glucose levels between 288 and 360 mg/dL and acute hyperglycemia have been shown to inhibit both solid and liquid emptying^[43]. In mild Gp, maintaining oral nutrition is the goal of therapy, while in severe disease conditions enteral or parenteral nutrition may be needed.

In cases of inadequate nutrient intake, enteral feeding through a nasoduodenal tube should be considered. This enables the patient to gain weight and to improve their nutritional status. Enteral nutrition should start slowly at 25 to 50 mL/h using feeds consisting of 1.5 calories per mL, with further progressive increases of 10 to 25 mL/h. Complications of nasojejunal feeding include infection, tube migration, and dislodgement^[37].

If a prolonged enteral nutrition is necessary, a direct access to the stomach or preferably to the jejunum (percutaneous endoscopic transgastric jejunostomy) should be created. Placement of a jejunal feeding tube should be preceded by a successful trial of nasojejunal feeding. In any case, enteral feeding should be the approach preferred to total parenteral nutrition, which should be avoided if possible. Total parental nutrition can in fact prompt various complications such as infections, access problems, and thrombosis.

PHARMACOLOGICAL THERAPY

Prokinetics

Antidopaminergic agents: Metoclopramide, a dopamine D2 receptor antagonist, has both antiemetic and prokinetic properties. It is the only medication specifically approved by the FDA for the treatment of Gp^[1,7,8]. Clinical studies have shown that, compared to placebo, metoclopramide decreases delayed emptying during scintigraphy and ameliorates gastroparetic symptoms. The drug is available as an intravenous, intramuscular, oral, and liquid form. Clinical guidelines recommend beginning with 5 mg 3 times a day 30 min before meals with a maximum dose of 40 mg a day^[37]. Due to the blood-brain barrier crossing, the use of metoclopramide is often limited by undesired side effects. These range from mild sedation and agitation, to extrapyramidal effects. For this reason its use should be limited to 12 wk to avoid tardive dyskinesia, although this risk is believed to be relatively small (< 1%).

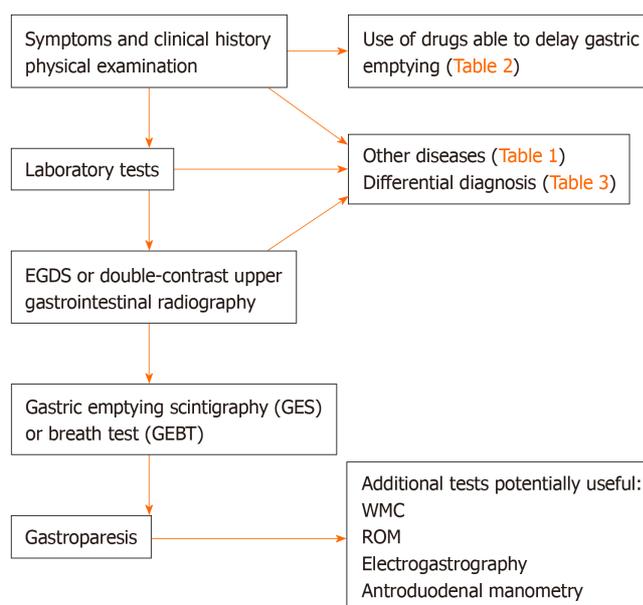


Figure 1 Diagnostic flow chart (modified from Szarka *et al.*^[36]). EGDS: Esophagogastroduodenoscopy; WMC: Wireless motility capsule; ROM: Gastric emptying of radiopaque markers.

Increases in prolactin stimulation from dopamine antagonism can also cause galactorrhea and menstrual irregularities in women^[37,43].

Domperidone is another dopamine receptor antagonist with the same efficacy, but with fewer extrapyramidal side effects compared to metoclopramide, since it does not cross the blood-brain barrier. It exerts the major effects on nausea and vomiting. The recommended starting dose is 10 mg 3 times a day with an increase to 20 mg 4 times a day, including bedtime^[35]. The main side effect is QT prolongation and the drug should not be administered if the corrected QT is longer than 470 ms in males and 450 ms in females. For this reason domperidone is available in the United States only through a FDA investigational drug application. Domperidone may also increase prolactin levels and result in galactorrhoea.

Finally, phenothiazines (*e.g.* prochlorperazine and chlorpromazine), generally used as antipsychotic agents, inhibit D1 and D2 receptors in the brain, leading to antiemetic effects and they can be considered a second line approach in Gp. Phenothiazines have potential extra-pyramidal side effects^[77].

