

# Management of Gastric Motility Disorder

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## **ABSTRACT**

*Gastric motility disorder or gastroparesis is an objective slowing of gastrointestinal emptying syndrome, in the absence of mechanical obstruction, with cardinal symptoms such as rapid feeling of fullness, fullness sensation after eating, nausea, vomiting, bloating, and upper abdominal pain. Patients with gastroparesis are at risk of weight loss, malnutrition, and lack of vitamins and minerals, as well as increasing morbidity and mortality. The prevalence and incidence data of gastroparesis do not describe the true reality, because of the complexity of diagnosis. Beside Diabetes mellitus, many other causes should also be considered. Several studies have shown that nausea, vomiting and fullness sensation in abdominal are the most associated symptoms with gastroparesis. A 4-hour solid phase gastric emptying scintigraphy is the diagnostic standard for the slowing of gastric emptying. Lowest effective dose metoclopramide starting with a dose of 3 x 5 mg is the first line for pharmacological therapy. For persistent or refractory gastroparesis with pharmacologic therapy, gastric electrical stimulation (GES) and surgical therapy may be considered. The management should involve relevant medical team by not forget to consider patient comfort.*

***Kata kunci:*** *impaired gastric motility, gastroparesis, slowing of gastric emptying*

## **ABSTRAK**

*Gangguan motilitas lambung atau gastroparesis adalah sindrom perlambatan pengosongan lambung secara obyektif, tanpa adanya obstruksi mekanis, dengan gejala kardinal seperti cepat merasa kenyang, rasa penuh setelah makan, mual, muntah, kembung, dan nyeri perut bagian atas. Pasien dengan gastroparesis berisiko mengalami penurunan berat badan, kekurangan gizi, dan kekurangan vitamin dan mineral, serta meningkatkan morbiditas dan mortalitas. Data prevalensi dan insidensi dari gastroparesis tidak menggambarkan realita sesungguhnya, karena cukup rumitnya penegakan diagnosis. Tidak hanya Diabetes mellitus, banyak penyebab lain juga harus dipikirkan. Beberapa studi menunjukkan mual muntah dan rasa penuh pada perut merupakan gejala yang paling berkaitan dengan gastroparesis. Pemeriksaan skintigrafi pengosongan lambung fase padat selama 4 jam merupakan standar baku untuk diagnostik perlambatan pengosongan lambung. Metoclopramide dosis efektif terendah dimulai dengan dosis 3 x 5 mg merupakan lini pertama untuk terapi farmakologis. Untuk gastroparesis persisten atau refrakter dengan terapi farmakologis dapat dipertimbangkan gastric electrical stimulation (GES) dan terapi pembedahan. Tata laksana harus melibatkan tim medis terkait dengan tidak lupa mempertimbangkan kenyamanan pasien.*

***Kata kunci:*** *gangguan motilitas lambung, gastroparesis, perlambatan pengosongan lambung*

## INTRODUCTION

Gastric motility disorder including gastroparesis are chronic abdominal motility abnormalities characterized by a slowing of gastric emptying.<sup>1</sup> Symptoms include rapid feeling of fullness, fullness sensation after eating, abdominal distension, nausea, and vomiting. Patients with gastroparesis may have eating-related symptoms, resulting in reluctance to eat and inadequate oral intake. Some patients experience prolonged nausea and vomiting, which make it difficult to maintain hydration and nutritional status. Thus, patients with gastroparesis are at risk of weight loss, malnutrition, and deficiencies of vitamins and minerals.<sup>2</sup>

Gastroparesis significantly affects quality of life, increases health care costs through inpatient care, emergency room, or physician visits, and is associated with morbidity and mortality.<sup>3</sup> Based on data in the United States Medicare on hospitalization related to gastroparesis in the United States from 1995 to 2004, it showed that hospitalization for gastroparesis has increased since 2000.<sup>4</sup>

Studies by Hyett et al regarding the slowing of gastric emptying predict negative health outcomes in diabetic patients with gastroparesis symptom. In this study, it was found that diabetic patients with gastroparesis complications used a significantly greater amount of health resources than non-gastroparesis diabetic patients. There are significant differences in the amount of health care usage, including inpatient rates, outpatient visits, sick days, ED visits, and frequency of treatments.<sup>5</sup> Gastrointestinal symptoms negatively affected health-related quality of life in patients with diabetes mellitus.<sup>6</sup>

## DEFINITION

Normal or peristaltic motility is ordered regular muscle contraction from top to bottom. Functional dyspepsia (non-ulcer dyspepsia): Abnormal gastric accommodation reflex or decreased fundal relaxation may lead to functional dyspepsia. The patients' symptoms are including pain or discomfort and bloating in the upper abdomen, fullness and nausea.<sup>7</sup> Gastroparesis is defined as objective slowing of gastrointestinal emptying syndrome in the absence of mechanical obstruction and cardinal symptoms including rapid feeling of fullness, fullness sensation after eating, nausea, vomiting, bloating, and upper abdominal pain.<sup>3</sup>

## EPIDEMIOLOGY

The high prevalence of gastroparesis have been reported in patients with type 1 diabetes (40%) and type 2 diabetics (10-20%). The study came from a tertiary academic medical center where the prevalence is estimated to be higher than the general population. Prevalence in the community is estimated to be ~ 5% among type 1 diabetics and 1% among type 2 diabetics.<sup>3</sup> On January 1<sup>st</sup> 2007, the means of age-adjusted prevalence of gastroparesis per 100,000 people were 24.2 (95% CI: 15.7-32.6) for both sexes, 9.6 (95% CI: 1.8-17.4) for men, and 37.8 (95% CI: 23.3-52.4) for women. The incidence rates corresponding for 1996-2006 were 2.4 (95% CI: 1.2-3.8) for men and 9.8 (95% CI: 7.5-12.1) for women.<sup>4</sup>

