Gastroparesis: Approach, Diagnostic Evaluation, and Management

Derek M. Tang, MD and Frank K. Friedenberg, MD

Gastroparesis is a chronic motility disorder of the stomach that involves delayed emptying of solids and liquids, without evidence of mechanical obstruction. Although no cause can be determined for the majority of cases, the disease often develops as a complication of abdominal surgeries or because of other underlying disorders, such as diabetes mellitus or scleroderma. The pathophysiology behind delayed gastric emptying is still not well-understood, but encompasses abnormalities at 3 levels—autonomic nervous system, smooth muscle cells, and enteric neurons. Patients will often cite nausea, vomiting, postprandial fullness, and early satiety as their most bothersome symptoms on history and physical examination. Those that present with severe disease may already have developed complications, such as the formation of bezoars or masses of undigested food. In patients suspected of gastroparesis, diagnostic evaluation requires an initial upper endoscopy to rule out mechanical causes, followed by a gastric-emptying scintigraphy for diagnosis. Other diagnostic alternatives would be wireless capsule motility, antroduodenal manometry, and breath testing. Once gastroparesis is diagnosed, dietary modifications, such as the recommendation of more frequent and more liquid-based meals, are encouraged. Promotility medications like erythromycin and antiemetics like prochlorperazine are offered for symptomatic relief. These agents may be frequently changed, as the right

Competing Interests. The authors declare no conflict of interest and have no financial disclosures to make. This manuscript has not been published previously and is not under consideration in another journal.
Dis Mon 2011;57:74-101
0011-5029/2011 $36.00 + 0
doi:10.1016/j.disamonth.2010.12.007

combination of effective medications will vary with each individual. In patients who are refractory to pharmacologic treatment, more invasive options, such as intrapyloric botulinum toxin injections, placement of a jejunostomy tube, or implantation of a gastric stimulator, are considered. Future areas of research are based on current findings from clinical studies. New medications, such as hemin therapy, are emerging because of a better understanding of the pathophysiology behind gastroparesis, and present treatment options, such as gastric electric stimulation, are evolving to be more effective. Regenerative medicine and stem cell-based therapies also hold promise for gastroparesis in the near future.

Introduction

Gastroparesis, or delayed gastric emptying, is a motility disorder of the stomach that is characterized by slowed emptying of food in the absence of mechanical obstruction.[1,2] Normal gastric motor function is a coordinated sequence of events influenced by the autonomic nervous system, smooth muscle cells, and enteric neurons.[3] Disturbances of any of these control pathways can lead to delayed gastric emptying or gastric stasis. A range of causes has been identified, most notably idiopathic, diabetic, and postsurgical etiologies.[1,4] Symptoms of gastroparesis are variable and nonspecific, but the most common include nausea, vomiting, bloating, early satiety, and abdominal pain.[4] As the severity of gastroparesis progresses, other disorders or complications, such as esophagitis, Mallory–Weiss tear, peptic ulcer disease, and bezoar formation, can develop.[1,5,6]

This article systematically reviews our current understanding of the epidemiology, basic science, etiology, and pathophysiology of gastroparesis. It also reviews recent advances in management, including patient evaluation, diagnosis, and treatment.

Epidemiology

The epidemiology of gastroparesis in the USA is not well-defined, but the condition is relatively common. A population-based study in Olmsted County, Minnesota identified 3604 potential cases, of which 83 met diagnostic criteria for definite gastroparesis.[7] The age-adjusted incidence per 100,000 person-years for definite gastroparesis was 2.5 for men and 9.8 for women, while the age-adjusted prevalence per 100,000 persons was 9.6 for men and 37.8 for women.[7] These statistics also support the

finding that gastroparesis more frequently affects females.[8] In a study that followed 146 individuals with gastroparesis over 6 years, 84% of the patients were women, and the mean age of onset was 34 years.[4] Although the reason behind this gender difference is unclear, healthy females have demonstrated slower gastric emptying than their male counterparts.[9]

Longstanding diabetes mellitus, among a number of other causes, can lead to gastroparesis. In 1958, it was originally believed that gastric retention was only associated with type 1 diabetes.[10] Now, it is being increasingly recognized in an equal number of type 2 diabetes cases.[11] Population-based studies have shown that 2-19% of diabetic patients report upper gastrointestinal symptoms.[12,13] Meanwhile, investigations at tertiary referral centers have shown that 48-65% of diabetic patients with abdominal symptoms have delayed gastric emptying.[14,15]

Gastroparesis is an increasingly recognized disorder on the rise because of heightened awareness and testing in the USA. Hospitalizations with gastroparesis as the primary and secondary diagnoses more than doubled from 1995 to 2004.[16] The increasing prevalence is in part because of the growing cases of diabetes mellitus, improving longevity of diabetic patients, and increasing number of surgeries for gastroesophageal reflux disease (GERD) and morbid obesity.[16] Moreover, gastroparesis-related hospitalizations have a significant economic impact in the USA. Compared with hospitalizations for GERD, gastric ulcers, gastritis, and nausea/vomiting, patients with gastroparesis had the longest duration of hospital stay and the highest or second highest total costs.[16]

Basic Science

The stomach is traditionally described as having 2 functional segments—the fundus and antrum.[3] Both participate in differing but complementary roles in gastric emptying. Although discrepancies exist, general opinion is that the fundus is more responsible for the gastric emptying of liquids, while the antrum is a greater contributor in the gastric emptying of solids.[17,18] During a meal, the fundus serves as a reservoir and facilitates the chemical digestion of food into large particles via gastric acid and proteases.[17] Its slow sustained contractions regulate intragastric pressure before food is advanced to the antrum. In contrast, the antrum provides continence for food and is mainly responsible for grinding, mixing, and trituration (process of reducing food into fine small particles).[17] In between meals, the resulting chyme is cleared from the stomach into the proximal duodenum through peristaltic antral contractions.[2]

Normal gastric emptying is a series of events that is controlled by the autonomic nervous system, smooth muscle cells, and enteric neurons.[3] Innervation of the vagus nerve by parasympathetic activity regulates fundic accommodation, antral contractions, and pyloric relaxation.[2] These actions are countered or inhibited by the celiac ganglia, which is supplied by sympathetic activity. Smooth muscle cells are responsible for contractions throughout the stomach. Depolarization of resting membrane potentials contracts the cells, and electrical coupling of neighboring muscle cells propagates this contraction.[19] The interstitial cells of Cajal, or pacemaker cells located within the enteric nervous system in the greater curvature, provide the patterned electrical activity and synaptic connectivity that initiate the smooth muscle cells.[19]

Several neurotransmitters are essential in gastric emptying, but nitric oxide (NO) is the one of greatest interest.[3] Closely associated with the interstitial cells of Cajal, this inhibitory neuromuscular transmitter mainly functions in the relaxation and accommodation of the fundus.[20] It does not seem to have an effect on the antrum, but does also serve to decrease the tone of the pylorus.[21] Chronic depletion of NO from neuronal NO synthase, the enzyme responsible for NO synthesis, leads to delayed gastric emptying of both solids and liquids.[20]

Etiology and Pathophysiology

Underlying conditions should be considered in patients who develop a gastrointestinal motility disorder. Of 146 patients, the most common etiologies of gastroparesis were idiopathic (36%), diabetic (29%), and postgastric surgery (13%); other associated disorders included Parkinson's disease, collagen vascular disorders, and intestinal pseudoobstruction.[4]

Idiopathic gastroparesis is an umbrella term used when no known cause can be identified. Postinfectious or postviral gastroparesis is regarded as a subgroup under this heading, representing 21% of idiopathic cases.[22] Acute gastroenteritis has been linked to gastric stasis, and implicated pathogens in adults include the herpes (ie, Epstein-Barr), Hawaii, and Norwalk viruses.[23,24] In children, rotavirus is the suspected cause.[25] Although the exact mechanism in which viruses cause abnormal gastric emptying is difficult to ascertain, it is postulated that the infecting agent induces a form of neuropathy by either directly affecting autonomic ganglia or inducing an immunologic and inflammatory response.[22,26] Postviral gastroparesis appears to be self-limiting, with most cases resolving within 18 months in adults and 24 months in children.[24,25]

Longstanding diabetes mellitus predisposes patients to developing gastric dysmotility. Referral center studies have shown that more than half of diabetic patients with gastrointestinal symptoms have delayed gastric emptying.[14,15] However, the prevalence of abdominal symptoms suggestive of diabetic gastroparesis is much lower, affecting up to 20% of patients in the community.[12,13,27] This discrepancy may be because patients at referral centers represent those with more severe disease. The pathogenesis of diabetic gastroparesis is multifactorial and results in a neuromyopathy. In diabetes mellitus, increased oxidative stress from low heme oxygenase-1 levels in addition to reduced insulin and insulin-like growth factor-1 signaling, not hyperglycemia, are responsible for the loss of the interstitial cells of Cajal.[28,29] Consequently, this depletion causes abnormalities in gastric slow waves, absence of peristalsis, and atrophy of gastric smooth muscle.[28,30,31]

