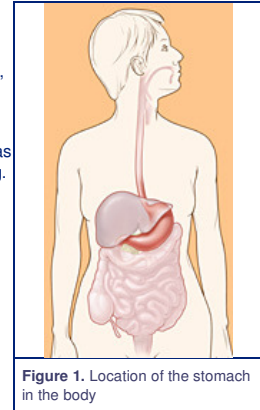


# Gastroparesis: Introduction

Gastroparesis, or **gastric stasis**, is a disorder of delayed **gastric** emptying in the absence of mechanical obstruction. It is manifest clinically through a set of largely non-specific symptoms such as early **satiety**, bloating, nausea, **anorexia**, vomiting, abdominal pain, and weight loss. Among these, vomiting and post-prandial fullness are the most specific. Common causes include **diabetes mellitus**, prior **gastric** surgery with or without **vagotomy**, a preceding infectious illness, pseudo-obstruction, **collagen vascular disorders**, and **anorexia nervosa**.

Gastroparesis often presents as a **subclinical** disorder; hence there is no true estimate of its incidence or prevalence. However, it has been reported that between 30-50% of diabetics suffer from delayed **gastric** emptying. The prevalence of suggestive symptoms (e.g. nausea, vomiting) is much lower—with only about 10% of diabetics affected.



## Gastric Motor Physiology

Normal gastric motility/emptying requires an integrated, coordinated interplay between the sympathetic, parasympathetic, and intrinsic-gut (enteric) nervous systems, and the gastrointestinal smooth muscle cells. Disturbance at any level has the potential to alter gastric function, and ultimately affect gastric emptying.

To better understand gastric motility, it is important to be familiar with both the functional zones and the major digestive functions of the stomach—including the difference between an empty and a full stomach.

On a functional basis, the stomach may be subdivided into two regions:

1. The proximal stomach comprises the cardia, fundus, and body—and is characterized by a thin layer of muscle that produces relatively weak contractions. Upon the ingestion of food, the proximal stomach exhibits receptive relaxation, with very little increase in intragastric pressure. This portion of the stomach is responsible for storage.
2. The distal stomach consists of the antrum and pylorus—and is characterized by a thick and powerful muscular wall. This is the part of the stomach that controls mechanical and enzymatic digestion. The pattern of contraction in the distal stomach also regulates the rate at which partially digested food is emptied into the duodenum.

The major digestive functions of the stomach are as follows:

1. Storage of large amounts of food. The volume of the stomach can vary between about 50ml (.05 qts.) in an empty state to nearly 1500ml (1.6 qts.) after ingestion.
2. Mechanical and enzymatic breakdown of larger particles into smaller particles (< 2 mm), known as chyme.
3. Slow delivery of chyme to the duodenum at a rate not to exceed the digestive and absorptive capacity of the small intestine.

## The Empty Stomach

Following digestion and absorption of a meal, contractions persist in the empty stomach and small intestine. These contractions are governed by the Migrating Myoelectric Complex (MMC). MMC contractions move slowly along the gastrointestinal tract, reaching the colon in about two hours, at which point another wave of contraction begins in the stomach. The function of MMC is to sweep any residuals out of the GI tract—hence the nickname 'housekeeper' (Figure 3).

It is not clear what factors regulate MMC, but they may involve neurohumoral influences—specifically the enteric nervous system and the hormone motilin.

"Hunger pains," and the sounds we refer to as "growling" are related to MMC contractions of the gastric smooth muscle, and may be associated with discomfort. These appear after 12-24 hours of fasting and may be related to low blood glucose levels. MMC's may be abolished by food intake.

Receptive relaxation facilitates food storage, allowing the proximal stomach (fundus and proximal corpus) to relax and increase its volume up to 15 times its empty state with very little increase in intragastric pressure (< 5 mmHg). This phenomenon occurs when a peristaltic wave reaches the lower esophageal sphincter, and is largely mediated through the synapse of vagal fibers with inhibitory (non-adrenergic non-cholinergic-NANC) neurons in the gastric plexuses.

## The Full Stomach

Peristaltic activity, manifested as "slow waves" of contraction of the stomach, occurs at the basal electrical rate (BER) of the stomach (which supposes a maximum of 3 waves/minute). These "slow waves" originate in the 'pacemaker-cells' (interstitial cells of Cajal) in the mid-portion of the greater curvature (the proximal corpus), and travel distally towards the pylorus at a frequency of about 3/minute. Propagating at a slightly faster velocity along the greater curve than along the lesser curve, the contraction waves reach the pylorus simultaneously (Figure 3).

In the proximal stomach (fundus), contraction waves propagate more slowly (< 1 cm/sec) and are quite weak. This allows some mixing of ingested food and gastric secretions, but more importantly, serves to facilitate food storage.

The waves are stronger and faster (traveling 3-4 cm/sec) in the antrum. In the early stages of the antral contraction cycle, the pylorus is open, thus allowing a few ml of gastric chyme to be propelled into the duodenum. This is soon followed by a forceful pyloric closure (as the wave reaches the pyloric sphincter), forcing intragastric contents back into the antrum and corpus. This repulsion is referred to as the 'pyloric pump', and serves to effectively mix food and gastric secretions, and to grind gastric contents into chyme. This process is essential to the digestion and breakdown of food in the stomach. Some evidence suggests that it is controlled by opiates, acetylcholine, and nitric oxide (NO).