## PATHOPHYSIOLOGY

Gastrointestinal motility disorder consists of impaired gastric accommodation, antroduodenal incoordination, and slowing of gastric emptying. Gastrointestinal motility disorder is one of the major mechanisms in the pathophysiology of functional dyspepsia, related to fullness sensation after eating, which may be abdominal distension, bloating, and fullness.<sup>8</sup>

Abnormal motility of the upper gastrointestinal tract involves functional abnormalities in the esophagus, stomach, and small intestine. There are three main components of functional gastrointestinal disorder: gastrointestinal motility or contraction, gastrointestinal tract sensations, and gastrointestinal brain dysfunction, all of which affect upper and lower gastrointestinal tract.<sup>7</sup>

In gastrointestinal functional disorder, muscle spasms can cause pain, or contractions could be very rapid or very slow, altering the speed or direction of gastrointestinal transit. Gastric nerves are sometimes so sensitive that even normal contractions can cause pain or discomfort in response to physiological stimuli, such as digesting food. The regulatory relationship between brain function and the gastrointestinal tract might be disrupted, causing disharmony in the way the brain and gastrointestinal systems communicate, altering the transit of luminal contents.<sup>7</sup>

## RISK FACTORS

Diabetes (29%), postoperative (13%), and idiopathic (36%) are the etiologies of most cases in tertiary referrals.<sup>1</sup> Diabetes accounts for about one-

third of all cases.<sup>5</sup> Longitudinal studies showed that the gastric emptying clearance encountered in 25-55% of patients with type 1 diabetes and about 30% of patients with diabetes type 2.<sup>9</sup> However, the real prevalence is unknown.<sup>5</sup> Furthermore, at least until some patients with long-standing diabetes, suffering from gastroparesis, remain mostly subclinical.<sup>9</sup>

In patients with refractory symptoms of gastroesophageal reflux disease (GERD), slowing of gastric emptying examination should be considered, as delayed gastric emptying may be associated with GERD and may exacerbate symptoms of ulcer disease, regurgitation, and other symptoms associated with GERD.<sup>3</sup>

## ETIOLOGY

### Idiopathic Gastroparesis

Patients with symptom of undetected slowing of gastric emptying, the primary abnormalities underlie the abnormal slowing of gastric emptying. This might be the most common form of gastroparesis. Most patients with idiopathic gastroparesis are women; usually young or middle aged. Symptoms of idiopathic gastroparesis overlap with functional dyspepsia; it may be difficult to give definitive differences between the two on the basis of symptoms, and many consider idiopathic gastroparesis and functional dyspepsia with slowing of gastric emptying as the same condition. Abdominal pain/discomfort is usually the main symptom of functional dyspepsia, whereas nausea, vomiting, full satiety, and bloating predominate in idiopathic gastroparesis. Therefore, the measurement of gastric emptying is very important, because therapy is different whether gastric emptying is slow, normal, or fast.<sup>3</sup>

### Postoperative Gastroparesis

Postoperative gastroparesis, often accompanied by vagotomy or vagal nerve injury, is the third most common etiology of gastroparesis. In the past, most cases originated from vagotomy performed in conjunction with gastric drainage to improve refractory or medically complicated peptic ulcers. Since the advent of laparoscopic techniques for the treatment of GERD, gastroparesis has been a known complication of fundoplication (possibly due to vagal injury during surgery) or bariatric surgery included in gastroplasty or bypass procedures.<sup>3</sup>

### Post-viral Infection Gastroparesis

Some patients with gastroparesis reported sudden onset of symptoms after viral prodromal symptoms, suggesting a possible viral etiology for their symptoms, and diagnosis of post-viral gastroparesis. Healthy subject has experienced sudden onset of nausea, vomiting, diarrhea, fever, and cramps which indicate systemic viral infections. However, instead of experiencing symptoms improvement, the individual is still experiencing persistent nausea, vomiting, and satiety. In general, the course of this disease is typical of post-viral gastroparesis which is not associated with autonomic neuropathy.<sup>3</sup>

On the other hand, a small proportion of patients with viral infections such as cytomegalo, Epstein Barr, and varicella zoster may develop into autonomic neuropathy (generalized or selective cholinergic disautonomia) that includes gastroparesis. Patients with this autonomic dysfunction may have a slower resolution of symptoms which may take several years and the prognosis is worse than post-viral gastroparesis without autonomic disorders.<sup>3</sup>

### Iatrogenic Gastroparesis

In addition to postoperative gastroparesis, other forms of iatrogenic gastroparesis are gastroparesis induced by pharmacological agents such as narcotic opiate analgesics, anticholinergic agents, and some diabetes drugs. Administration of  $\mu$ -opiate receptor agonists causes a slowing of gastric emptying and may also cause nausea and vomiting. This group includes agents such as morphine, as well as oxycodone and tapentadol, but less with tramadol. Therefore, patients receiving the drug should first undergo drug discontinuation before assuming a diagnosis of gastroparesis.<sup>3</sup>