Postsurgical gastroparesis occurs after injury to the vagus nerve usually following upper abdominal operations, such as fundoplication for GERD and bariatric surgery for morbid obesity.[32] In 60 patients who developed stasis after gastric surgery, 80% had received a partial gastrectomy with a gastroenterostomy.[33] Surgeries involving the pancreas and esophagus have been implicated as well. In one study, 67% of patients receiving pancreatic cancer cryotherapy and 4.8% receiving pancreaticoduodenectomy developed delayed gastric emptying in the early postoperative period.[34] There have been data associating gastrointestinal complications with organ transplantation. Among 208 lung transplant recipients, 6% developed gastroparesis over a median follow-up period of 3.5 years.[35] Meanwhile, the majority (83%) of patients who received heart-lung transplantation developed severe medication-refractory gastroparesis over a mean follow-up period of 2.6 years.[35-37] Lastly, endoscopic variceal sclerotherapy has been demonstrated to induce transient alterations in gastrointestinal motility and subsequent bezoar formation.[38,39] In these cases of postsurgical gastroparesis, damage to the vagus nerve seems to be the culprit, leading to reduced antral contractions and loss of pyloric relaxation.[32]

Less common causes of delayed gastric emptying include medications, neurological conditions, and connective tissue disorders. Alpha-2 adrenergic agonists and tricyclic antidepressants slow gastrointestinal motility by mainly increasing sympathetics through adrenergic receptor stimulation. Diseases that affect the central nervous system (CNS) are Parkinson's disease, multiple sclerosis, and amyloidosis. Impaired gastric emptying is the most common nonmotor feature of Parkinson's disease and is caused by neuronal degeneration in the dorsal nucleus of the vagus

nerve and gastrointestinal myenteric plexuses by Lewy bodies.[40-42] In multiple sclerosis, lesions involving the white matter, especially in the vagal parasympathetic fibers, is believed to be the trigger.[43] Finally, in amyloidosis and connective tissue disorders like systemic sclerosis, dysmotility occurs in patients in the later stages of presentation. Infiltration into the autonomic nerves and smooth muscle leads to progressive fibrosis and altered function of enteric neurons.[44-46]

History and Physical Examination

Careful history taking and an understanding of the patient's symptoms can help discern other disorders before making a preliminary diagnosis. Several conditions can mimic the clinical presentation of gastroparesis, including esophagitis, peptic ulcer disease, malignancy, bowel obstruction, and pancreaticobiliary disorders.[5] Medication side effects and uremia should be considered as well.[5]

Patients suspected of gastroparesis usually present with several concurrent but nonspecific abdominal complaints. The symptom profile of 146 patients in one study was as follows: nausea (92%), vomiting (84%), bloating (75%), early satiety (60%), and abdominal pain (46%).[4] A smaller study with 28 patients yielded similar results, but only with nausea and abdominal pain as the most reported symptoms.[47]

The severity, nature, and frequency of the nausea and vomiting should be further characterized, as these may be useful in narrowing the differential diagnosis. Abdominal pain is a prominent symptom that correlates with a patient's quality of life, rather than the severity of delayed gastric emptying.[48] Patients often describe it as burning, vague, or crampy in nature, with a minority of patients localizing it to the epigastric region.[47] Sharp well-localized pain is not characteristic, and other causes, such as pancreatitis, need to be ruled out in these situations.[2] The timing of the abdominal pain may vary widely, either manifesting after meals or during nighttime sleep.[47]

Various tools have been developed over the years to gauge the severity of symptoms in patients with gastroparesis. One reliable and valid modality, known as the Gastroparesis Cardinal Symptom Index (GCSI), has allowed for better subjective symptom reporting from patients and higher correlation of these symptoms with gastric emptying. Compiled from clinician recommendations, interviews with patient focus groups, and literature reviews, the GCSI is an assessment of symptom severity over 2 weeks and incorporates 9 symptoms focusing on 3 areas—early satiety, nausea/vomiting, and bloating.[49,50] A GCSI daily diary was later developed to minimize potential patient recall effects related to the

2-week symptom period.[51] This instrument helps quantify gastrointestinal symptoms in patients across institutions.

Physical examination may reveal epigastric or diffuse tenderness during abdominal palpation, but patients can sometimes present with no evident findings. The remainder of the examination should be devoted to identifying characteristics of underlying disorders. For instance, patients suspected of systemic sclerosis may have discoloration (Raynaud's phenomenon) of the distal extremities on inspection, large joint contractures on musculoskeletal examination, and a split S_2 or loud P_2 suggestive of pulmonary hypertension on cardiac auscultation.[52]

Diagnostic Tests and Imaging

Initial laboratory testing is generally not useful in diagnosing patients with presumed gastroparesis, but routine blood tests should be tailored toward the outcome of the history and physical examination. They can also be performed to rule out other differentials. For example, pancreatitis should be considered in patients presenting with abdominal pain in the epigastric region, and a serum lipase would be most helpful. When other conditions are ruled out, then gastroparesis should be given more consideration.[53]

Diagnostic evaluation generally encompasses an esophagogastroduodenoscopy initially. This endoscopy is to rule out structural disorders of the upper gastrointestinal tract and to visualize any source of mechanical obstruction, such as malignancy or peptic ulcer disease. If this upper endoscopy yields organic etiologies, those specific disorders will need to be treated. Otherwise, if the endoscopy yields negative findings, patients will need additional testing to assess their rate of gastric emptying.

Gastric-Emptying Scintigraphy

Gastric-emptying scintigraphy (GES) is currently regarded as the gold standard for measuring motility of the stomach. This noninvasive, quantitative method involves the patient eating a radiolabeled solid meal, and then gastric counts, which correlate with the amount of meal remaining in the stomach, are measured scintigraphically at particular time points.[54] Although GES has long been the standard in evaluating delayed gastric emptying, there has been a lack of standardization of this test, such as differences in the meals used, patient positioning, and frequency or duration of imaging.[54] This consequently limits the clinical utility of the test and presents obstacles for both patients and physicians, as the latter try to interpret results from other institutions.[54]

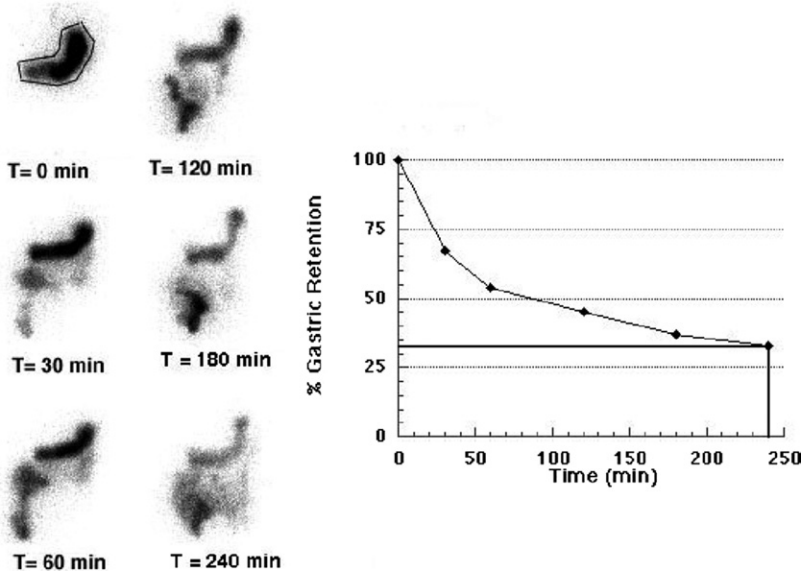


FIG 1. Abnormal results from a gastric-emptying scintigraphy. The left half of this figure depicts the gastric emptying of a radiolabeled meal at particular time points from start to 4 hours. The right half of the figure shows a chart plotting the percentage of remaining radiolabeled meal in the stomach (*y*-axis) versus time in minutes (*x*-axis). This patient has an abnormal 4 hour gastric-emptying scintigraphy, because there is 32.5% gastric retention at 240 minutes (or 4 hours). Gastric retention greater than 60% at 2 hours and/or greater than 10% at 4 hours is diagnostic for delayed gastric emptying. Note that this patient has normal gastric emptying at 120 minutes (or 2 hours), with about 45% of the radiolabeled meal remaining in the stomach.