Motilin agonists: Erythromycin, a macrolide antibiotic, is a motilin agonist that enhances gastric emptying, increases antral contractions and antroduodenal coordination, and reduces fundic volume and compliance in health and disease, although the effects on gastrointestinal symptoms remain controversial. It is commonly used off-label in Gp^[7,8,37,77]. Hospitalized patients can be treated with intravenous erythromycin at a dosage of 3 mg/kg every 8 h. For outpatients, oral doses of 50 to 100 mg 4 times a day given 30 to 45 min before each of the 3 main meals and at bedtime may be suggested. Unfortunately, long-term use of erythromycin is limited because of the onset of bacterial resistance and tachyphylaxis. Problems with cytochrome P450 interactions can also limit its use and carries a risk of sudden cardiac death.

Another macrolide antibiotic, Azithromycin, has been shown to be as effective as Erythromycin, but without the cardiac risk and cytochrome interactions^[43]. Camicinal, another motilin receptor agonist, has been shown to improve gastric emptying in diabetic Gp without a decrease in response after 28 d of use^[77].

5HT₄-receptor agonists: Cisapride is a 5HT₄ receptor agonist that increases antral contraction and improves gastric emptying. It was initially approved by the FDA but was subsequently withdrawn in 2000 due to cardiac arrhythmias caused by QT prolongation. Tegaserod, also a 5HT₄ agonist, proposed in the treatment of irritable bowel syndrome with constipation, can be potentially useful in Gp and without effects on QT prolongation. One study in critically ill patients with impaired motility showed that tegaserod was effective within 24 h of administration. In a preliminary study, Carbone *et al.*^[78] demonstrated the efficacy of prucalopride, a 5HT₄ agonist tailored for chronic constipation. Another 5HT₄ agonist, Velusetrag (15, 30 or 50 mg daily), administered to patients with chronic idiopathic constipation for 4 wk, was

Table 4 Therapeutic strategies

	Mild gastroparesis	Moderate gastroparesis	Severe gastroparesis
Diet and nutritional support	Adequate oral nutrition Small frequent meals; Low fat, low fibre; Glycemic control in diabetics	Disturbed oral nutrition Small, frequent meals; Low fat, low fibre; Glycemic control in diabetics; Caloric liquids; Artificial nutrition rarely required	Compromized oral nutrition Liquid nutrient supplements; Nutrition by PEG-J
Prokinetics	Metroclopramide; Domperidone; Levosulpiride	Metroclopramide; Domperidone; Levosulpiride	¹ Metroclopramide; Domperidone; ¹ Levosulpiride; ¹ Erythromycin; Prucalopride
Antiemetics and symptom modulators	Rarely needed	Ondansetron	¹ Ondansetron; Tricyclic antidepressant; Cannabinoids Drug-refractory patients
Endoscopic techniques	Not needed	Not needed	Botulin toxin; Transpyloric stenting; Ballon dilatation; G-POEM
Gastric electrostimulation	Not needed	Not needed	Compassionate use
Gastric procedures	Not needed	Not needed	Laparoscopic Pyloroplastic

¹Available for intravenous administration. PEG-J: Percutaneous endoscopic transgastric jejunostomy; G-POEM: Gastric peroral endoscopic myotomy.

well tolerated and accelerated gastric emptying after 4–9 days of treatment^[76].

Finally, levosulpiride, a prokinetic 5HT₄ agonist/D₂ antagonist, can be used to improve gastric emptying in patients with dyspepsia and diabetic or idiopathic Gp. Due to dopamine antagonism, prolactin can be stimulated by levosulpiride and cause galactorrhea and menstrual irregularities in women^[79].

Ghrelin agonists: Ghrelin is an endogenous peptide produced by the endocrine cells of the stomach. It increases food intake and is also involved in stimulation of phase III of the MMC. Relamorelin is a potent synthetic ghrelin agonist. It has been shown to improve gastric emptying half-time and GCSI scores in diabetic patients with Gp. In a 4 wk phase II study in type 1 diabetic patients, relamorelin accelerated gastric emptying and reduced upper gastrointestinal symptoms in patients with vomiting^[78,77]. A recent meta-analysis confirmed that, compared with placebo, ghrelin agonists are effective and well-tolerated for the treatment of diabetic Gp^[80].

Agents active on gastric accommodation: Acotiamide, a muscarinic antagonist and an acetylcholinesterase inhibitor, has been shown to be effective in functional dyspepsia. It enhances gastric accommodation and emptying and relieves dyspeptic symptoms. It is approved in Japan for treatment of functional dyspepsia. At present no studies using acotiamide in the treatment of Gp are available^[81].

Symptom modulators

5-HT₃ receptor antagonists are commonly used off-label for the treatment of nausea and vomiting in patients with Gp. Ondansetron is available in both parenteral and enteral forms, while granisetron is available only in a transdermal form. Transdermal granisetron (3.1 mg/24 h) has been seen to be effective in decreasing symptom scores in patients with refractory Gp^[77].