GLP-1 analogue, like exenatide, used for the treatment of type 2 diabetes mellitus can slow gastric emptying. Unlike the GLP-1 analogue, which substantially increases plasma GLP-1 concentrations, dipeptidyl peptidase IV inhibitors, which increases plasma GLP-1 concentrations by inhibiting GLP-1 metabolism, does not slow gastric emptying.<sup>3</sup>

Antirejection drugs, cyclosporine, can slow gastric emptying. Thus, in patients with previous transplants treated with antirejection treatment with cyclosporine, there may be a slowing of gastric emptying. This does not apply to other calcineurin inhibitors, tacrolimus, derived from macrolide molecules and retains prokinetic properties.<sup>3</sup>

## Other Rare Etiologies

Other rare causes of gastroparesis include diseases which affect extrinsic neural control (such as Parkinsonism, amyloidosis, and paraneoplastic disease) or disorders that result in infiltration or degeneration of the muscle lining of the stomach (such as scleroderma). Mesenteric ischemia should also be considered a rare cause of possibly reversible gastroparesis.<sup>3</sup>

## SIGNS AND SYMPTOMS

Various symptoms of dyspepsia are common in patients with gastroparesis, such as nausea, vomiting, upper abdominal pain, abdominal distension and bloating. Individual symptoms generally have a low specificity to predict the delay in emptying. Flatulence has been reported to be significantly correlated with delayed emptying of diabetic gastroparesis. In another study, fullness after-meal was statistically associated with a slowing of gastric emptying. When gastroparesis is associated with weight loss and patients need nutritional support to maintain weight, it is considered a more severe form of gastroparesis.<sup>10</sup>

Abdominal pain is a symptom that is often overlooked in gastroparesis. In a multicentre study of the NIH consortium on gastroparesis, 72% of gastroparesis patients had abdominal pain, but were the dominant symptom in only 18% of patients, reflecting the heterogeneous population of patients in this group. A tertiary referral study showed that abdominal pain was reported in 90% of 68 patients with a slowing of gastric emptying. Pain induced by eating (72%), occurred at night (74%), and disturbed sleep (66%). The severity of abdominal pain is in the same range as other symptoms (such as fullness sensation, bloating, and nausea) and is not correlated with the level of gastric emptying, but is associated with decreased quality of life.<sup>3</sup>

Objectively, patients with abdominal symptoms significantly interfere with their quality of life, but there is no correlation between their symptoms and the level of gastric emptying. Future research should aim to investigate not only gastric emptying but also gastric accommodation and visceral hypersensitivity, as not all symptoms can be explained by the slowing of gastric emptying.<sup>11</sup> Female gender, relevant and severe fullness sensation after eating, and severe vomiting are independently associated with slowing of gastric emptying in patients with functional dyspepsia.<sup>12</sup> The presence of anxiety or depression has been associated with more severe symptoms.<sup>3</sup>

## DIAGNOSIS

There are three tests that can objectively demonstrate slowing of gastric emptying: scintigraphy, wireless motility capsule (WMC), and breath test. For all types of gastric emptying tests, patients should discontinue treatment that may affect gastric emptying. Both drugs which slow and accelerate gastric emptying should be discontinued, so that the tests do not give wrong results. Most drugs take time about 48-72 hours. Hyperglycemia (glucose levels > 200 mg/dL) may slow gastric emptying in diabetic patients. It is advisable to delay testing of gastric emptying until relative euglycemia levels (blood glucose < 275 mg/dL) is achieved in diabetics to obtain reliable emptying parameters in the absence of acute metabolic disorders.<sup>3</sup>

### Scintigraphy

Gastric emptying scintigraphy from solid-phase foods is considered a standard for the diagnosis of gastroparesis, as it measures the emptying of physiologic calorie foods. For solid phase testing, most centers use egg sandwiches labeled 99m Tc colloid as test food, with standard imaging at time of 0, 1, 2, and 4 hours. A 4-hour test of gastric emptying scintigraphy using EggBeaters (ConAgra Foods Inc., Omaha, NE, USA) with jam, toast and water is recommended by the Society of Nuclear Medicine and the American Neurogastroenterology and Motility Society.<sup>3</sup>

Assessment of gastric emptying for 4 hours is necessary. Emptying of solid foods with shorter duration or emptying of a single liquid food with scintigraphy, is associated with lower diagnostic sensitivity. The most reliable parameter for reporting gastric emptying is gastric retention at 4 hours. However, it is also important to assess the emptying at least 1 and 2 hours after the consumption of food with radiolabel, since elongation of the initial phase of emptying can also be attributed to the symptoms of gastroparesis, although retention of the stomach at 4 hours is normal or slightly slowed.<sup>3</sup>

### Wireless Motility Capsule (WMC)

WMCs which measure pH, pressure, and temperature can assess gastric emptying by measuring the transit time of the stomach acid of the capsule. Gastric emptying is determined when there is a rapid increase in pH which indicates the emptying of the acidic to the basic duodenal acids. The transit time in the stomach of the WMC (e.g., SmartPill, Given Imaging, Yoqneam, Israel) has an 85% high correlation

with T-90% gastric emptying scintigraphy (which is when there are only 10% of food left in the stomach), indicating that the transit time of the WMC represents the time towards the end of solid food emptying. The overall correlation between gastric emptying at WMC and gastric emptying at 4 hours with scintigraphy is 0.73. 5-hour gastric transit time of WMC is the best way to differentiate subjects with normal or slow gastric emptying based on skintigraphy performed concurrently with 83% sensitivity and 83% specificity.<sup>3</sup>