Consensus standards for GES have been published by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. The recommended protocol involves a low-fat, egg-white meal with imaging at 0, 1, 2, and 4 hours after meal ingestion. The technetium-99m sulfur colloid radiolabeled meal would comprise 2 large eggs, 2 slices of bread, and jam with water.[54] Delayed gastric emptying would be present if there is >90% gastric retention at 1 hour, >60% at 2 hours, and >10% at 4 hours (Fig 1); these numbers are based on results from the largest multi-institutional study that investigated gastric-emptying rates in healthy individuals.[54,55] In patients who have a normal percentage of gastric retention after 2 hours, completing or extending the GES to 4 hours is recommended. Studies have shown that the data at 2 hours have greater accuracy for detecting accelerated gastric emptying, while the data at 4 hours have higher accuracy for identifying gastric stasis.[56,57]

A multitude of individual factors can influence the results of GES, including medications, tobacco smoking, and hyperglycemia. Anticholin-

ergics, tricyclic antidepressants, narcotic analgesics, and adrenergic agents can slow gastric emptying, while prokinetic drugs (ie, metoclopramide, cisapride, domperidone, erythromycin) can accelerate emptying.[58] Because these medications can cause a false-positive or -negative result, they should be discontinued for at least 48 hours before the GES.[54] Cigarette smoking has been shown to delay the gastric emptying of solids, and although it is unclear whether nicotine is responsible, patients should be advised to cease smoking in the morning before the test.[54,59,60] Mild elevations in blood glucose (≥144 mg/dL) can delay gastric emptying, while other studies have demonstrated that modest elevations (≥288 mg/dL) can significantly retard it in diabetic patients.[61,62] Thus, it is recommended that diabetics should have their glucose checked on the morning before the GES; if it is ≥275 mg/dL, then insulin should be administered to lower the level, or the study should be rescheduled.[54] Those caring for patients with gastroparesis need to recognize that there is often a discrepancy between patient symptoms and rates of gastric emptying.[63]

Wireless Capsule Motility

The SmartPill GI Monitoring System (SmartPill Corporation, Buffalo, NY) was approved by the US Food and Drug Administration (FDA) in 2006 for evaluation of delayed gastric emptying and chronic constipation (Fig 2). This indigestible capsule provides a nonradioactive and comparable alternative to GES. After the pill is swallowed, it measures gastric-emptying time by sensing luminal pH, pressure, and temperature as it traverses through the digestive tract.[64,65] Gastric emptying is demarcated when there is a sudden change in pH from the acidity of the stomach to the alkaline environment of the duodenum.[63] Using miniaturized wireless sensor technology, the pill relays information to a receiver that can be worn on the patient's belt or around his/her neck. The SmartPill is excreted from the gastrointestinal tract after 1 or 2 days, and when the patient returns to clinic, information from the receiver is downloaded to a computer to be analyzed. Gastric emptying by wireless capsule motility seems to correlate with the T-90% GES and the return of phase III of the migrating motor complex (MMC) of the fasting period.[66]

Antroduodenal Manometry

Antroduodenal manometry assesses the coordination of gastrointestinal motor function in fasting and postprandial periods through pressure measurements.[67] With the help of radiographic fluoroscopy or endoscopy, proper positioning of a catheter or transducer with pressure sensors allows

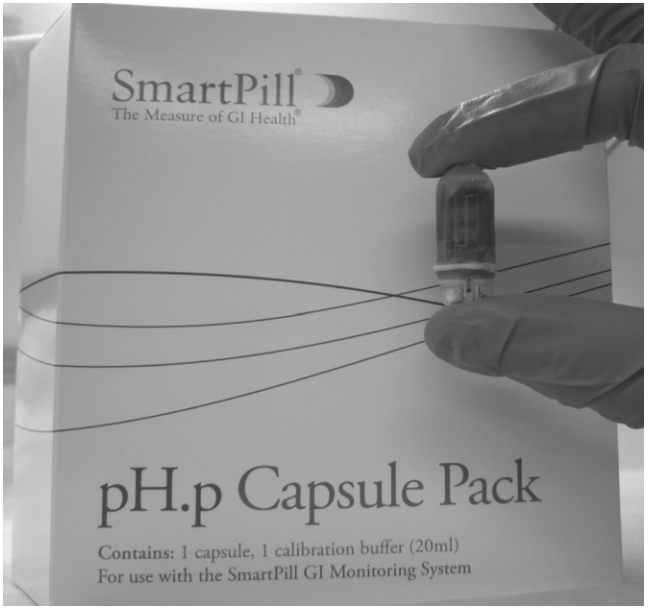


FIG 2. Image of the SmartPill (SmartPill Corporation, Buffalo, NY). The SmartPill is often described as the size of a large multivitamin pill. It measures approximately 1.3 cm by 2.6 cm.

for recording gastric and duodenal contractions. This technique can be performed over a 5- to 8-hour period in a stationary setting or a 24-hour period in an ambulatory one. In patients with gastroparesis, there is a disturbance in the relationship between antral, pyloric, and duodenal pressure waves that result in a reduced antral motility index.[68] This test is particularly valuable in distinguishing between processes suggestive of myopathy (ie, systemic sclerosis) and neuropathy (ie, diabetes mellitus).[58] In myopathic etiologies, manometry demonstrates less frequent low-amplitude antral MMCs. Meanwhile, in patients with neuropathic causes, antral MMCs are generally poorly coordinated, but of normal amplitude.[69-72]

Breath Testing

Breath testing is a noninvasive method that can be used in the ambulatory setting. It indirectly measures the gastric-emptying rate of solids with similar reliability to GES.[73,74] It involves a stable nonradioactive ^{13}C isotope bound to a digestible substance, such as octanoic acid, acetate, or *Spirulina platensis* (algae).[73-75] ^{13}C-labeled octanoic acid is more commonly used, and this is then mixed into a solid meal, such as a

muffin.[76,77] As ^{13}C-octanoate is ingested and absorbed into the small intestine, it is metabolized into ^{13}C-CO_2, which is expelled from the lungs and collected; the rate-limiting step of this reaction is the rate of solid gastric emptying.[53] The main advantage of breath testing is its lack of radiation exposure to the patient, while its disadvantage is that patients with select disorders, like celiac disease or cirrhosis, have impaired metabolism of octanoate into CO_2. There have been recent attempts to develop a more standardized meal to be used with the ^{13}C-octanoic acid breath test that does not carry side effects and can be used in patients with lactose intolerance, diabetes mellitus, and celiac disease.[78]

Other Imaging Studies

Transabdominal ultrasonography and magnetic resonance imaging (MRI) are two other studies that can evaluate gastric emptying in patients, but are less frequently used. Ultrasonography is a simple and noninvasive technique that can assess structural and functional abnormalities of gastric motility. Two-dimensional ultrasound can indirectly provide information about gastric emptying by quantifying changes in antral area over time.[79] A study has shown that diabetics have a wider antral area in fasting and postprandial states than healthy individuals.[80] Three-dimensional ultrasound provides more detailed information by being able to assess intragastric meal distribution and volume, but requires an operator with considerable technical experience.[81] MRI of gastrointestinal function is a recently developing tool that is comparable to GES in reliably assessing the gastric emptying of mixed solid and liquid meals.[82] Because it can distinguish between gastric air and fluid, its high-resolution imaging capabilities can simultaneously measure gastric emptying, gastroduodenal motility, and gastric secretions.[83] Disadvantages of this MRI technique include its relatively expensive cost, need for specialized equipment, and lack of standardization across institutions. Currently, transabdominal ultrasonography and MRI are used more as clinical research tools, rather than definitive diagnostic tests, in the workup of patients with gastroparesis.