Liquids pass through the pylorus in spurts. Solids have to be reduced to between 1-2mm in size before they can be successfully delivered to the duodenum. As a consequence, relatively large, indigestible solids remain in the stomach unless they are eliminated by vomiting.

## Electrical Activity of GI Muscle - Electrical Control Activity (ECA), or Basal Electrical Rhythm (BER)

The resting membrane potential (RMP) in distal stomach muscle cells is between 60–70 mV. This potential, however, is unstable and oscillates rhythmically by 10-15 mV intervals over a uniform time course. In due course, these depolarizations propagate to adjacent cells through gap junctions (Figure 4). Spontaneous "slow waves" result from a balanced inward depolarizing Ca flux and a repolarizing K efflux. The BER is continuous, and determines the maximal rate (frequency) of gastric muscle contractions (~3/min). In and of itself, the BER is not synonymous with gastric muscle contraction. It constitutes a basal electrical activity that may or may not translate into a contraction, thus setting a maximal rate frequency for contractions (Electrical Response Activity—ERA). Whether or not muscle cells respond to these

basal depolarizations and contract is largely dictated by neural and hormonal mechanisms. ERA therefore occurs at a rate that is equal to or less than that of the BER, and is largely the byproduct of a series of integrated enteric nervous system (ENS) reflexes and the interactions of different layers of gastric muscle—all of which are modulated by the autonomic nervous system and gut hormones.

### Control of Gastric Motility

#### Myogenic Mechanisms

All of the stomach's smooth muscle cells have the ability to produce electric depolarizations ("slow waves") from resting potential. These rhythmic contractions are thought to originate in the non-smooth muscle pacer cells, (possibly, in the interstitial cells of Cajal). However, because there exists a gradient in the resting membrane potential between the different segments—from -50 mV at the fundus to -80 mV at the pylorus—the frequency of contractions in the antral portion of the stomach is less than that at the corpus.

The fundus is not coupled to the more distal segments of the stomach. The "slow waves" initiated in the pacer cells (of the greater curvature) do not spread to the more proximal fundus because it has a less negative resting membrane potential among other myoelectric characteristics limiting its excitability. Instead, the fundus is under vagal excitatory control. NANC (e.g. Nitric Oxide), and adrenergic neurons have an inhibitory influence on fundic contractions.

Two properties control the propagation of contractions in the rest of the stomach: 1) the gradient in slow wave intrinsic frequencies in different segments (corpus>antrum>pylorus), and 2) the conduction velocity of the action potential of different segments (4 cm/sec in the distal antrum vs. 0.5 cm/sec in the corpus).

#### Neurohumoral Mechanisms

In the proximal stomach, receptive relaxation is mediated through stimulation of mechanoreceptors. These mechanoreceptors initiate a vago-vagal reflex arc via the tractus solitarius neurons. This, then, is the basis for the decrease in gastric accommodation, and gastric compliance (increased luminal pressure) post-vagotomy. Some evidence also suggests a role for vagal fibers in maintaining basal fundic tone. Sympathetic fibers modulate tonic activity through inhibition.

Several other factors influence fundic motor activity: Gastrin-releasing peptide (GRP), gastrin, cholecystokinin (CCK), secretin, VIP, somatostatin, glucagon, and bombesin all have a relaxation effect; whereas both motilin and thyrotropin-releasing hormone (TRP) increase fundic contractions. More distal regions of the intestinal tract reflexly modulate fundic contractility. Duodenal distention, which is mediated by NANC neurons, reduces fundal tone (Figure 5). This reflex is diminished by either vagotomy or splanchnicectomy, and abolished if both are severed. Duodenal acid, protein, and fat also inhibit fundic contraction. NANC neurons are implicated in this reflex. Recent evidence suggests that NO neuronal pathways mediate lipid-induced effects. Postprandial release of CCK levels with increased duodenal fat, and amino-acids decreases fundal tone.

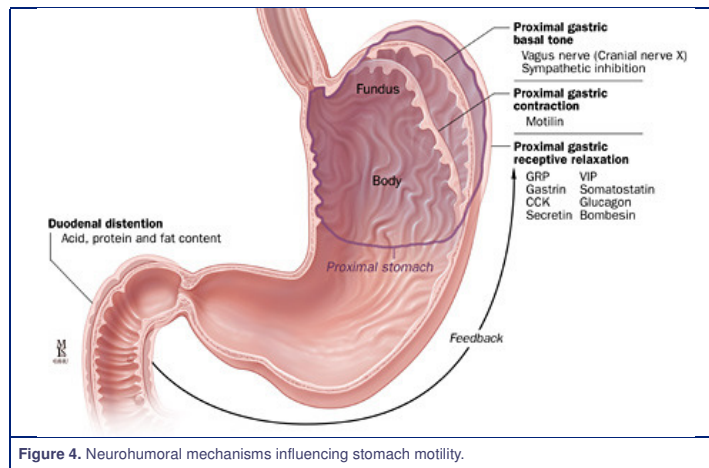


Figure 4. Neurohumoral mechanisms influencing stomach motility.

The distal stomach has two distinct rhythms:

1. A fasting state rhythm (MMC);
2. A fed state rhythm

It is not entirely clear what multiplicity of factors modulate MMC. There is some evidence to suggest modulatory vagal effects, in that vagotomy down regulates MMC. On the other hand, Motilin enhances MMCs. Other hormones have also been implicated in MMC modulation (e.g. opioids). Intraduodenal contents either abolish (e.g. hydrochloric acid) or induce (e.g. alkalinization) MMC. Certain disease states that alter MMC predispose a patient to bezoars.

