Patients commonly present to their primary care physician with nausea and vomiting. In this setting, the challenge is to correctly diagnose the cause of the patient's complaints and provide symptomatic relief. Although relatively uncommon compared with other conditions causing nausea and vomiting, such as gastroenteritis, bowel obstruction, and medication side effects, gastroparesis should be considered in the differential diagnosis. Gastroparesis is delayed gastric emptying in the absence of mechanical obstruction. Establishing etiology, making a diagnosis, and selecting a treatment can be challenging, but with adequate information the vast majority of patients with this condition can experience substantial improvements in health status and quality of life.

**Gastrointestinal Anatomy**

A clear understanding of gastroparesis begins with a discussion of the general anatomy and physiology of the upper gastrointestinal (GI) tract. The stomach, a hollow organ, serves as a reservoir for food and liquid. It is divided into 3 areas: the proximal area (fundus), the body, and the distal area (antrum) (Figure 1). Liquids pass through the stomach into the duodenum. Solids are stored in the fundus, which dilates and stretches to accommodate the bolus of food. Peristaltic waves are triggered by the food bolus and progress distally to the antrum. Larger food particles (>5 mm to 6 mm) are not able to pass through the contracted pyloric sphincter, and are retrojected into the stomach body for further grinding and mixing (trituration) for 30 to 50 minutes. When solid food becomes chymous (i.e., when the stomach acids have begun to liquefy it), it passes through the pyloric sphincter into the duodenum. Nondigestible solids are emptied after digestible ones. Gastric motility is therefore dependent on the fundus, the pylorus, and the antrum working in concert, and is measured functionally by measuring the speed at which solid food passes out of the stomach.

**Abstract**

Primary care physicians commonly evaluate patients with nausea and vomiting. Gastroparesis, which can be defined as delayed gastric emptying in the absence of mechanical obstruction, is a common cause of nausea and vomiting and should be considered when encountering these symptoms. Characteristics of the nausea and vomiting, such as timing and frequency, can be helpful in assessing the likelihood of gastroparesis. This article will review the anatomy and physiology of the upper gastrointestinal tract; the proper evaluation of patients with suspected gastroparesis; and therapeutic strategies for treating this condition. The gastric pacemaker, a newly developed therapy, will be discussed.

Contractions in the body and the antrum occur in response to an organized gastric electrical rhythm referred to as a slow wave, a gastric pacemaker wave, or the pacemaker potential. This is analogous to cardiac contractions in response to myoelectrical activity. However, unlike the heart and its sinoatrial node (a single cell group), there is a less discrete transition in the stomach from electrically silent areas to electrically active areas (interstitial cells of Cajal). Vagal nerve impulses stimulate the smooth muscle contractility of these cells, as do gastrointestinal (GI) peptides and hormones released into the blood, such as motilin and cholecystokinin. The maximal contraction rate is 3 contractions per minute (cpm).

**Pathophysiology of Gastroparesis**

Gastroparesis generally results from a disruption of the timing and strength of gastric contractility. In diabetic patients, gastroparesis is thought to be a manifestation of vagal autonomic neuropathy. Electrogastrography (similar to electrocardiography) has revealed that gastroparesis is accompanied by dysrhythmias of the gastric pacemaker in about one third of patients. These can be either too fast (tachygastria) or too slow (bradygastria). Tachygastria is defined as a rhythm of more than 4 cpm for more than 30% of a given measurement period and bradygastria is defined as fewer than 2 cpm. Antral fibrillation, akin to atrial fibrillation in the heart, is disorganized electrical impulses in the antral portion of the stomach. Vagal nerve dysfunction also may lead to pyloric spasms.

**Etiology of Gastroparesis**

Gastroparesis can result from several causes. A study of 146 gastroparesis patients seen over 6 years at a referral center reveals that approximately 29% have diabetic gastroparesis; 36% have idiopathic gastroparesis; and 13%, gastroparesis related to surgical injury. Parkinson's disease and other neurological conditions account for 7.5% of cases, 4.8% are related to collagen-related vascular disorder, 4.1% are related to intestinal pseudo-obstruction, and the remaining 6% of cases include other miscellaneous conditions and disorders incorrectly diagnosed as gastroparesis, such as rumination syndrome, which is discussed below (Figure 2).