Treatment

General Approach

General principles for patient management include (1) hydration with correction of electrolyte imbalances; (2) identification and treatment of the underlying disorder (ie, diabetes mellitus); and (3) alleviation of symptoms (ie, nausea, vomiting) with medications.[84] A list of the

patient's current medications should be reviewed, and those that may precipitate gastric dysmotility or limit the advantages of antiemetics and prokinetic agents should be discontinued.[1] Diabetics with symptoms of gastroparesis should monitor their blood glucose closely and have their insulin regimen or medications optimized, as hyperglycemia has been shown to exacerbate symptoms.[61,62,85]

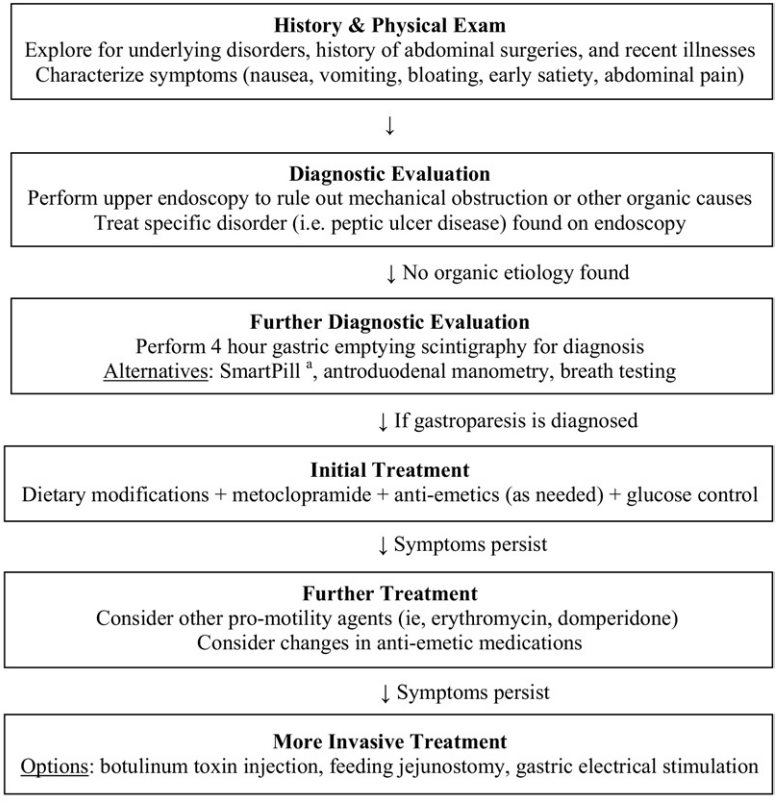
For symptomatic patients with mild disease, dietary modifications and symptomatic management with medications are recommended initially. Patients with more severe manifestations, such as pronounced dehydration or intractable vomiting, may need hospitalization or more invasive interventions.[1] These include intrapyloric botulinum toxin (Botox) injections, placement of a feeding jejunostomy, or implantation of a gastric electrical stimulator. The diagnostic approach to patients with gastroparesis (Fig 3) should ultimately be based on the collective experiences and opinions of clinicians who specialize in their care.[1]

Dietary Modifications

Dietary recommendations mainly involve adjustments to meal content and frequency. Patients should be encouraged to eat more liquid-based meals, such as soups or stews, since individuals with gastroparesis often have preserved gastric emptying of liquids. Intake of fats and nondigestible fibers should be reduced, because these foods generally retard gastric emptying through various mechanisms. Fats are time-dependent on the lipolysis of triglycerides to fatty acids via gastric hormones, while high-fiber fruits and vegetables (ie, green beans, apples, brussel sprouts) predispose to phytobezoar formation because of reduced interdigestive antral motility.[86,87] Smaller portioned meals should be suggested, and the meals should be spread throughout the day.[88] Meals of larger weight and higher calorie content have been demonstrated to have longer gastric-emptying times.[89,90] Patients with severe symptoms may not be able to tolerate smaller, more frequent, and more liquid-based meals. As a result, they may require liquidized or homogenized meals with vitamin supplements. Enteral nutrition via a jejunostomy tube may be necessary, while parenteral nutrition should be reserved for patients who fail enteral feeding.[91]

Prokinetic Medications

Prokinetic agents promote the movement of contents from the stomach by increasing antral contractility, correcting gastric dysrhythmias, and improving coordination between the antrum and duodenum.[91] These medications provide only modest efficacy, and because there is a



[a] SmartPill Corporation, Buffalo, NY, USA

FIG 3. Approach to gastroparesis. This flowchart depicts the approach to gastroparesis, from history and physical examination to treatment.

discrepancy between improvement in gastric emptying and symptom relief, response to treatment should be judged clinically.[92] The three primary promotility agents in the USA are metoclopramide, domperidone, and erythromycin (Fig 4). Unlike erythromycin, metoclopramide and domperidone have antiemetic properties as well.[93-95]

Metoclopramide is currently the only FDA-approved medication used in the treatment of gastroparesis. It is a substituted benzamide derivative that is structurally similar to procainamide and primarily acts as a dopamine D_2 receptor antagonist. As the agent blocks dopamine D_2 receptors and stimulates 5-HT_4 receptors, there is an augmented release of acetylcholine within the gut wall.[96] This leads to increased lower

Medication	Main Mechanism	Starting Oral Dose	Main Adverse Effects	Comments
Metoclopramide (Reglan) [a]	Central & peripheral dopamine-2 receptor antagonist	10 mg TID & qHS	Extrapyramidal movement disorders (i.e. tardive dyskinesia), hyperprolactinemia	Only FDA-approved drug for the treatment of gastroparesis in the United States; has additional anti-emetic properties
Domperidone (Motilium) [b]	Peripheral dopamine-2 receptor antagonist	10 mg TID & qHS	Hyperprolactinemia	Available only through an investigational program in the United States; has additional anti-emetic properties
Erythromycin	Motilin receptor agonist	125 mg BID	Gastrointestinal upset, arrhythmias (i.e. QT interval prolongation), interactions with other drugs	Macrolide antibiotic with anti-microbial activity that also works to increase gastric emptying; has no anti-emetic properties

[a] Schwarz Pharma US, Atlanta, GA, USA
[b] Janssen Pharmaceutica, Titusville, NJ, USA

FIG 4. Summary of primary promotility agents. Properties of the main promotility agents used in the pharmacologic treatment of gastroparesis are shown.

esophageal sphincter tone, antral contractility, fundic tone, and antroduodenal peristalsis.[2,96] The resulting effect of accelerated gastric emptying has been demonstrated in several studies.[94,97,98] Because metoclopramide can cross the blood–brain barrier, patients should be monitored for any neurological changes that would warrant discontinuation of the drug. Metoclopramide has been closely linked to causing or precipitating extrapyramidal movement disorders, such as Parkinsonism, tardive dyskinesia, and akathisia.[96,99,100] The FDA issued a black box warning in 2009 highlighting the risk of tardive dyskinesia from metoclopramide; available data show that this risk may be $<1\%$.[96] Those at greatest risk include elderly people (>70 years old) and those on continuous therapy for more than 3 months. Other adverse CNS effects include somnolence, anxiety, depression, and reduced mental acuity.[94]

Domperidone is approved only on an investigational basis in the USA, but is otherwise available in Canada, Mexico, and Europe. In the USA, this drug is available at specific compounding pharmacies, but requires an institutional review board approval and signed consent form for use. This benzimadole derivative chiefly acts as a peripheral dopamine D_2 receptor antagonist with a mechanism of action similar to that of metoclopramide. The drug accelerates gastric emptying by inhibiting fundic relaxation while promoting antroduodenal coordination.[2] Because domperidone does not cross the blood–brain barrier, CNS side effects should be less evident. Release of prolactin (the pituitary sits outside of the blood–brain barrier) is promoted by both domperidone and metoclopramide because of their antidopaminergic activity, which can lead to menstrual irregularities and lactation in younger women. Both domperidone and metoclopramide are equally effective and efficacious in improving symptoms of gastroparesis.[94,101]

Erythromycin is a macrolide antibiotic that has been secondarily used to promote gastric emptying. The drug is believed to act as a motilin receptor agonist, and thereby, mimics the effects of motilin, a gastrointestinal polypeptide involved in gastric smooth muscle contractions.[102,103] Studies have shown that erythromycin has potent prokinetic capabilities comparable to metoclopramide.[104,105] However, an inadequate number of controlled trials limits the data regarding the clinical utility of erythromycin in treating gastroparesis.[106] Side effects of the antibiotic include abdominal cramps, nausea, diarrhea, and prolongation of the QT interval.[107] Concomitant use with calcium channel blockers and a variety of medications that can prolong the QT interval limit erythromycin's utility. Long-term usage of the drug can result in tachyphylaxis, in addition to adverse effects from prolonged antibiotic administration, such as pseudomembranous colitis.[107,108]

Other promotility medications are cisapride and Tegaserod. Cisapride is a 5-HT_4 receptor agonist that facilitates the release of acetylcholine from efferent motor neurons within the gut wall. It has been previously FDA-approved, but has since been withdrawn from the market in 2000 because of risk of arrhythmia-associated death.[109] Tegaserod is another 5-HT_4 receptor agonist, but was previously FDA-approved for the treatment of irritable bowel syndrome and constipation. It was pulled from the market in 2007 because of increased risk of cardiovascular ischemic events, although a recent study shows no correlation.[110]