The fed state motor pattern is initiated 5-10 minutes after a meal. Both consistency and composition of a meal are key in determining contraction amplitude: particulate foods induce more powerful antral contractions than homogenized foods, and meals of higher caloric content induce a more prolonged contractile response (fats > proteins > carbohydrates).

Neurohumoral factors control the fed state, although the specific mediators are still unknown. It is known that vagal pathways are implicated, as vagotomy increases the threshold for contraction initiation, and shortens its duration. On the other hand, stimulation of other vagal fibers inhibits distal gastric contractility (possibly through VIP release). Nitric Oxide is also believed to be a distal gastric relaxant. Other mediators such as CCK, substance P, bombesin, and endogenous opiates increase antral contractions (though with an unclear physiologic role); Secretin, somatostatin, GRP, glucagon, GRP, and TRH all inhibit antral contractions. Reflex arcs from distant segments of the gut also modulate antral contraction. A fundo-antral reflex is believed to increase antral contractions in response to fundal distention, and may serve in mixing and peristalsis. Duodenal distention, intraduodenal fat, protein, and hydrochloric acid all inhibit antral contractions.

The pylorus has many unique features that distinguish it from the distal stomach (antrum). These features include neural, muscular and histological components. Furthermore, certain neurotransmitters are increased in the pylorus (such as VIP, substance P, and neuropeptide Y). These neurotransmitters suggest an inhibitory neural predominance resulting in pyloric relaxation. Optimally, the pylorus is open in a fasting state, and has prolonged periods of closure in a fed state. The presence of stomach acid and food components (specifically fats, amino acids, and glucose) in the duodenum triggers a reflex that feeds back onto the pylorus and results in pyloric closure and duodenal relaxation.

# Gastroparesis: Anatomy

## **Anatomy**

Three muscle layers comprise the stomach: the circular, oblique, and longitudinal layers. The circular layer thickens at the pylorus to form an anatomic sphincter. The oblique layer differentiates the stomach from other portions of the gastrointestinal (GI) tract, and serves in complex grinding.

Intrinsic neurons are layered in two plexuses: the submucosal and myenteric. The stomach is also innervated by autonomic fibers: sympathetic fibers travel from the spinal cord (T7 and T8 ventral roots) via the greater and lesser splanchnic nerves. The vagus nerve provides parasympathetic (PS) innervation, originating in the dorsal motor nucleus of the medulla.

The mid-portion of the greater curvature is the site of the gastric pacemaker. The electrical coupling of pacer cells with neighboring cells propagates electrical activity, which is the basis for the generation and propagation of contractility. Many different stimuli and conditions can modify the stomach's contractility.

# Gastroparesis: Causes

## Idiopathic Gastroparesis

Up to one third of patients with delayed gastric emptying have no identifiable cause of their disorder, and are thus classified as having idiopathic gastroparesis. 30-50% of these patients may provide a prior history of a viral illness. It is believed that the viral illness may result in damage to the myenteric plexus, smooth muscle cells, and interstitial cells of Cajal. This may result in neurogenic and/or myogenic disturbances of the stomach leading to gastroparesis.

This subgroup of patients may pose a challenging diagnostic dilemma since unless suspected; underlying gastroparesis may easily be overlooked. Therefore, clinical suspicion is important for diagnosis. Many patients may have abdominal pain only as a presenting symptom and therefore other gastrointestinal pathologic conditions such as ulcer disease must be ruled out. There is some preliminary evidence that patients with idiopathic gastroparesis may have a different EGG myoelectric pattern than those with gastric outlet obstruction.

## Diabetes Mellitus

Nearly 6% of adults suffer from diabetes (with another 5% estimated to have a subclinical form of the disease). Evidence suggests that after 10-20 years of clinically apparent diabetes, 30-60% of diabetics develop overt signs of visceral autonomic neuropathy—of which gastroparesis, or gastric stasis, is one form.

Diabetic gastroparesis (or gastroparesis diabetorum), the most recognizable form of delayed gastric emptying, is detected with equal frequency in type 1 and type 2 diabetics. Delayed gastric emptying, however, has not been associated with a specific type of myoelectric or motor disturbance on manometry, nor has any correlation been observed between it and clinical autonomic neuropathy.

Although vagal neuropathy has long been suspected of impairing gastric motility in diabetics, the pathogenesis remains largely unknown. Diabetics produce only about 1/3rd of the gastric acid output of non-diabetics, and they exhibit slowing of afferent vagal conduction. But, evidence suggests that vagotomy inhibits postprandial liquid emptying in diabetics—even though it accelerates this same process in non-diabetic subjects. This suggests that vagal dysfunction is not the sole mechanism of gastric motor dysfunction in diabetics. Aberrant sympathetic function, and impaired gastric smooth muscle cellular response are also thought to play a part in the etiopathogenesis of gastroparesis. Moreover, it has been observed that hyperglycemia, in the absence of prior neuropathy, can alter normal antral contractions. In fact, delays of both gastric liquid and solid emptying have been reported during hyperglycemic states, which corrected with reinstatement of euglycemia. Moreover, hypoglycemia has been noted to enhance gastric liquid emptying. In addition to its effects on gastric motor function, hyperglycemia has also been implicated in the alteration of gastric sensory function, hence intensifying symptoms such as nausea.