Gastroparesis is very common in patients with long-standing diabetes, with a prevalence as high as 30% to 50%. In diabetic patients, gastroparesis can precede renal failure, peripheral neuropathy, and the vascular complications of diabetes; many have a history of diabetic ketoacidosis as teenagers or young children. Gastroparesis as a consequence of surgery is largely thought to be secondary to inadvertent or unavoidable injury to the vagal nerve. This may be seen in patients who undergo laparoscopic fundoplication surgery, as the coagulators or probes may touch and damage the vagal nerve.

Idiopathic gastroparesis usually presents suddenly. It is thought that various viruses can cause nerve damage within the stomach. These patients may have complete or partial recovery of gastric motility over subsequent months or years.

Migraine headaches are another possible cause of cyclic nausea and vomiting, which is defined as...
vomiting every 3 or 4 weeks or every few months with periods of wellness in between. Patients who have gastroparesis associated with migraine may benefit from taking a triptan or a tricyclic antidepressant (eg, amitriptyline).

Women appear to be disproportionately susceptible to gastroparesis. Overall, 82% of gastroparesis patients are female and the mean age is 33.7 years.

One theory suggests that because women have naturally higher levels of progesterone, which inhibits smooth muscle function, any insult to gastric smooth muscle control is accentuated.

**PRESENTATION AND WORKUP**

The typical symptoms of gastroparesis include abdominal fullness or bloating, early satiety, epigastric pain and distress, heartburn, anorexia, nausea, vomiting, and weight loss. Not all of these are required for a diagnosis of gastroparesis, but enough of them usually are present to signal the possibility. Morning nausea and bloating may be particularly suggestive of gastroparesis, as undigested food remains in the stomach overnight in delayed gastric emptying, while the stomach is usually empty in unaffected individuals after a nighttime fast.

Further characterization of the symptoms also can be helpful for differentiating gastroparesis from other causes of nausea and vomiting. For example, it is important to determine the timing of nausea in relationship to a meal. Nausea and vomiting that occur immediately after eating are unlikely to be caused by this disorder. Food needs to have remained in the stomach for 1 to 2 hours after eating to signal gastroparesis. The degree of disability also is important. Frequent hospitalizations for refractory vomiting and dehydration, malnutrition, and inability to remain employed are all factors that should trigger a more aggressive approach.

Following a detailed history and physical examination, a diagnostic workup should be performed on the patient with suspected gastroparesis. The physical examination should include palpation and auscultation of the abdomen, listening for a succussion splash. It is necessary to perform diagnostic imaging with barium contrast studies and direct visualization with upper endoscopy to exclude mechanical obstruction (eg, gastric outlet obstruction, a small-bowel problem, or compression of the duodenum by the superior mesenteric artery). Then, a functional assessment of the patient's gastric emptying time should be performed. This is best done at a nuclear medicine facility. A patient is fed a radio-labeled substance, serial scintigraphic images are obtained, and the percentage of retained intragastric contents is calculated. The precise technique for performing this test varies from center to center, but the most reliable method involves a standardized meal with hourly upright anterior and posterior scintigraphy for a total of 4 hours after ingestion. If gastroparesis is detected, the laboratory workup should include complete blood counts and tests for thyroid function, hemoglobin A1C, adrenal function, and electrolytes.

**RUMINATION SYNDROME OR GASTROPARESIS**

Rumination syndrome deserves special mention, as it is frequently confused with gastroparesis. The involuntary regurgitation of food within minutes after eating, a characteristic of this syndrome, often is confused with vomiting. The regurgitation rarely involves retching, typically begins within a few minutes of eating a meal (liquid or solid), and does not occur at night or during sleep. Rumination is very common and is one of the most underdiagnosed causes of vomiting. Because the storage capacity of the stomach, it is impossible to bring liquids back within 1 minute of consumption, unless the patient has achalasia (failure to relax the smooth muscle fibers of the G1 tract at any junction), a large pharyngeal diverticulum, or a tight peptic stricture. Rumination syndrome is also referred to as psychogenic vomiting because it is clearly related to stress and psychological factors. The challenge for the physician is to determine the presence of stressors, as patients may not be forthcoming with that information. Prokinetic medications are not useful for treating rumination. In fact, nausea is minimal and precedes the vomiting event by only a few seconds. Often, patients simply incorporate rumination into their daily routine. Treatment for rumination syndrome involves relaxation techniques, such as meditation, breathing exercises, or hypnosis.