Antiemetic Medications

In conjunction with prokinetic medications, antiemetics are used for symptomatic relief of nausea and vomiting in patients with gastroparesis. These work through a range of peripheral or central neural pathways. The main classes of these agents are phenothiazine derivatives (ie, prochlorperazine), serotonin 5-HT_3 receptor antagonists (ie, ondansetron), dopamine receptor antagonists (ie, metoclopramide), histamine H_1 receptor antagonists (ie, diphenhydramine), and benzodiazepines (ie, lorazepam) (Fig 5).[84]

Prochlorperazine and ondansetron are commonly prescribed, as they are known for their significant and clinically effective antiemetic properties.[84] Prochlorperazine is a phenothiazine derivative that acts as a dopamine receptor antagonist. It specifically blocks the chemoreceptor trigger zone of the area postrema, a structure that controls vomiting and is located in the fourth ventricle of the CNS.[2] Its principal side effects include sedation and extrapyramidal symptoms.[91] In comparison, ondansetron is a serotonin 5-HT_3 receptor antagonist that targets the chemore-

Phenothiazine Derivatives
Prochlorperazine (Compazine) [a]

Serotonin 5-HT_3 Receptor Antagonists
Ondansetron (Zofran) [a]

Dopamine Receptor Antagonists
Metoclopramide (Reglan) [b]
Domperidone (Motilium) [c]

Histamine H_1 Receptor Antagonists
Diphenhydramine (Benadryl) [d]
Promethazine (Phenergan) [e]
Meclizine (Antivert) [f]

Benzodiazepines
Lorazepam (Ativan) [e]

[a] GlaxoSmithKline, London, UK
[b] Schwarz Pharma US, Atlanta, GA, USA
[c] Janssen Pharmaceutica, Titusville, NJ, USA
[d] Johnson & Johnson Corporation, New Brunswick, NJ, USA
[e] Wyeth Pharmaceuticals, Madison, NJ, USA
[f] Pfizer, Inc., New York, NY, USA

FIG 5. List of primary antiemetic agents. This is a list of the main antiemetic classes and their respective members in the treatment of nausea and vomiting in patients with gastroparesis.

ceptor trigger zone of the area postrema, but is believed to be have additional peripheral effects on afferent vagal nerve fibers.[2] The exact mechanism of action is still unclear, and the drug appears to be relatively well-tolerated.[111]

Invasive and Surgical Interventions

Refractory gastroparesis is seen in patients who fail medical therapy with prokinetics and/or antiemetic agents and who are unable to meet their nutritional requirements. There is no general consensus in the management of recalcitrant gastroparesis, but for patients that exhaust all attempts at pharmacotherapy, endoscopic and surgical options are then considered.[1]

Endoscopic treatment of gastroparesis involves the injection of Botox into the pyloric sphincter. This neurotoxin is produced by the anaerobic *Clostridium botulinum* bacterium and causes muscle paralysis through inhibition of acetylcholine release from nerve terminals.[112,113] Botox

injections have been used successfully in the past on the lower esophageal sphincter in patients who suffer from achalasia.[114] Pyloric muscle spasms are believed to contribute to delayed gastric emptying, and these injections offer localized reduction of these contractions.[115] Earlier nonrandomized studies of Botox injections have demonstrated significant temporary improvement in symptoms and subsequent gastric-emptying tests for 3-6 months.[77,116-119] Nevertheless, results from more recent randomized controlled studies have not been as promising, showing that Botox improves symptoms of gastroparesis for no more than one month, with no added benefit of a second injection.[120,121] Data from more randomized controlled studies are still needed, but presently, intrapyloric Botox injections are not recommended for widespread treatment of gastroparesis.[121]

Surgical placement of a jejunostomy tube is performed in patients with severe refractory gastroparesis. This therapeutic option is often considered in patients who have had frequent hospitalizations that need access to hydration, nutrition, and medications. Laparoscopic jejunostomy can be performed safely, although major complications, such as displacement, obstruction, and aspiration pneumonia, may result after the procedure.[122] Despite these postoperative risks, overall health status has been demonstrated to improve with jejunostomy tube placement. In one retrospective study of patients with diabetic gastroparesis, 39% reported fewer symptoms of nausea and vomiting, 52% reported fewer hospitalizations, 56% reported better nutritional status, and 83% reported improved overall health.[123] In addition to laparoscopic jejunostomy, simultaneous insertion of a gastric tube may be necessary to facilitate abdominal decompression and symptomatic relief.

Gastric electrical stimulation is a surgical option that was FDA-approved in 2000 for the treatment of drug-refractory diabetic or idiopathic gastroparesis. It involves the placement of a gastric pacemaker or neurostimulator (ie, Enterra Therapy; Medtronic, Inc, Minneapolis, MN) in a subcutaneous pouch often in the right abdominal quadrant (Fig 6). The small device sends continuous high-frequency and low-energy waves through electrodes that are connected to the muscle wall of the antrum.[124] These waves stimulate and enhance autonomic vagal function to allow for more gastric accommodation.[125] Gastric electric stimulation has been shown to significantly decrease gastrointestinal symptoms and improve quality of life from as little as 6 weeks of therapy.[126] Over the long term, the neurostimulator maintains symptomatic relief and recovery of nutritional status for several years, with one study reflecting continued improvement for up to 5 years.[124,127,128] The

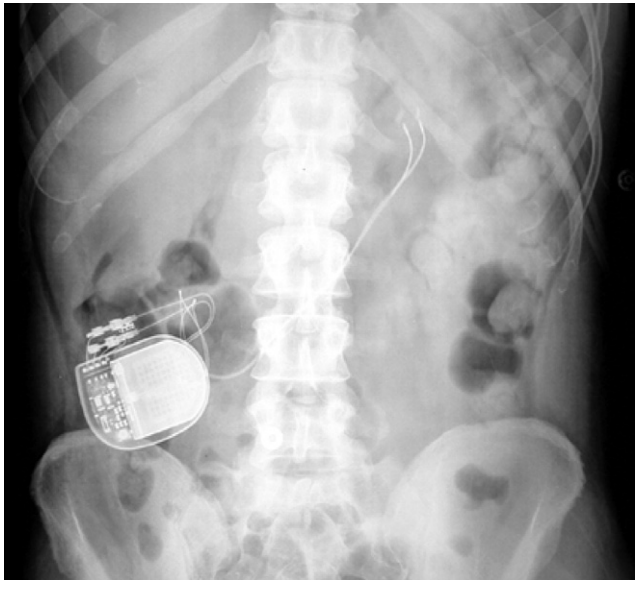


FIG 6. Implantation of a gastric electrical stimulator. This x-ray shows the placement of a gastric electrical stimulator in a subcutaneous pouch in the right lower quadrant of the abdomen. Leads from the stimulator connect to the muscle wall of the stomach's antrum.

most common complication associated with gastric electrical stimulation is infection, leading to device removal in 5-10% of patients.[1]

Future Direction

There has been considerable progress in the management of gastroparesis over the last 5 years, and overall, the outlook is encouraging (Fig 7).[129]

Advances in our understanding of the pathophysiology have led to the development of potentially useful new medications. The etiology of diabetic gastroparesis is multifactorial and has not been completely elucidated yet. Induction of the heme oxygenase-1 pathway has been shown previously to counter cellular changes related to the gastrointestinal complications of diabetes. It is believed that high levels of heme oxygenase-1 exert its protective effect by decreasing oxidative stress on the interstitial cells of Cajal.[29] The recent discovery that CD206-positive M2 macrophages are responsible for heme oxygenase-1 upregulation suggests a new therapeutic option for patients.[130] Presently, there is a pilot study investigating the efficacy of hemin, a therapy that induces heme oxygenase-1 expression in macrophages.

Key Points

1. Gastroparesis is delayed emptying of the stomach without evidence of mechanical obstruction.
2. Most common causes are idiopathic and diabetic etiologies.
3. Symptoms include nausea, vomiting, bloating, early satiety, postprandial fullness, and abdominal pain.
4. Four hour gastric emptying scintigraphy is the gold standard test for diagnosis.
5. Metoclopramide is the only FDA-approved drug for treatment of gastroparesis.
6. Endoscopic and surgical options are pursued for patients who have failed all pharmacotherapy attempts.

FIG 7. Summary of key points. The chart highlights important take-home points in the approach and management of gastroparesis.