### Breath Test

Breath test has been used in clinical research to determine gastric emptying. This breath test using 13 C-octanoate or -spirulina gives reproducible results that correlate with results in gastric emptying scintigraphy, including response to pharmacologic therapy.<sup>3</sup>

### Electrogastrogram (EGG)

EGG is a diagnostic tool used to measure electrical control of gastric contractions. EGG often identifies the presence of dysrhythmias, particularly after meals, in patients with gastroparesis, chronic dyspepsia, anorexia nervosa and bulimia, cyclic vomiting syndrome, and other conditions characterized by slowing of gastric emptying. Dysrhythmias can be caused by abnormalities of the specialized muscle conduction system present in the stomach.<sup>7</sup>

EGG is similar to the electrocardiogram (EKG) of the heart, the EGG recording electrical signals that travel through the abdominal muscles that control muscle contraction. In addition, the EGG measures the neural activity of the stomach wall before and after food consumption, as well as conduction and coupling between muscle cells. The new EGG system records on four channels simultaneously, allowing complete collection of activity data over a short period of time.<sup>7</sup>

EGG is a non-invasive test, relatively inexpensive, and easy to do. Electrodes are placed on the abdominal skin above the stomach. While the patient is lying down, the electrodes record the electrical activity of the stomach. Initially, gastric activity is recorded after fasting, then again after a small meal. Sometimes EGG is performed simultaneously with or after gastric emptying study to diagnose and manage functional dyspepsia and idiopathic gastroparesis. By using computer analysis, the electric current power of the gastric muscle is measured. In normal gastric muscles, a regular electric rhythm produces an increase in the current after a meal. In people with irregular muscles

or nerves, the electrical rhythm after an irregular meal or a voltage does not increase.<sup>7</sup>

### Barostat Studies

Barostat studies measure the tone and stretching of the esophagus and upper stomach. It also measures gastric accommodation and stomach sensation. Barostat studies can show whether the upper stomach relaxes adequately during meals and how much stomach filling is needed to cause pain or discomfort. The intra-gastric balloon measures the resistance and volume changes. In some patients, barostat is used to diagnose GERD and GERD conditions which may be caused by altered esophageal and abdominal pressures. The advantage of barostat for gastrointestinal examination is close contact with the abdominal wall. The manometric test can accurately detect abdominal wall contractions in the esophagus, pylorus and small intestine. But it does not accurately measure gastrointestinal tone.<sup>7</sup>

### Manometry

The pylorus manometry can measure the pyloric pressure by using water-perfused Dent Sleeve or e-sleeve from a high-resolution manometric system. The contribution of pylorus to gastric emptying disorders can be measured and treated promptly. Antroduodenal manometry measures pressure waves in the stomach and adjacent small intestine before and after physiological stimuli (eg food, erythromycin), and notes changes in antrum and duodenum pressure so that it can give information about how well the muscles and nerves in the stomach and small intestine work. The manometric catheter is placed in the stomach and small intestine. Catheter records muscle signals and pressure changes in fasting states and also when food or fluids are digested. Antroduodenal manometry notes muscle contraction and initiation site, propagation direction, frequency, and duration.<sup>7</sup>

### Differential Diagnosis

Secondary gastritis due to *Helicobacter pylori* infection, peptic ulcer, and functional dyspepsia are some of the differential diagnoses of gastroparesis. Because rapid gastric emptying and functional dyspepsia may also occur with symptoms similar to gastroparesis, evidence of a retardation of gastric emptying is required before selecting therapy.<sup>3</sup>

Patients with unresolved vomiting may have gastroparesis rather than functional dyspepsia and should be investigated appropriately. We felt that a

solid phase 4-hours gastric emptying scan should be performed in functional dyspepsia patients with symptoms of predominantly severe nausea and vomiting which failed with empirical therapy.<sup>13</sup> Patients with functional dyspepsia with persistent nausea and vomiting may have marked gastric emptying retardation.<sup>14</sup>

The presence of rumination syndrome and/or eating disorders (including anorexia nervosa and bulimia) should be considered when evaluating gastroparesis patients. This disorder may be associated with a slowing of gastric emptying, and the identification of these disorders may alter management. Cyclic vomiting syndrome defined as episodic episodes of recurrent nausea and vomiting should also be considered during the patient's history taking. These patients may require other alternative therapies.<sup>3</sup>

### CLINICAL APPROACH

The American Journal of Gastroenterology has given recommendation of step by step approach algorithm for the management of gastroparesis (Figure 1 and 4).<sup>3</sup>

### MANAGEMENT

Recent management of gastroparesis is unsatisfactory and this is an unmet need and an opportunity for the pharmaceutical industry to develop.<sup>15</sup>

#### Nutrition

Dietary management is often the first step in treating gastroparesis patients. Current dietary recommendations for gastroparesis patients include suggestions which compensate for the disturbance of gastric emptying by consuming low-fat and low-fibre meal, because fat and fiber can slow gastric emptying. To maintain caloric intake, it is recommended to eat in small quantities and often.<sup>16</sup>

In the study by Parkman et al, only 32% of patients received nutritional/dietary consultation after their gastroparesis diagnosis. This suggests that dietary history and treatment are often neglected in patients with gastroparesis. Nutrition consultation is more common in sicker and hospitalized patients. It is interesting that diabetic patients with gastroparesis tend to be less likely to have micronutrient deficiencies, this may reflect an increase in dietary education they