## Post-operative Gastroparesis

Prior gastric surgery may result in gastroparesis. Around 5% of patients who undergo vagotomy as part of their surgical correction for peptic ulcer disease or malignancy develop symptoms of nausea, early satiety, and bloating from gastric stasis, in the absence of a mechanical obstruction. This has also been observed after highly selective vagotomies (Figure 6). Disturbances of fundic and antral contractility have been documented on several occasions. Non-motor factors may also be involved, as symptoms do not always correlate with delays in gastric emptying.

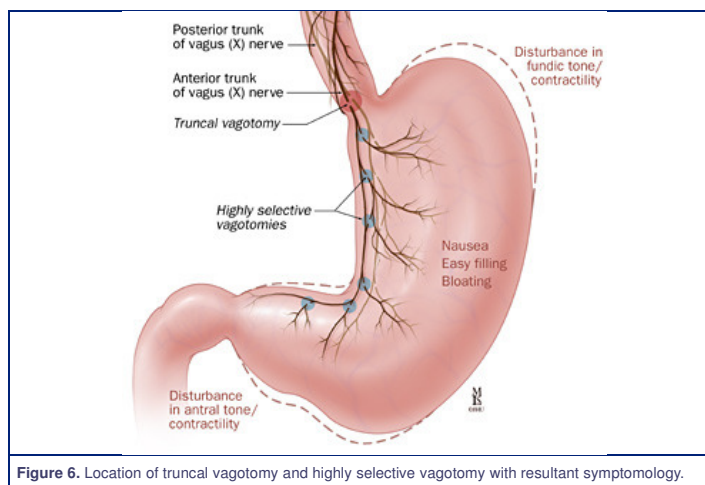


Figure 6. Location of truncal vagotomy and highly selective vagotomy with resultant symptomatology.

Some patients experience intractable nausea and vomiting after Roux-en-Y surgery. Although gastric stasis has been documented in some of these patients, the mechanism of its development remains unknown.

Nausea and bloating have also been reported after surgery for gastroesophageal reflux disease, including the newer laparoscopic fundoplication. It remains largely unknown, however, whether the observed gastric motor disturbances reported in this group of patients antedates, or is a result of, the surgery.

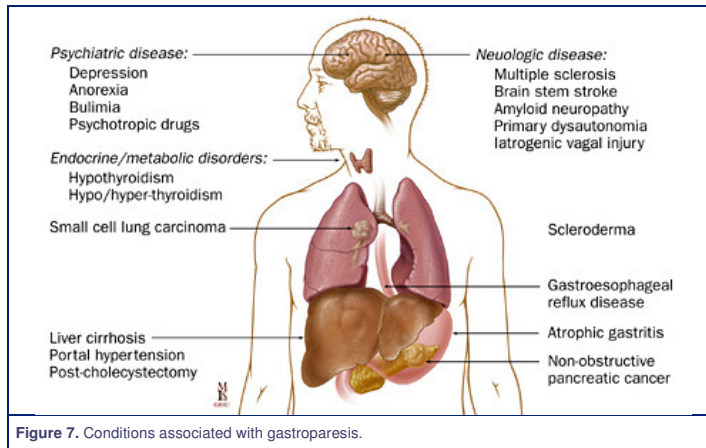
Other surgeries, such as esophagectomy with gastric pull-through (esophageal cancer), the pylorus preserving Whipple procedure (pancreatic cancer) and chronic pancreatitis surgery are often complicated by gastroparesis. In addition, gastroparesis is common in patients who have recently undergone heart-lung transplantation, and increases the risk for microaspirations in the transplanted lung.

## Miscellaneous Conditions

Delayed liquid and solid gastric emptying has been documented in patients with gastroesophageal reflux disease. Isolated delayed solid emptying has been noted with atrophic gastritis, whether associated with pernicious anemia or not.

Malignancy predisposes to gastroparesis; this has been reported with both non-obstructive pancreatic cancer and small cell lung carcinoma (Figure 7). The latter patients often develop symptoms of gastroparesis and intestinal pseudoobstruction. Immune mechanisms are proposed in this group.

It is worth noting that gastric stasis from malignancy has a poor response to medical therapy, and often requires surgical drainage (e.g. gastrojejunostomy). Intolerance to both solids and liquids is common following abdominal irradiation, and may not necessarily be due to delayed gastric emptying.



### Scleroderma

When Scleroderma affects the stomach, it rarely causes intractable nausea and vomiting, but may exacerbate esophageal reflux symptoms. In the most severe cases, however, delayed gastric emptying may result in weight loss and nutritional deficiencies. Moreover, Scleroderma patients with gastric involvement often have clinically evident systemic skin, pulmonary, and esophageal disease.

### Neurologic Disease

Disorders such as multiple sclerosis, brain stem stroke, amyloid neuropathy, primary dysautonomia and iatrogenic vagal injury may result in gastroparesis. Generalized or degenerative disorders such as AIDS or Parkinsons, or conditions of congenital pyloric stenosis, may also affect the myenteric plexus.

### Psychiatric Diseases

Depression, classical eating disorders (anorexia, bulimia), and psychotropic medications can be associated with gastric dysrhythmias, making intrinsic motility problems and eating disorders difficult to distinguish.

The rumination syndrome, in which undigested food is effortlessly regurgitated, is a behavioral disorder most often observed in mentally disabled patients, although it is also seen among adults of normal mental capacity. Abnormalities of gastric or duodenal motility have not been consistently documented with this syndrome.