Other medications arising from a better understanding of pathophysiology include ghrelin (ligand that binds to receptors on vagal afferent neurons and enteric neurons), ghrelin receptor agonists (ie, TZP-101), and acotiamide hydrochloride (or Z-338; muscarinic M1/M2 receptor antagonist that increases acetylcholine release).[131-134] These medications may possibly represent two new classes of prokinetic drugs. Herbal agents, such as iberogast (STW-5), have also shown symptomatic benefits in patients with functional dyspepsia and gastroparesis, although it is unclear whether the herbal extract truly accelerates gastric emptying.[135]

Meanwhile, there are studies investigating enhancements and alternatives to currently available medications, such as macrolides. Gastroparesis can result in altered nutrition and inadequate medication delivery within the stomach. One study intended to develop a transmucosal system that bypasses intestinal absorption to better deliver erythromycin than the standard oral or parenteral methods. Although successful in rats, the buccal delivery of erythromycin with permeation enhancers did not translate well into humans.[136] Further research is aimed at studying macrolide derivatives that are motilin receptor agonists without antimicrobial activity. One macrolide, ABT-229, has already been shown to not be effective in relieving symptoms in patients with gastroparesis or functional dyspepsia.[137,138] However, another agent, mitemcinal (GM-611), was demonstrated to accelerate gastric emptying in diabetic canines and rhesus monkeys.[139,140] One randomized controlled study revealed that mitemcinal at different doses accelerates gastric emptying in both diabetic and idiopathic patients with gastroparesis.[141] More clinical trials will need to be conducted to confirm this finding.

Treatment options for delayed gastric emptying have been limited, but gastric electrical stimulation has shown promise in improving gastrointestinal symptoms and sustaining relief over time. With the goal of achieving sustainable stimulation, alternative ways include long-pulse high-energy, single-channel, and multichannel with long pulse gastric electrical stimulation.[63,129] Other future treatment possibilities involve advances in regenerative medicine, particularly stem cell-based therapies. Stem cells are uncommitted cells characterized by their ability to undergo mitotic division and cultivate into a variety of differentiated, specialized cells.[142] Upon reprogramming, these stem cells would theoretically be able to provide an unlimited source of patient-specific replacement cells.[142] Stem cell-based therapies would aim to restore tissue integrity, such as in regeneration of the interstitial cells of Cajal, that are lost in diabetic gastroparesis or alleviation of inflammatory changes seen in idiopathic gastroparesis.

REFERENCES

1. Parkman HP, Hasler WL, Fisher RS, et al. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology 2004;127(5):1592-622.
2. Friedenberg FK, Parkman HP. Advances in the management of gastroparesis. Curr Treat Options Gastroenterol 2007;10(4):283-93.
3. Vittal H, Farrugia G, Gomez G, et al. Mechanisms of disease: the pathological basis of gastroparesis—a review of experimental and clinical studies. Nat Clin Pract Gastroenterol Hepatol 2007;4(6):336-46.
4. Soykan I, Sivri B, Sarosiek I, et al. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. Dig Dis Sci 1998;43(11):2398-404.
5. Parkman HP, Schwartz SS. Esophagitis and gastroduodenal disorders associated with diabetic gastroparesis. Arch Intern Med 1987;147(8):1477-80.
6. Brady PG, Richardson R. Gastric bezoar formation secondary to gastroparesis diabeticorum. Arch Intern Med 1977;137:1729.
7. Jung HK, Choung RS, Locke GR, 3rd, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. Gastroenterology 2009;136(4):1225-33.
8. Stanghellini V, Tosetti C, Paternico A, et al. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. Gastroenterology 1996;110(4):1036-42.
9. Datz FL, Christian PE, Moore J. Gender-related differences in gastric emptying. J Nucl Med 1987;28(7):1204-7.
10. Kassander P. Asymptomatic gastric retention in diabetics (gastroparesis diabeticorum). Ann Intern Med 1958;48(4):797-812.
11. Bharucha AE, Camilleri M, Forstrom LA, et al. Relationship between clinical features and gastric emptying disturbances in diabetes mellitus. Clin Endocrinol 2009;70(3):415-20.

12. Bytzer P, Talley NJ, Leemon M, et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. Arch Intern Med 2001;161(16):1989-96.
13. Maleki D, Locke GR, 3rd, Camilleri M, et al. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. Arch Intern Med 2000;160(18):2808-16.
14. Jones KL, Russo A, Stevens JE, et al. Predictors of delayed gastric emptying in diabetes. Diabetes Care 2001;24(7):1264-9.
15. Kong MF, Horowitz M, Jones KL, et al. Natural history of diabetic gastroparesis. Diabetes Care 1999;22(3):503-7.
16. Wang YR, Fisher RS, Parkman HP. Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995-2004. Am J Gastroenterol 2008;103(2):313-22.
17. Kelly KA. Gastric emptying of liquids and solids: roles of proximal and distal stomach. Am J Physiol 1980;239(2):G71-6.
18. Collins PJ, Houghton LA, Read NW, et al. Role of the proximal and distal stomach in mixed solid and liquid meal emptying. Gut 1991;32(6):615-9.
19. Sanders KM, Koh SD, Ward SM. Interstitial cells of cajal as pacemakers in the gastrointestinal tract. Annu Rev Physiol 2006;68:307-43.
20. Mashimo H, Kjellin A, Goyal RK. Gastric stasis in neuronal nitric oxide synthase-deficient knockout mice. Gastroenterology 2000;119(3):766-73.
21. Anvari M, Paterson CA, Daniel EE. Role of nitric oxide mechanisms in control of pyloric motility and transpyloric flow of liquids in conscious dogs. Dig Dis Sci 1998;43(3):506-12.
22. Bityutskiy LP, Soykan I, McCallum RW. Viral gastroparesis: a subgroup of idiopathic gastroparesis—clinical characteristics and long-term outcomes. Am J Gastroenterol 1997;92(9):1501-4.
23. Meeroff JC, Schreiber DS, Trier JS, et al. Abnormal Gastric Motor function in Viral Gastroenteritis. Ann Intern Med 1980;92(3):370-3.
24. Naftali T, Yishai R, Zangen T, et al. Post-infectious gastroparesis: clinical and electerogastrographic aspects. J Gastroenterol Hepatol 2007;22(9):1423-8.
25. Sigurdsson L, Flores A, Putnam PE, et al. Gastroparesis: presentation, treatment, and outcome. J Pediatr 1997;131(5):751-4.
26. Fujii N, Tabira T, Shibasaki H, et al. Acute autonomic and sensory neuropathy associated with elevated Epstein–Barr virus antibody titre. J Neurol Neurosurg Psychiatry 1982;45(7):656-8.
27. Enck P, Rathmann W, Spiekermann M, et al. Prevalence of gastrointestinal symptoms in diabetic patients and non-diabetic subjects. Z Gastroenterol 1994; 32(11):637-41.
28. Horvath VJ, Vittal H, Ordog T. Reduced insulin and IGF-I signaling, not hyperglycemia, underlies the diabetes-associated depletion of interstitial cells of Cajal in the murine stomach. Diabetes 2005;54(5):1528-33.
29. Choi KM, Gibbons SJ, Nguyen TV, et al. Heme oxygenase-1 protects interstitial cells of Cajal from oxidative stress and reverses diabetic gastroparesis. Gastroenterology 2008;135(6):2055-64, 2064.e1-2.
30. Forster J, Damjanov I, Lin Z, et al. Absence of the interstitial cells of Cajal in patients with gastroparesis and correlation with clinical findings. J Gastrointest Surg 2005;9(1):102-8.