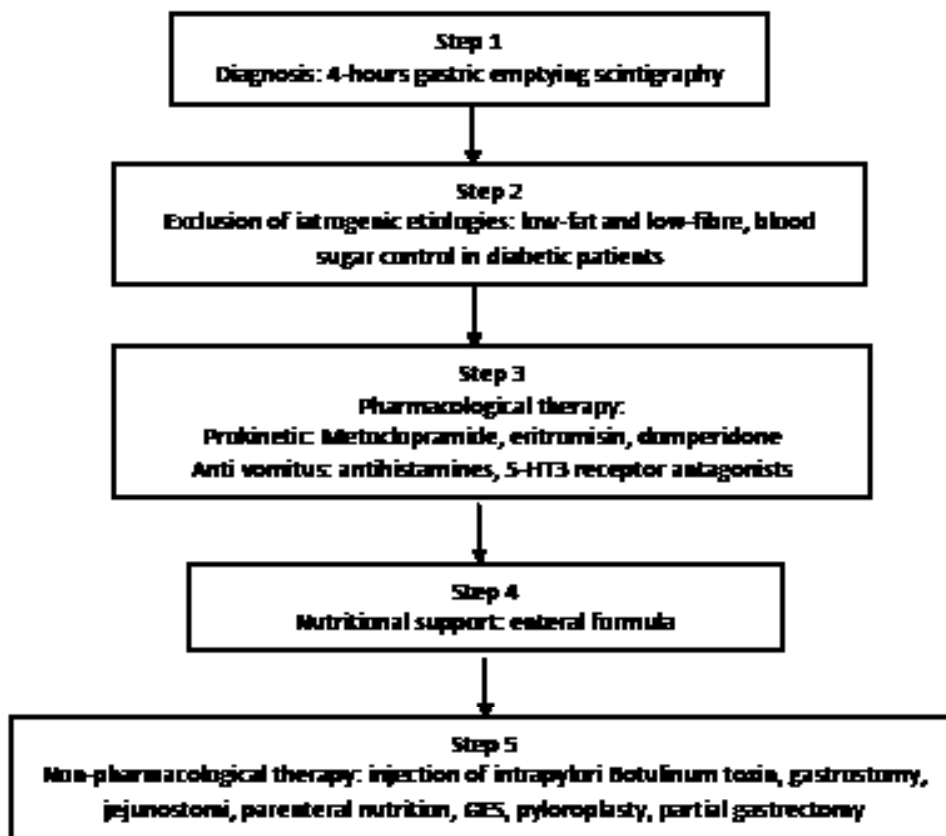


Figure 1. Algorithm for diagnosis and management of patients with gastroparesis<sup>3</sup>

receive. Multivariable logistic regression suggests that those who received prior nutritional counseling were more likely to meet their daily energy needs. Nutrition consultation by dietitians may be useful and should be considered in gastroparesis patients. Dietary compliance can be improved with multiple meetings rather than only single visits. This suggests dietary modification and nutrition consultation will improve patient intake with gastroparesis to reduce malnutrition and improve symptoms.<sup>2</sup>

### Oral Nutrition

Foods with low fat content and low residuals should be recommended for gastroparesis patients, since fat and fiber tend to slow gastric emptying. Small meal size is recommended because the stomach is only able to empty about 1-2 kcal/minute. Therefore, small meal size, low fat and low fiber, with a frequency of 4-5 times a day, suitable for gastroparesis patients. Increasing the liquid nutrient component of the diet should be recommended, since gastric emptying for fluids is often normal in patients with slowing of solid food emptying.<sup>3</sup>

In some patients, carbonated beverages, with the release of carbon dioxide, can worsen gastric distention; this type of intake should be minimized. Alcohol and smoking should be avoided as both can alter gastric emptying. In diabetic patients, control of near-normal sugar levels with diet and hypoglycemic drugs should be targeted, as improved blood sugar levels can accelerate gastric emptying.<sup>3</sup>

### Enteral Nutrition

For patients with gastroparesis who can not maintain oral intake of nutrients, nutrition through jejunostomy tube, which passes through problemed stomach, can improve symptoms and reduce frequency of hospitalization. Placement of the jejunal feeding tube, if necessary for alimentation, should be preceded by successful nasojejunal feeding trials. Occasionally, bowel dysfunction can occur in gastroparesis patients causing intolerance to jejunal feeding. Enteral administration should always be preferred over parenteral nutrition for many practical reasons, such as cost, potential complications, and ease of giving.<sup>3</sup>

### Blood Sugar Control

Gastroparesis may alter blood sugar control in diabetic patients, as slow gastric emptying lowers postprandial glucose peak and insulin requirements

and increases the risk of postprandial hypoglycemia. According to study by Punkkinen et al, the rate of gastric emptying for solid foods is associated with autonomic neuropathy, but not with blood sugar control. To target optimal blood sugar control is essential in the prevention and treatment of diabetic gastroparesis, because good long-term blood sugar control will protect against the development of autonomic neuropathy.<sup>11</sup>

Acute hyperglycemia induced in experimental clinical studies has been shown to worsen gastric emptying or inhibit antral contractility, although its association with symptoms is unclear. The efficacy of long-term improvement in blood sugar control to normalization of gastric emptying and symptoms in diabetic patients is controversial. However, short-term and long-term blood sugar control is indicated to increase long-term diabetes outcomes.<sup>3</sup>