### Endocrine and Metabolic Disorders

Gastroparesis and intestinal pseudo-obstruction reportedly complicate hypothyroidism, as well as hypoparathyroidism and hyperparathyroidism. Hyperthyroid patients have normal gastric emptying. Patients with gallbladder disorders, post-cholecystectomy patients, and those with cirrhosis and portal hypertension have also been known to experience delayed gastric emptying.

Gastric stasis is also associated with ethanol (alcohol), smoking, and marijuana use.

Patients with hereditary syndromes such as Turner's syndrome have reportedly been found to have gastroparesis. Pregnancy and chronic renal failure with or without dialysis have inconsistently been associated with gastric motor slowing.

# Gastroparesis: Diagnosis

## History and Physical Examination

The most common presenting symptoms in gastric stasis are nausea (98%), abdominal pain (90%), early satiety (86%), and vomiting (68%). Abdominal pain is of a varied nature, and may be described as burning, cramping, or diffuse. Most patients report exacerbation of pain after meals, and difficulty sleeping.

The physical exam may reveal varying degrees of abdominal distention and/or tenderness; guarding, however, is absent. A succussion splash may be noted on auscultation by gently rocking the patient. The rest of the exam should be directed to identifying signs of underlying diseases/disorders (e.g. sclerodactyly suggests scleroderma, malar rash suggests systemic lupus erythematosus, peripheral neuropathy may point to diabetes and other neurologic diseases, lymphadenopathy, palpable masses, and cachexia, suggest neoplastic disease resulting in either mechanical or functional gastric obstruction).

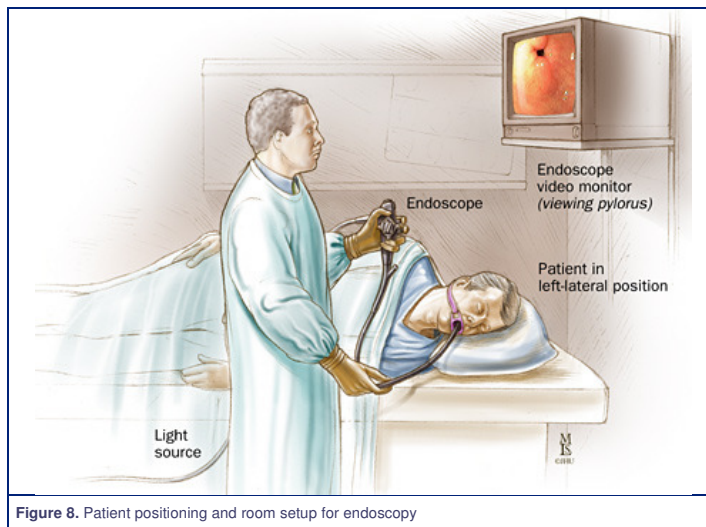
## Laboratory Testing

There are no sensitive or specific laboratory tests currently available to aid in the diagnosis of gastric stasis disorders. There are, however, tests available that aid diagnosis of underlying systemic illnesses. The following is a list of general tests that are recommended when evaluating suspected cases of gastroparesis:

- Hemoglobin
- Fasting glucose
- Total protein/albumin
- TSH
- ANA
- Vitamin B12
- Chest and plain abdominal x-ray films

## Endoscopy

All patients should have an upper endoscopy to rule out mechanical obstruction (Figure 8). Gastric stasis may be suggested by the finding of retained food residue (in extreme cases bezoars) after an overnight fast and subsequent endoscopy



## Radiology

An oral barium contrast x-ray is an alternative to endoscopic evaluation. This will detect delays in liquid phase emptying from the stomach (or small bowel).

## Gastric Emptying Scintigraphy

Gastric Emptying Scintigraphy is the most widely used test to confirm gastric stasis (Figure 9). The requirements of the test are as follows:

The patient meal should be of solid consistency, and adequate caloric content (at least 200 kcal), to induce powerful gastric contractions

The radiotracer should be effectively bound to the substrate (meal), and resistant to a wide pH range (1-7.5), as the substrate may be exposed to a wide range of acidity for long hours (Usually, it is an egg meal with  $^{99m}\text{Tc}$ -Amberlite pellets)

Scans are taken immediately, as well as at intervals of 2 and 4 hours after ingestion. Insofar as the 2-hour test is highly sensitive and specific (both 90%) for evaluation of dumping (>47% emptied vs. normal 53-76%), the 4-hour test has been found to be similarly sensitive and specific (100% and 70%, respectively) for gastric stasis evaluation (normal residue at 4 hours 0-40%).

Although liquid emptying is rarely delayed, it may be assessed (usually in a research setting) through a double tracer study, which generally requires more frequent scans—on the order of one every 15 minutes.

In the absence of mechanical obstruction, an abnormal scintigraphic study usually confirms the diagnosis of gastroparesis.

## **Gastroduodenal Manometry**

Gastroduodenal Manometry involves peroral insertion of a catheter, for a six-hour time period, in order to measure antro-duodeno-jejunal pressures (Figure 10). The first few hours of observation are reserved for fasting-state pressure recordings. Later, pressure recordings are monitored after the patient has eaten a solid meal—which facilitates testing on the effects of different prokinetic agents.