31. Ordog T, Takayama I, Cheung WK, et al. Remodeling of networks of interstitial cells of Cajal in a murine model of diabetic gastroparesis. Diabetes 2000;49(10): 1731-9.
32. Shafi MA, Pasricha PJ. Post-surgical and obstructive gastroparesis. Curr Gastroenterol Rep 2007;9(4):280-5.
33. Fich A, Neri M, Camilleri M, et al. Stasis syndromes following gastric surgery: clinical and motility features of 60 symptomatic patients. J Clin Gastroenterol 1990;12(5):505-12.
34. Dong K, Li B, Guan QL, et al. Analysis of multiple factors of postsurgical gastroparesis syndrome after pancreaticoduodenectomy and cryotherapy for pancreatic cancer. World J Gastroenterol 2004;10(16):2434-8.
35. Paul S, Escareno CE, Clancy K, et al. Gastrointestinal complications after lung transplantation. J Heart Lung Transplant 2009;28(5):475-9.
36. Sodhi SS, Guo JP, Maurer AH, et al. Gastroparesis after combined heart and lung transplantation. J Clin Gastroenterol 2002;34(1):34-9.
37. Yiannopoulos A, Shafazand S, Ziedalski T, et al. Gastric pacing for severe gastroparesis in a heart-lung transplant recipient. J Heart Lung Transplant 2004; 23(3):371-4.
38. Davion T, Delamarre J, Reix N, et al. Gastric bezoar: another side effect of endoscopic variceal sclerotherapy. Scand J Gastroenterol 1989;24(7):818-20.
39. Masclee AA, Lamers CB. Effect of endoscopic sclerotherapy of esophageal varices on vagus nerve integrity. J Hepatol 1994;21(5):724-9.
40. Wang HB, Hsu CH. Severe gastroparesis in a patient with advanced Parkinson's disease. Wien Klin Wochenschr 2009;121(13-14):445.
41. Djaldetti R, Baron J, Ziv I, et al. Gastric emptying in Parkinson's disease: patients with and without response fluctuations. Neurology 1996;46(4):1051-4.
42. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Parkinsonism Relat Disord 2010 [epub ahead of print].
43. Raghav S, Kipp D, Watson J, et al. Gastroparesis with multiple sclerosis. Mult Scler 2006;12(2):243-4.
44. Domsic R, Fasanella K, Bielefeldt K. Gastrointestinal manifestations of systemic sclerosis. Dig Dis Sci 2008;53(5):1163-74.
45. Reddy AB, Wright RA, Wheeler GE, et al. Nonobstructive gastroparesis in amyloidosis improved with metoclopramide. Arch Intern Med 1983;143(2): 247-8.
46. Sjogren RW. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum 1994;37(9):1265-82.
47. Hoogerwerf WA, Pasricha PJ, Kalloo AN, et al. The overlooked symptom in gastroparesis. Am J Gastroenterol 1999;94(4):1029-33.
48. Cherian D, Sachdeva P, Fisher RS, et al. Abdominal pain is a frequent symptom of gastroparesis. Clin Gastroenterol Hepatol 2010;8(8):676-81.
49. Revicki DA, Rentz AM, Dubois D, et al. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. Qual Life Res 2004;13(4):833-44.
50. Revicki DA, Rentz AM, Dubois D, et al. Development and validation of a patient-assessed gastroparesis symptom severity measure: the gastroparesis Cardinal Symptom Index. Aliment Pharmacol Ther 2003;18(1):141-50.

51. Revicki DA, Camilleri M, Kuo B, et al. Development and content validity of a gastroparesis cardinal symptom index daily diary. Aliment Pharmacol Ther 2009;30(6):670-80.
52. Varga J. Systemic sclerosis: an update. Bull NYU Hosp Jt Dis 2008;66(3):198-202.
53. Friedenberg FK, Parkman HP. Delayed gastric emptying: whom to test, how to test, and what to do. Curr Treat Options Gastroenterol 2006;9(4):295-304.
54. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Am J Gastroenterol 2008;103(3):753-63.
55. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. Am J Gastroenterol 2000; 95(6):1456-62.
56. Thomforde GM, Camilleri M, Phillips SF, et al. Evaluation of an inexpensive screening scintigraphic test of gastric emptying. J Nucl Med 1995;36(1):93-6.
57. Guo JP, Maurer AH, Fisher RS, et al. Extending gastric emptying scintigraphy from two to four hours detects more patients with gastroparesis. Dig Dis Sci 2001;46(1):24-9.
58. Camilleri M, Hasler WL, Parkman HP, et al. Measurement of gastrointestinal motility in the GI Laboratory. Gastroenterology 1998;115(3):747-62.
59. Miller G, Palmer KR, Smith B, et al. Smoking delays gastric emptying of solids. Gut 1989;30(1):50-3.
60. Nowak A, Jonderko K, Kaczor R, et al. Cigarette smoking delays gastric emptying of a radiolabelled solid food in healthy smokers. Scand J Gastroenterol 1987; 22(1):54-8.
61. Fraser RJ, Horowitz M, Maddox AF, et al. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1990;33(11): 675-80.
62. Schvarcz E, Palmer M, Aman J, et al. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. Gastroenterology 1997;113(1):60-6.
63. Parkman HP, Camilleri M, Farrugia G, et al. Gastroparesis and functional dyspepsia: excerpts from the AGA/ANMS meeting. Neurogastroenterol Motil 2010;22(2):113-33.
64. Kuo B, McCallum RW, Koch KL, et al. Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. Aliment Pharmacol Ther 2008;27(2):186-96.
65. Rao SS, Kuo B, McCallum RW, et al. Investigation of colonic and whole gut transit with wireless motility capsule and radioopaque markers in constipation. Clin Gastroenterol Hepatol 2009;7(5):537-44.
66. Cassilly D, Kantor S, Knight LC, et al. Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. Neurogastroenterol Motil 2008;20(4): 311-9.
67. Soffer E, Thongsawat S. Clinical value of duodenojejunal manometry. Its usefulness in diagnosis and management of patients with gastrointestinal symptoms. Dig Dis Sci 1996;41(5):859-63.

68. Fraser RJ, Horowitz M, Maddox AF, et al. Postprandial antropyloroduodenal motility and gastric emptying in gastroparesis—effects of cisapride. Gut 1994;35(2):172-8.
69. Vantrappen G, Janssens J, Hellemans J, et al. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest 1977;59(6):1158-66.
70. Rees WD, Leigh RJ, Christofides ND, et al. Interdigestive motor activity in patients with systemic sclerosis. Gastroenterology 1982;83(3):575-80.
71. Camilleri M, Malagelada JR, Stanghellini V, et al. Gastrointestinal motility disturbances in patients with orthostatic hypotension. Gastroenterology 1985;88(6): 1852-9.
72. Camilleri M, Malagelada JR. Abnormal intestinal motility in diabetics with the gastroparesis syndrome. Eur J Clin Invest 1984;14(6):420-7.
73. Braden B, Adams S, Duan LP, et al. The [13C]acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. Gastroenterology 1995;108(4):1048-55.
74. Ghoos YF, Maes BD, Geypens BJ, et al. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology 1993;104(6):1640-7.
75. Szarka LA, Camilleri M, Vella A, et al. A stable isotope breath test with a standard meal for abnormal gastric emptying of solids in the clinic and in research. Clin Gastroenterol Hepatol 2008;6(6):635-643:e1.
76. Choi MG, Camilleri M, Burton DD, et al. Reproducibility and simplification of 13C-octanoic acid breath test for gastric emptying of solids. Am J Gastroenterol 1998;93(1):92-8.
77. Bromer MQ, Kantor SB, Wagner DA, et al. Simultaneous measurement of gastric emptying with a simple muffin meal using [13C]octanoate breath test and scintigraphy in normal subjects and patients with dyspeptic symptoms. Dig Dis Sci 2002;47(7):1657-63.
78. Perri F, Bellini M, Portincasa P, et al. (13)C-octanoic acid breath test (OBT) with a new test meal (EXPIROGer): toward standardization for testing gastric emptying of solids. Dig Liver Dis 2010;42(8):549-53.
79. Hausken T, Odegaard S, Matre K, et al. Antroduodenal motility and movements of luminal contents studied by duplex sonography. Gastroenterology 1992;102(5): 1583-90.
80. Undeland KA, Hausken T, Svebak S, et al. Wide gastric antrum and low vagal tone in patients with diabetes mellitus type 1 compared to patients with functional dyspepsia and healthy individuals. Dig Dis Sci 1996;41(1):9-16.
81. Tefera S, Gilja OH, Olafsdottir E, et al. Intragastric maldistribution of a liquid meal in patients with reflux oesophagitis assessed by three dimensional ultrasonography. Gut 2002;50(2):153-8.
82. Feinle C, Kunz P, Boesiger P, et al. Scintigraphic validation of a magnetic resonance imaging method to study gastric emptying of a solid meal in humans. Gut 1999;44(1):106-11.
83. Schwizer W, Maecke H, Fried M. Measurement of gastric emptying by magnetic resonance imaging in humans. Gastroenterology 1992;103(2):369-76.
84. Quigley EM, Hasler WL, Parkman HP. AGA technical review on nausea and vomiting. Gastroenterology 2001;120(1):263-86.