### Pharmacological Therapy

#### Metoclopramide

Metoclopramide, Dopamine-D2 receptor antagonist, is the only drug approved by the United States FDA for the treatment of gastroparesis not later than 12 weeks unless the patient has therapeutic benefits that exceed the potential risk.<sup>3</sup> Metoclopramide may benefit both with central anti-vomitus effect as well as improve gastric emptying.<sup>15</sup>

The most common adverse extrapyramidal side effect of metoclopramide is acute dystonia (incidence rate 0.2%). A case series in the UK suggest the incidence of acute dystonia is higher in women, patients receiving higher doses, children, and young adults. While prolonged reactions are more common in elderly patients. Based on reports for 15 years, involuntary movements caused by metoclopramide about 95% were dystonia, 4% parkinsonism types, and 1% tardive dyskinesia. This involuntary movement is more likely to appear after parenteral administration. The reaction of this dystonia can be treated with antihistamines (eg, 25-50 mg IV diphenhydramine, more than 2 minutes), benzodiazepines (eg, diazepam 5-10 mg IV) or central anticholinergic agents (eg, benztropin 1-4 mg IV to 6 mg / day). Metoclopramide may also be associated with a prolonged corrected QT interval.<sup>3</sup>

Recommendations on when and how to use metoclopramide for the treatment of gastroparesis in clinical practice include careful monitoring of patients for early signs of tardive dyskinesia (which can be overcome by early recognition and discontinuation

of therapy), use the lowest effective dose for each patient, starting with 3 x 5 mg before meals, use a liquid preparation to increase absorption and facilitation of dose titration to a maximum dose of 40 mg/day and use "drug holidays" or dose reduction (eg 5 mg, before two large meals a day) whenever clinically possible. Drug interactions may occur when administration of drugs that alter the function of cytochrome P450-2D6 (CYP2D6).<sup>3</sup>

### Domperidone

Domperidone is a type II dopamine antagonist similar to metoclopramide, which has equivalent efficacy but with lower central side effects. This drug effectively overcomes nausea and vomiting. The initial dose is 3 x 10 mg which can be increased to 3 x 20 mg and before sleep. Given the domperidone tendency to prolong corrected QT intervals and rarely lead to cardiac arrhythmias, it is recommended that early electrocardiogram examination and after administration. This agent should be retained if corrected QT > 470 ms in men and > 450 ms in women. Domperidone can also cause an increase in prolactin levels and lead to lactation. Drug interactions may occur simultaneously with the administration of drugs that alter the function of CYP2D6. Drugs affecting CYP2D6 include antiemetics and antidepressants often given together in gastroparesis patients.<sup>3</sup>

Domperidone, does not cross the blood brain barrier as much as metoclopramide so it does not have the same neurological risk. However, this drug is not approved in the United States. Furthermore, even in countries where the drug is approved, the drug is spotlighted because of the risk of sudden death and cardiac arrhythmia associated with inhibition of hERG

channel activity, which inhibits the rapid component of the cardiac delayed rectifier K (β) current (I (Kr)).<sup>15</sup>

### Erythromycin

Erythromycin lactobionate is effective when administered IV at a dose of 3 mg/kg every 8 hours (through IV infusion for 45 minutes to avoid sclerosis veins), as shown in diabetic patients in hospital with gastroparesis. Many motilin agonists, including erythromycin, when given orally may improve gastric emptying and symptoms for several weeks, but with longer periods of administration often associated with tachyphylaxis due to downregulation of motilin receptors. Clinical response decreased after 4 weeks of oral erythromycin administration, but some patients may continue to benefit. Erythromycin also undergoes drug interactions with agents that alter or are metabolized by CYP3A4. Erythromycin administration may also be associated with a corrected QT extension.<sup>3,15</sup>

Suggestions for the prokinetic dose are described in Figure 2. Clearly, there are specializations on this approach based on individual differences: The degree of malnutrition or weight loss, the rate of decreased gastric emptying (or gastric retention at 4 hours), and previous treatment response.<sup>3</sup>

### 5HT4 Receptor Agonist

Other agents that have been used for a long time are 5HT4 receptor agonists, such as cisapride, mosapride, prucalopride, renzapride, sulpiride, zacopride. Initial agents in this class of drugs have side effects on the heart; newer 5-HT4 agonists with little or no adverse effects on the heart are currently being evaluated.<sup>15</sup>