Manometry is useful in distinguishing between myopathic (amyloid, scleroderma) and neuropathic processes (diabetes, idiopathic autonomic neuropathy, amyloid neuropathy). Whereas the former are associated with low amplitude complexes, the contractions in the latter are typically of normal amplitude and abnormal organization. Manometry should only be considered in cases in which standard therapeutic measures have failed, for those for whom surgery and/or jejunostomy are being considered, and for those with unexplained nausea.

## **Other Tests**

### **Ultrasonography**

Ultrasonography, which records gastric volume after liquid meal ingestion, is an increasingly common means of evaluating gastroparesis. Solid meals, however, cannot be evaluated through ultrasonography due to their echogenicity.

### **MRI**

Magnetic Resonance Imaging (MRI) can also be used to assess gastric emptying. Despite the fact that MRI technology produces results similar to those obtained through scintigraphy, the procedure has not gained popularity. It is prohibitively expensive, and MRI machines are not widely available to physicians.

### **Breath Tests**

Breath tests after <sup>13</sup>C-octanoate or <sup>13</sup>C-acetate ingestion are useful in assessing gastric emptying in patients in whom radioactive tracer administration is contraindicated, such as children or pregnant women. This modality relies on the measurement of <sup>13</sup>CO<sub>2</sub> concentration in a patient's breath, which is proportional to what has been absorbed by the duodenum. This test, however, is only applicable to those patients with normal absorptive function.

### **Electrogastrography**

Electrogastrography (EGG) records gastric electrical activity with cutaneous electrodes. Although cutaneous gastric electrical recordings were successfully obtained as far back as 1921, it is only in recent years that this method has begun to attract interest as a means of evaluating gastric motor dysfunction. This is partly the result of the poor quality of the initial recordings, and partly due to the lack of standardization for reporting and interpreting the recorded signals.

EGG recordings are obtained by placing EKG-type electrodes on the epigastric abdominal surface. Leads transmit electrical activity to a filter-equipped amplifier set to detect tracings between 0.6 and 15 cycles-per-minute (cpm). Tracings are recorded on a strip chart, and simultaneously digitalized. Computer analysis of EGG signals is commonly referred to as running spectral analysis (RSA).

After a baseline EGG tracing is obtained, the patient is given a Water Load Test. This test is conducted during a 5-minute interval in which the patient drinks water to fullness. EGG tracing is then obtained for the 30 minutes that follow water ingestion, thus allowing the determination of gastric myoelectric response to water load. The Water Load Test is reproducible, and is regarded as a provocative test for assessing gastric capacity, and rhythmicity. In fact the ingested water volume reflects capacity, and the corresponding EGG tracing reflects an unaltered, "pure" myoelectric gastric response to a given load, without the modifying effects of nutrients (such as fat, carbohydrates).

RSA represents an objective means of analyzing electrical activity in the EGG.

Gastric dysrhythmias refer to deviations in the normal 3/minute gastric contraction cycle. These are frequently associated with ineffective gastric contractions with resultant altered emptying. Bradygastria refers to any activity measuring between 1.0 and 2.5 cpm; tachygastria measures between 3.7-10.0 cpm. Nonspecific dysrhythmia is a combination of bradygastria and tachygastria.

The use of EGG in patients with upper gastrointestinal symptoms and those with symptoms suggestive of gastroparesis is limited to highly specialized centers. Hence, there is currently no consensus on the role of EGG in the work-up of such patients. There is accumulating evidence, however, to suggest a correlation between gastric dysrhythmias and upper gastrointestinal symptoms.

Furthermore, in a subset of patients (such as diabetics and those with nausea/dyspepsia related to pregnancy), resolution of symptoms was observed when pharmacologic therapy resulted in normalization of gastric rhythm.

A few considerations are worth noting, however:

1. Gastric dysrhythmias may or may not be associated with gastroparesis.
2. Both gastric dysrhythmia and gastroparesis may be intermittent, thus adding complexity to the management of patients with epigastric distress.



# Gastroparesis: Therapy

## Overview

The primary goal in the management of gastroparesis is to reverse or correct underlying etiologies. If that is not possible, treatment should aim to promote **gastric** emptying and relieve symptoms. Medications that inhibit or delay **gastric** emptying should immediately be discontinued, if possible.

## Dietary Measures

The prime goal of therapy is to maintain adequate nutrition. For the majority of patients, dietary modifications are an effective means of reducing symptoms while maintaining nutrition. Solid foods should be reduced and replaced by liquids (these empty more readily from the stomach). Patients should eat several smaller meals per day, rather than two or three large meals. Diet should be low in fiber and fat, as both have an inhibitory effect on **gastric** emptying. Diabetics should avoid **hyperglycemia**, as it acutely delays **gastric** emptying.

## Medical Therapy

### Prokinetic Therapy

In most patients, medications that promote **gastric** emptying have become a cornerstone of disease management. The most commonly used medications worldwide are metoclopramide, cisapride, erythromycin, and domperidone.

At present, however, only erythromycin and metoclopramide are FDA approved for use in the United States.