Tricyclic antidepressants can be considered in patients with Gp with refractory nausea and vomiting even if one placebo-controlled, randomized trial carried out in 130 Gp patients showed no difference between the nortriptyline group and placebo^[77]. Tricyclic antidepressants could however be considered as an off label option to treat pain related to Gp, although they have the potential to delay gastric emptying. Furthermore, an open-label study of mirtazapine, an antidepressant with central adrenergic and serotonergic activity, found improvements in nausea, vomiting, and loss of appetite in patients with Gp^[82].

Synthetic cannabinoids (*e.g.*, dronabinol, nabilone) are approved for the treatment of nausea and vomiting associated with chemotherapy, but their use in Gp is controversial. In a recent population study, a third of patients with Gp symptoms actively used cannabinoids, with the majority of them perceiving an improvement^[83]. However, it should also be taken into account that these agents have the potential to worsen gastric emptying and Gp symptoms.

Aprepitant, a neurokinin antagonist approved for the treatment of nausea and vomiting associated with chemotherapy, was effective in the treatment of nausea in patients with Gp^[84].

Endoscopic management

Botulinum toxin: As already mentioned, delayed gastric emptying in Gp can be associated with pylorospasm. Botulinum toxin directly inhibits smooth muscle contractility, as shown by a decreased contractile response to acetylcholine. An open-label study using intrapyloric botulinum type A toxin showed a decrease in Gp symptoms at 1–4 mo in 51.4% of patients. There was greater benefit observed with a 200-unit compared to a 100-unit dose, in females, in patients < 50 years, and in idiopathic Gp. Two double-blind studies showed an improvement in gastric emptying and symptoms compared to placebo. However, botulinum toxin injections may provide only temporary relief, lasting 3 mo on average^[7,8,85].

Transpyloric stenting: The efficacy of an expandable metal transpyloric stent has been tested in small, open-label studies, typically in patients with refractory Gp^[7,8,85,86]. The best results were obtained when the stent was anchored with endoscopic suturing, avoiding stent migration. Greater clinical and gastric functional results were achieved in patients with adequate follow-up and a better response was observed in nausea and vomiting than in pain.

Balloon dilatation of the pylorus: A balloon 20 mm in diameter and 5 cm in length passed into the pyloric channel under direct vision is an alternative endoscopic technique. The balloon is inflated to 20 mm diameter with 50 mL of water for 2 min and then deflated and removed. Clinical and scientific evidence is however limited. An open-label study showed an improvement of symptoms in 4 out of 8 Gp patients and the need for repeated endoscopic treatments^[86].

Gastric per-oral endoscopic myotomy: Based on positive results with per-oral endoscopic myotomy (POEM) in the management of esophageal achalasia, a minimally invasive method termed “per-oral pyloromyotomy” or “gastric POEM” (G-POEM) has been recently introduced. Over the last few years, some observational studies and case reports have shown promising results of G-POEM in the treatment of refractory Gp. Seven studies with a total of 196 patients with refractory Gp were included in a recent meta-analysis^[87]. After the procedure, mean GCSI values at 5 d and mean values of gastric emptying at 2–3 mo significantly decreased.

G-POEM had clinical success in treating refractory Gp in another recent systematic review with meta-analysis. Idiopathic Gp, prior treatment with botulinum injections and gastric stimulator appear to be positive predictive factors and clinical outcomes seem comparable to surgical pyloroplasty^[88].

Gastric electric stimulation

Gastric electrical stimulation was developed to enhance gastric emptying by means of a high frequency stimulation that appears to interfere with sensory transduction to the brain. Gastric electrical stimulation has been approved by the FDA for the compassionate treatment of intractable nausea and vomiting secondary to diabetic or idiopathic Gp in patients aged 18–70 years after failure of pharmacologic treatments^[89]. A moderate effectiveness of this treatment was reported in 43% of 151 unresponsive patients from a single center. In any case, two systematic reviews and meta-analyses suggest caution in recommending gastric electrical stimulation outside of research studies^[7].

Surgical procedures

Pyloroplasty may relieve symptoms in gastroparetic patients who are unresponsive to other treatments and is often combined with jejunal tube placement to support nutrition. Recently, laparoscopic pyloroplasty showed normalization of gastric emptying in 60% of cases and significantly reduced symptom severity in a retrospective study involving 46 patients^[90]. Subtotal gastrectomy with Roux-Y reconstruction may be instead needed for gastric atony secondary to post-surgical Gp.

CONCLUSION

Gp is a relatively frequent and still poorly known clinical condition, often causing considerable distress and an impaired quality of life. Considerable efforts have been devoted in recent years to a better understanding of its pathophysiological mechanisms. However, the results obtained so far are still unsatisfactory and further evidence is needed to fully understand the basic mechanisms of this disorder, in order to have better options for a more targeted and effective therapeutic approach.

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