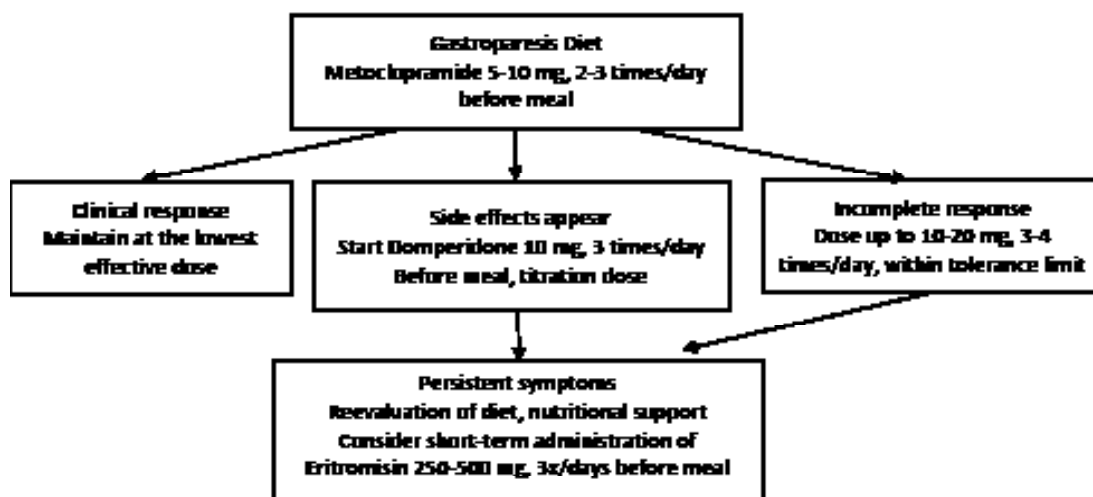


Figure 2. Algorithm for prokinetic therapy in gastroparesis<sup>3</sup>



### Tricyclic Antidepressants (TCA)

TCA may be considered for refractory nausea and vomiting in gastroparesis but will not improve gastric emptying and potentially inhibit gastric emptying. TCA in low doses may decrease symptoms of nausea, vomiting, and abdominal pain in gastroparesis. However, some TCA agents, such as amitriptyline, have anticholinergic effects and should be avoided in gastroparesis patients, as they slow down gastric emptying. Nortriptyline has a lower incidence of anticholinergic effects than amitriptyline. The 5-HT<sub>2</sub> receptor antagonist, mirtazapine, has been reported to be effective for gastroparesis in one case report.<sup>3</sup>

### Other Drugs

In addition to prokinetics, symptomatic treatment of these symptoms remains empirical and off-label for of nausea and vomiting non-specific indications, or emesis therapy induced by chemotherapy and palliative care. The most commonly prescribed antiemetic drugs are phenothiazines (including prochlorperazine and thiethylperazine) or antihistamine agents (including promethazine). There is no study comparing the efficacy of phenothiazines with newer antiemetics (such as the 5-HT<sub>3</sub> serotonin receptor antagonist) for gastroparesis. There is no evidence that ondansetron is superior to metoclopramide and promethazine in reducing nausea in adults. The 5-HT<sub>3</sub> receptor antagonist is a reasonable second-line drug; neurokinin receptor antagonist, aprepitant, is effective in the treatment of severe vomiting and recurrent ketoacidosis episodes in diabetic patients.<sup>3</sup>

Synthetic cannabinoids, dronabinol, are also used in practice, but there is a risk of withdrawal hyperemesis, and the optimal treatment strategy is unclear. Transdermal scopolamine, which is effective for nausea associated with motion sickness, is used for nausea and vomiting of gastroparesis, although without peer-reviewed publication to support this practice. Among the alternative treatment therapies, acupuncture is the most studied method in the treatment of nausea and vomiting; one study reported a remarkable improvement in 94% of patients.<sup>1</sup>

Clinical guidelines and a summary of evidence on this and other therapies have been published in recent years and are summarized in Table 1. This table precedes the results of the NORIG trial, which fails to demonstrate the beneficial effects of low-dose nortriptyline in patients with idiopathic gastroparesis. This trial, however, is remarkable for low placebo

response rates (23%) suggesting a general impression that high placebo level is a barrier to prove their effectiveness under these conditions.<sup>15</sup>

**Table 1. Current approach to gastroparesis treatment<sup>15</sup>**

Therapy	Recommendation	Level of evidence
Prokinetics	Strong	Moderate
Metoclopramide	Moderate	Moderate
Domperidone	Moderate	Moderate
Erythromycin	Strong	Moderate
Anti-vomitus	Conditional	Moderate
Tricyclic	Conditional	Low
Botulinum Toxin	Strongly not recommended	High
Gastric electrical stimulation	Conditional	Moderate

### Injection of Intrapyloric botulinum Toxin

The manometric study of patients with diabetic gastroparesis showed prolonged period of increased pyloric tone and phasic contractions, a phenomenon known as "pyloric spasm". Botulinum toxin is a powerful neuromuscular transmission inhibitor. Several open label studies on a small number of patients with gastroparesis showed mild improvement of gastric emptying and symptoms for several months. Two double-blind, placebo-controlled studies have shown some improvement in gastric emptying, but no improvement in symptoms compared with placebo. If this therapy is effective, then the outcome of this treatment does not last long and repeat of procedures may be necessary. Long-term effects of repetition procedures have not been well studied. Thus, botulinum toxin injection into the pylorus is not recommended as a treatment for gastroparesis, although there is a need for further research in patients with evidence of pyloric spasms.<sup>3,17</sup>

### Gastric Electrical Stimulation (GES)

GES Enterra™ therapy, implanted laparoscopically, is a tool for treating gastroparesis, improving gastric emptying and symptoms.<sup>7</sup> The illustration scheme of the device for GES, two leads inserted through the gastric serosa with a distal needle so it is not insulated, the electrode part is located in the muscle layer and fixed by the anchors and clips. Lead is connected to the impulse generator connector block (Figure 3).<sup>10</sup>

GES provides high frequency (several times higher than the intrinsic electrical frequency of the stomach) electrical stimulation of lower energy to the stomach. Complications from this tool such as local infection or migration, as well as surgical complications can occur in up to 10% of implanted patients. There is no consensus or specific guidance on patient selection (eg, therapeutic failure, or malnutrition) for GES use.