85. Lehmann R, Honegger RA, Feinle C, et al. Glucose control is not improved by accelerating gastric emptying in patients with type 1 diabetes mellitus and gastroparesis. A pilot study with cisapride as a model drug. Exp Clin Endocrinol Diabetes 2003;111(5):255-61.
86. Gentilcore D, Chaikomin R, Jones KL, et al. Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes. J Clin Endocrinol Metab 2006;91(6):2062-7.
87. Emerson AP. Foods high in fiber and phytobezoar formation. J Am Diet Assoc 1987;87(12):1675-7.
88. Friedenberg FK, Parkman HP. Management of delayed gastric emptying. Clin Gastroenterol Hepatol 2005;3(7):642-6.
89. Moore JG, Christian PE, Brown JA, et al. Influence of meal weight and caloric content on gastric emptying of meals in man. Dig Dis Sci 1984;29(6):513-9.
90. Moore JG, Christian PE, Coleman RE. Gastric emptying of varying meal weight and composition in man. Evaluation by dual liquid- and solid-phase isotopic method. Dig Dis Sci 1981;26(1):16-22.
91. Parkman HP, Hasler WL, Fisher RS, et al. American Gastroenterological Association medical position statement: diagnosis and treatment of gastroparesis. Gastroenterology 2004;127(5):1589-91.
92. Talley NJ. Diabetic gastropathy and prokinetics. Am J Gastroenterol 2003;98(2): 264-71.
93. Longstreth GF, Malagelada JR, Kelly KA. Metoclopramide stimulation of gastric motility and emptying in diabetic gastroparesis. Ann Intern Med 1977;86(2):195-6.
94. Patterson D, Abell T, Rothstein R, et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol 1999;94(5):1230-4.
95. Ricci DA, Saltzman MB, Meyer C, et al. Effect of metoclopramide in diabetic gastroparesis. J Clin Gastroenterol 1985;7(1):25-32.
96. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther 2010;31(1):11-9.
97. Perkel MS, Moore C, Hersh T, et al. Metoclopramide therapy in patients with delayed gastric emptying: a randomized, double-blind study. Dig Dis Sci 1979;24(9):662-6.
98. McCallum RW, Ricci DA, Rakatansky H, et al. A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care 1983;6(5):463-7.
99. Miller LG, Jankovic J. Metoclopramide-induced movement disorders. Clinical findings with a review of the literature. Arch Intern Med 1989;149(11):2486-92.
100. Ganzini L, Casey DE, Hoffman WF, et al. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. Arch Intern Med 1993;153(12):1469-75.
101. Sugumar A, Singh A, Pasricha PJ. A systematic review of the efficacy of domperidone for the treatment of diabetic gastroparesis. Clin Gastroenterol Hepatol 2008;6(7):726-33.
102. Hasler WL, Heldsinger A, Chung OY. Erythromycin contracts rabbit colon myocytes via occupation of motilin receptors. Am J Physiol 1992;262(1 Pt 1): G50-5.

103. Peeters T, Matthijs G, Depoortere I, et al. Erythromycin is a motilin receptor agonist. Am J Physiol 1989;257(3 Pt 1):G470-4.
104. Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. N Engl J Med 1990; 322(15):1028-31.
105. Erbas T, Varoglu E, Erbas B, et al. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. Diabetes Care 1993;16(11): 1511-4.
106. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. Am J Gastroenterol 2003;98(2):259-63.
107. O'Donovan D, Feinle-Bisset C, Jones K, et al. Idiopathic and diabetic gastroparesis. Curr Treat Opt Gastroenterol 2003;6(4):299-309.
108. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Am J Gastroenterol 1993;88(2):203-7.
109. Hennessy S, Leonard CE, Newcomb C, et al. Cisapride and ventricular arrhythmia. Br J Clin Pharmacol 2008;66(3):375-85.
110. Loughlin J, Quinn S, Rivero E, et al. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. J Cardiovasc Pharmacol Ther 2010;15(2):151-7.
111. Bodis S, Alexander E, 3rd, Kooy H, et al. The prevention of radiosurgery-induced nausea and vomiting by ondansetron: evidence of a direct effect on the central nervous system chemoreceptor trigger zone. Surg Neurol 1994;42(3):249-52.
112. Montecucco C, Molgo J. Botulinal neurotoxins: revival of an old killer. Curr Opin Pharmacol 2005;5(3):274-9.
113. Pasricha PJ, Ravich WJ, Kalloo AN. Effects of intrasphincteric botulinum toxin on the lower esophageal sphincter in piglets. Gastroenterology 1993;105(4):1045-9.
114. Porter RF, Gyawali CP. Botulinum toxin injection in dysphagia syndromes with preserved esophageal peristalsis and incomplete lower esophageal sphincter relaxation. Neurogastroenterol Motil 2010 [epub ahead of print].
115. Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. Gastroenterology 1986;90(6):1919-25.
116. Lacy BE, Zayat EN, Crowell MD, et al. Botulinum toxin for the treatment of gastroparesis: a preliminary report. Am J Gastroenterol 2002;97(6):1548-52.
117. Lacy BE, Crowell MD, Schettler-Duncan A, et al. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. Diabetes Care 2004;27(10):2341-7.
118. Miller LS, Szych GA, Kantor SB, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. Am J Gastroenterol 2002;97(7):1653-60.
119. Reddymasu SC, Singh S, Sankula R, et al. Endoscopic pyloric injection of botulinum toxin-A for the treatment of postvagotomy gastroparesis. Am J Med Sci 2009;337(3):161-4.
120. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. Aliment Pharmacol Ther 2007;26(9):1251-8.
121. Friedenberg FK, Palit A, Parkman HP, et al. Botulinum toxin A for the treatment of delayed gastric emptying. Am J Gastroenterol 2008;103(2):416-23.

122. Hotokezaka M, Adams RB, Miller AD, et al. Laparoscopic percutaneous jejunostomy for long term enteral access. Surg Endosc 1996;10(10):1008-11.
123. Fontana RJ, Barnett JL. Jejunostomy tube placement in refractory diabetic gastroparesis: a retrospective review. Am J Gastroenterol 1996;91(10):2174-8.
124. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 2003;125(2):421-8.
125. McCallum RW, Dusing RW, Sarosiek I, et al. Mechanisms of symptomatic improvement after gastric electrical stimulation in gastroparetic patients. Neurogastroenterol Motil 2010;22(2):161-7:e50-1.
126. McCallum RW, Snape W, Brody F, et al. Gastric electrical stimulation with enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clin Gastroenterol Hepatol 2010;8(11):947-954:e1.
127. Cutts TF, Luo J, Starkebaum W, et al. Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term health care benefits? Neurogastroenterol Motil 2005;17(1):35-43.
128. Abell T, Lou J, Tabbaa M, et al. Gastric electrical stimulation for gastroparesis improves nutritional parameters at short, intermediate, and long-term follow-up. JPEN J Parenter Enteral Nutr 2003;27(4):277-81.
129. Kashyap P, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. Gut 2010;59(12):1716-26.
130. Choi KM, Kashyap PC, Dutta N, et al. CD206-positive M2 macrophages that express heme oxygenase-1 protect against diabetic gastroparesis in mice. Gastroenterology 2010;138(7):2399-409, 2409.e1.
131. Tack J, Depoortere I, Bisschops R, et al. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. Aliment Pharmacol Ther 2005;22(9):847-53.
132. Murray CD, Martin NM, Patterson M, et al. Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. Gut 2005;54(12):1693-8.
133. Ejskjaer N, Vestergaard ET, Hellstrom PM, et al. Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic gastroparesis. Aliment Pharmacol Ther 2009;29(11):1179-87.
134. Seto K, Sasaki T, Katsunuma K, et al. Acotiamide hydrochloride (Z-338), a novel prokinetic agent, restores delayed gastric emptying and feeding inhibition induced by restraint stress in rats. Neurogastroenterol Motil 2008;20(9):1051-9.
135. Braden B, Caspary W, Borner N, et al. Clinical effects of STW 5 (iberogast) are not based on acceleration of gastric emptying in patients with functional dyspepsia and gastroparesis. Neurogastroenterol Motil 2009;21(6):632-8:e25.
136. McLemore R, Lunt B, Salameh S, et al. Development of a transmucosal technique for erythromycin delivery to treat gastroparesis. J Pharmacol Sci 2010;99(6): 2905-13.
137. Talley NJ, Verlinden M, Geenen DJ, et al. Effects of a motilin receptor agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitus: a randomised, double blind, placebo controlled trial. Gut 2001;49(3):395-401.
138. Talley NJ, Verlinden M, Snape W, et al. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial. Aliment Pharmacol Ther 2000;14(12):1653-61.

139. Onoma M, Ozaki K, Yogo K, et al. Mitemcinal (GM-611), an orally active motilin receptor agonist, improves delayed gastric emptying in a canine model of diabetic gastroparesis. Clin Exp Pharmacol Physiol 2008;35(7):788-96.
140. Yogo K, Onoma M, Ozaki K, et al. Effects of oral mitemcinal (GM-611), erythromycin, EM-574 and cisapride on gastric emptying in conscious rhesus monkeys. Dig Dis Sci 2008;53(4):912-8
141. McCallum RW, Cynshi O, investigative Team. Clinical trial: effect of mitemcinal (a motilin agonist) on gastric emptying in patients with gastroparesis—a randomized, multicentre, placebo-controlled study. Aliment Pharmacol Ther 2007;26(8): 1121-30.
142. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell 2008;132(4):567-82.