**Erythromycin:** This is a macrolide antibiotic, and an analogue to motilin, the **hormone** believed to be the regulator of the **gastroduodenal** migrating motor complex (MMC). Erythromycin is a potent stimulant of **gastric** emptying and promotes solid and liquid emptying through induction of forceful antral contractions similar to those initiated through the migrating motor complex. Both oral and **intravenous** routes of administration are effective. A liquid erythromycin formulation helps to titrate. In addition to being useful in improving diabetic gastroparesis, erythromycin has benefited patients after **vagotomy**, **subtotal gastrectomy**, and **esophagectomy**. In addition, it helps relieve radiation- and scleroderma-induced gastroparesis. Unfortunately, erythromycin may adversely interact with a number of medications, and many patients have reportedly become resistant to its effects after several weeks (tachyphylaxis) of use. A variety of doses have been used: oral-dosing ranges from 50-250mg four times daily. The **intravenous** form of delivery is more efficacious, especially for the **acute** management of symptoms in hospitalized patients. The recommended **intravenous** dose is 1-2mg/kg every 8 hours. Abdominal cramps and nausea are common side effects of treatment.

**Metoclopramide:** Metoclopramide belongs to the benzamide class. It is a central **dopamine** (D2) and **serotonin** (5-HT3) receptor **antagonist**, hence its **anti-emetic** effect. It also promotes prokinetic effects through facilitation of **acetylcholine** release from **enteric neurons** (5-HT4), antagonism of myenteric **dopamine** (D2) receptors, and sensitization of **smooth muscle muscarinic** receptors. Prokinetic benefits are limited to the **proximal** gut and result in increased esophageal and antral contractions, decreased pyloric and duodenal **tone**, and increased **gastric** emptying and small bowel **motility**. Metoclopramide is the sole FDA-approved agent for diabetic gastroparesis in the United States. Improvement of **gastric tone** has also been reported in patients with prior **vagotomy** and/or **gastrectomy**, as well as in patients with **anorexia nervosa**. Prokinetic effects are noted 3 minutes after an **intravenous** dose, and 60 minutes following an oral dose. The usual adult oral dose is 5-20mg four times a day, taken 30 minutes before meals, and at bedtime. **Intravenous** dosing (usually in an inpatient setting) is 10mg every 2-3 hours as needed. **Subcutaneous** injections can also be given (5-10mg three to four times daily). Numerous side effects have been reported, primarily due to the drug's central nervous system effects. Drowsiness, dystonic reactions, and agitation are the most **acute** dystonic reactions can occasionally develop, and should be treated with discontinuation, and use of diphenhydramine. Extrapyrmidal movements may develop in chronically treated, and may even be irreversible—especially in the elderly. Other adverse effects include depression, hyperprolactinemia, galactorrhea, **amenorrhea**, and impotence.

### Other Agents

**Bethanechol:** Bethanechol, a **muscarinic** agent that causes uncoordinated **gastric** contractions, is of historical value, but has no current role in the management of gastroparesis.

**Cisapride:** Cisapride is a **serotonin** (5-HT4) **agonist** that facilitates **acetylcholine** release at the level of the **Myenteric plexus**, and a (5-HT3) receptor **antagonist**, causing **gastric smooth muscle contraction** and possibly having an **anti-emetic** effect. Its prokinetic effects are those of increased lower esophageal sphincter tone, and improved antral, jejunal, and colonic **motility**. Cisapride provides **symptomatic** relief for a wide spectrum of patients, and has become the treatment of choice for medium and long-term management of gastroparesis. The routine dose is 10-20mg four times daily (preferably given 30 minutes before meals and at bedtime). The drug's side effects generally stem from its physiologic properties, in that it may cause abdominal cramping and diarrhea. The major concern, however, are the more than 270 cases of serious cardiac arrhythmias that have been associated with cisapride use. In fact, it is thought that cisapride may prolong the QT interval thus predisposing users to Torsades de Pointes. Although a rare occurrence, this ventricular **arrhythmia** may result in **hypotension**, **syncope**, or even sudden death. Medications that increase cisapride levels should be avoided (viz. macrolide antibiotics—erythromycin, clarithromycin, and azole anti-fungals, nefazodone, and **protease** inhibitors). Medications that prolong the QT-interval should also obviously be avoided (particularly anti-arrhythmics such as quinidine, amiodarone, procainamide, sotalolol). Moreover, patients with personal or family history of QT prolongation, those with history of, and/or at risk for, cardiac arrhythmias/significant cardiac disturbances should not be given Cisapride. Recently, it has been recommended that a baseline electrocardiogram (QTc should be < 450msecs), **electrolytes**, and **serum creatinine** be obtained prior to initiating treatment. As a result, cisapride has been withdrawn from the open market, and is only available on special request from the manufacturer.

**Domperidone:** A benzimidazole derivative, Domperidone acts as a **peripheral Dopaminergic** (D2) receptor **antagonist**. Its effects are similar to those of metoclopramide. Because it minimally crosses the blood-brain barrier, domperidone is devoid of metoclopramide central nervous system side effects: it very rarely causes hyperprolactinemia, **gynecomastia**, galactorrhea, impotence, and **amenorrhea**. Dystonic reactions are extremely rare. It also has no effect on **serotonin**, as do metoclopramide and cisapride. Domperidone, however, has **anti-emetic** properties as a result of its action on the **chemoreceptor** trigger zone. It is generally dosed orally, 10-40mg four times daily. A suppository form is also available. Although widely used for the **chronic** management of gastroparesis in many countries, domperidone has not been FDA-approved for use in the U.S.