GES may be considered for patients with refractory symptoms, particularly nausea and vomiting.<sup>3</sup>

The first open labeled study showed improvements in specific and global gastroparesis symptoms as well as improvements in gastric emptying. A double-blind, randomized crossover study reported improved weekly frequency of vomiting and quality of life in diabetic gastroparesis and across patient groups, but not in the idiopathic gastroparesis subgroup. A recent meta-analysis of GES showed similar results and identified diabetic gastroparesis patients as being most responsive to GES, both subjectively and objectively, while the idiopathic gastroparesis subgroup and postoperative gastroparesis were less responsive.<sup>3</sup>

Several predictors for better clinical response to GES have recently been identified, particularly the etiology of diabetes and nausea and vomiting as the main symptoms. However, the individual response to GES remains unpredictable. The GES working mechanism is also poorly understood. The stimulation parameters received in clinical practice do not regulate the slow-wave activity of the stomach and have an inconsistent effect on gastric emptying. Despite these limitations, GES has remained very helpful in interventions in some patients with severe gastroparesis who failed to respond to medical therapy.<sup>18</sup>

### Surgical Therapy

In patients with significant upper gastrointestinal abnormalities, gastrostomy surgery, with or without enterostomy ventilation, reduces the rate of hospitalization fivefold during the year following installation. The results of endoscopic ventilation (percutaneous endoscopic gastrostomy and direct

percutaneous endoscopic jejunostomy) on nutritional outcomes and symptoms of gastroparesis have not been studied and remain unclear. In open label studies, the patient experienced marked improvement in symptoms, weight was maintained, and symptoms decreased up to 3 years post gastrostomy ventilation. It is assumed that the same result occurs with percutaneous endoscopic gastrostomy, although this is not proven.<sup>3</sup>

Several types of surgical interventions have been tried for the treatment of gastroparesis: gastrojejunostomy, pyloromyotomy, and subtotal or complete gastrectomy. A recent study reported on a series of 28 patients with gastroparesis in which pyloroplasty resulted in symptom improvement, with a significant increase in gastric emptying and a reduction in the need for prokinetic therapy when followed for 3 months postoperatively. It is not clear whether the efficacy of pyloroplasty depends on the function of the remaining antral motors; therefore, in some diabetics included in this series, there is no significant increase in gastric emptying, and further studies with longer follow-up are needed to determine the overall efficacy and optimal candidate for pyloroplasty in the treatment of gastroparesis. Pyloroplasty can relieve symptoms of gastroparesis and is often combined with the placement of a jejunal tube to support the nutrients.<sup>3</sup>

Complete or subtotal gastrectomy is applied mostly to gastroparesis which occurs after gastric surgery for peptic ulcer disease; the experience of the tertiary referral center shows that, in carefully selected patients, major gastric surgery can reduce vomiting due to severe gastroparesis and improve quality of life in seriously affected patients where the risk of subsequent renal failure is high and where life expectancy is poor.



Figure 3. GES: Generator impuls (Enterra, Medtronic, Minneapolis, Minnesota, USA) and lead<sup>10</sup>

The usefulness of complete or subtotal gastrectomy in patients with intact gastroparesis is not favorable.<sup>3</sup>

In a study by Papasavas et al, none of the patients required prokinetic therapy after surgery and each person had significant symptom improvement. More importantly, this study found that Roux-en-Y gastric bypass (RYGB) is a safe surgical procedure for obese patients. The results of this study indicate that gastroparesis is believed to cause patients becoming underweight, may appear in morbid obese patients and may be treated with RYGB.<sup>19</sup>

### Complementary and Alternative Treatment

Like many chronic conditions which are poorly understood, patients may seek alternative therapies. These could include: diet manipulation, physical training modalities (autogenic retraining as developed by NASA for space motion sickness), and therapies such as acupuncture. Dietary manipulation has been discussed above. The use of autonomic retraining in a series using NASA technology showed that patients with more intact autonomic nervous system activity respond better than patients whose autonomic function is more disturbed. Other therapies, such as acupuncture, have been tried in a more systematic way than other alternative therapies of gastroparesis. Several recent studies, including one single blinded study with false treatment control, have shown that acupuncture may be beneficial in gastroparesis.<sup>3</sup>

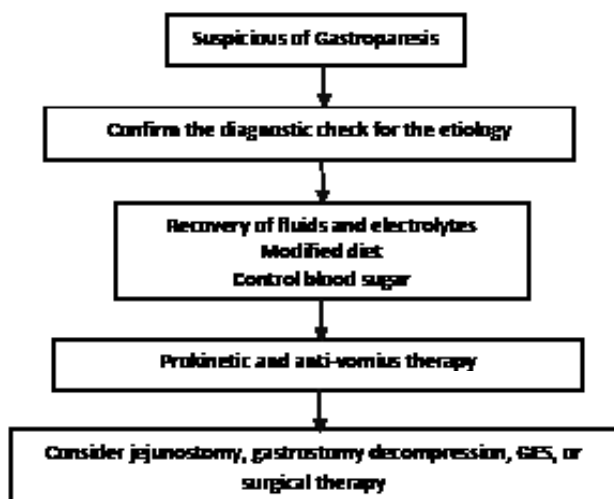


Figure 4. Gastroparesis management algorithm<sup>3</sup>

### CONCLUSION

Gastric motility disorders including gastroparesis are very common. Determination of diagnosis and management are still a challenge. Clinical manifestations are varied between each individual,

which require medical personnels' skills. Persistent nausea and vomiting are one of the main symptoms of gastroparesis. Various diagnostic tests can be customized to the patient's condition and needs.

Comprehensive gastroparesis management, which involves team, not only gastroenterologists, and patient is required to achieve the best outcome. Management guideline can be applied consistently, without ignoring patient's wills.

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