### Anti-Emetic Therapy

Prokinetic therapy will, for the most part, offer relief from the nausea and vomiting that accompany gastroparesis—either indirectly by promoting **motility**, or through the **anti-emetic** properties of substances such as metoclopramide and domperidone. Occasionally, however, a **refractory** patient is encountered for whom additional therapy is required. Several options exist for these patients. Phenothiazine derivatives (promethazine and prochlorperazine) act by antagonizing **dopamine** receptors. Other **anti-emetic** agents include thiethylperazine and trimethobenzamide, the use of which may be limited by extrapyramidal side effects, especially if used in conjunction with metoclopramide. In addition, the relatively new 5-HT3 antagonists (ondansetron, granisetron, and dolasetron) are potent anti-emetics and have been proven efficacious in treating **chemotherapy** and radiation-induced nausea and vomiting. They are available as oral or **intravenous** preparations. Ondansetron is available as a liquid and lingual dissolving tablet, of which both are well tolerated and quickly absorbed. Side effects include constipation, headache, and sedation. **Chronic** use of these agents may be limited due to excessive cost.

### Endoscopic Therapy



Decompressive Gastrostomy: Some patients who are **refractory** to dietary and medical interventions may benefit from an endoscopically placed gastrostomy tube (surgical or fluoroscopic placement can be undertaken when endoscopic placement is unsuccessful or not feasible) . This device helps drain the stomach, thus aiding in the avoidance of nausea and vomiting flares. Some patients, however, will fail a gastrostomy tube. In such cases, in order to avoid dehydration and malnutrition, a **jejunostomy** tube may be considered. Complications of percutaneously placed tubes include: 1% procedure death, 25% infectious complications, in addition to peristomal leak, **perforation**, **fistula** formation, dislodgement, or tube dysfunction from clogging.

Intravenous hydration will occasionally be required in **acute** flares. Only rarely will **parenteral** nutrition be required.

### Surgical Therapy

Surgical intervention has not been studied, and thus has no role in the management of gastroparesis.

### Novel Therapies

#### Botulinum Toxin

Studies suggest that type I diabetics suffer from poor coordination of antro-pyloro-duodenal **contraction** and relaxation functions. More importantly, when they do experience contractions, they suffer a failure of pyloric relaxation. Unfortunately, there are no **systemic** medications to target the **pylorus**. Botulinum toxin, a product of the bacteria Clostridium botulinum, is a **neurotoxin** that prevents **acetylcholine** release from nerve terminals. When locally injected into **striated** or **smooth muscle** segments, it prevents muscle **contraction**. As a result, **botulinum toxin** has been reported as a **therapeutic** agent in several **spastic** muscular conditions, including **achalasia**, hypertensive lower esophageal **sphincter**, anismus, **sphincter** Of Oddi dysfunction (go to the **Sphincter** of Oddi Dysfunction section), and **chronic** anal fissure. Similarly, in patients with gastroparesis due to pylorospasm, there is excessive **smooth muscle tone** with failure to relax. Prolonged pyloric contractions may cause **functional** resistance to **gastric** outflow. To date, only a few patients have been treated with pyloric injections of **botulinum toxin**. Preliminary reports, however, have described good response in decreasing pyloric resistance and improving **gastric** emptying.

#### Gastric Pacing

There has recently been increasing interest in treating gastroparesis by **gastric** electric stimulation. Although early tests did not meet with success, more recent studies have demonstrated some effect. The concept consists of implanting electrodes on the **gastric serosa** (through open or **laparoscopic** approach), thus providing continuous or intermittent (e.g. at meal time) electric stimulation. The expectation is increased contractility, and hence improved **gastric** emptying. The largest study to date on **gastric** pacing (WAVESS: Worldwide Anti-Vomiting Electrical Stimulation Study) was an open label study that enrolled 33 patients. Although researchers reported 80% improvement in symptoms, emptying times improved only modestly. Side effects included infection, pacer migration, and stomach wall **perforation**. A few smaller, later studies have reported some success, such that treated patients no longer needed **jejunostomy** tube feedings.

#### Novel Potential Agents

There is considerable ongoing research aimed at identifying novel therapies for gastroparesis. Putative agents include:

Sildenafil (potentiates **nitric oxide**) improves pyloric relaxation. Definitive improvement on gastroparesis has not been documented, however.

Levosulpiride (**Dopamine** receptor D2-**antagonist**) is expected to reverse dopaminergic inhibition on **gastric contraction**. A **randomized** trial has demonstrated effectiveness comparable to cisapride.

Loxiglumide (CCK-A **antagonist**) was found to increase antral **motility**. It remains under investigation.

Clonidine (a 2-receptor **agonist**), a commonly used anti-hypertensive, decreases antro-duodenal contractions. Although in studies clonidine did not alter **gastric** emptying in healthy adults, it did improve emptying in diabetics. The exact mechanism remains unclear. Further studies are needed.

Tegaserod (5-HT4 partial **agonist**) increased **gastric** emptying in tested diabetic mice, but not in healthy volunteers. More studies are in progress.

Clarithromycin (a newer macrolide) has shown promise in improving **gastric** emptying. Further studies are awaited.

### Overview

In addition to dehydration and malnutrition, severe vomiting may result in Mallory-Weiss tears and aspiration pneumonia in some patients with gastroparesis.

Some patients may also develop phytobezoars (Figure 12). Presenting symptoms include abdominal pain, nausea, fullness, early satiety, and bloating. An abdominal mass may at times be palpable. Bezoars may be endoscopically lavaged and removed (enzymatic digestion such as with N-acetylcysteine may be helpful). Prevention consists of avoiding foods high in indigestible fibers.