**TREATMENT APPROACHES**

Treatment of gastroparesis involves a pyramid approach, beginning with restoration of hydration and nutrition (Table 1). A low-fat, low-fiber, soft diet should be initiated immediately, and high caloric liquid supplements often are needed. Antiemetics are used to treat nausea while prokinetic agents attempt to restore coordinated gastric and small-bowel motility. Antiemetics should be used liberally and prophylactically to prevent nausea and vomiting rather than treating after onset. Preventing nausea and vomiting is particularly important for diabetic gastroparesis, because nausea often precedes vomiting, which can become refractory and lead to ketoacidosis, emergency department visits, and hospitalization.
A surgically placed jejunal feeding tube (jejunostomy) may be required if the patient is admitted frequently to the hospital; not functioning outside the home; or not able to maintain hydration. Full-thickness, small-bowel biopsy can be considered at the time of jejunostomy placement to examine the enteric ganglia for inflammation and viral inclusion bodies, as well as to stain for the interstitial cells of Cajal. Gastric pacing, described below, has also become a first-line procedure for severe gastroparesis. In general, percutaneous endoscopic gastrostomy tubes or combination percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy tubes have no role in gastroparesis. Direct installation of nutrition into the stomach does not bypass the primary motility problem in gastroparesis, and jejunostomy tubes placed through the stomach are frequently expelled back into the stomach from the jejunum with vomiting.

PHARMACOTHERAPY

The currently available prokinetic agents are limited and have variable efficacy (Table 2). The most commonly used drug is metoclopramide, an antidopaminergic substituted benzamide. Other options include domperidone, erythromycin, cholinergic agents, somatostatin analogs, and, in cases of menstrual gastroparesis (in which the patient vomits just before her menstrual cycle), gonadotropin-releasing hormone agonists, which block menses and, therefore, progesterone production.

Metoclopramide is effective in improving gastric emptying, but as many as 40% of patients cannot tolerate this drug because of side effects to the central nervous system (Table 2). A one strategy for patients who do not tolerate this agent is to administer it subcutaneously and prescribe a step-down therapeutic approach once the patient goes home. Subcutaneous metoclopramide can be self-administered by the patient (2 cc [10 mg] bid or tid) with oral medication, while stepping down to oral therapy alone.

Like metoclopramide, domperidone is a very effective dopamine-2 antagonist but without as

### Table 1. Treatment of Gastroparesis

- Restore hydration and nutrition (diet, liquid supplement)
- Treat nausea (antiemetics)
- Restore coordinated gastric and small-bowel motility (prokinetic agents)
- Employ jejunal feeding tube, biopsy, and/or gastric pacing

### Table 2. Prokinetic Agents for Gastroparesis

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Typical Dose Range</th>
<th>Common Side Effects</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>Oral (tablets or liquid): 10 mg qid</td>
<td>Nervousness, agitation, fatigue, diarrhea</td>
<td>Dopamine antagonist</td>
</tr>
<tr>
<td></td>
<td>IV: 10 mg q 6-8 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SC: 10 mg bid-tid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domperidone</td>
<td>Oral: 10 mg to 30 mg tid-qid</td>
<td>Dry mouth, breast tenderness, nipple discharge (currently not available in US)</td>
<td>Dopamine antagonist</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Oral: 125 mg bid or tid</td>
<td>Diarrhea, abdominal cramping, rash</td>
<td>Motilin-receptor agonist</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>Oral: 6 mg bid before a meal</td>
<td>Abdominal pain, diarrhea, chest pain, facial flushing, vertigo, syncope, increased liver enzymes, fecal incontinence, sleep disorder, depression, asthma, appendicitis</td>
<td>5-HT4-receptor agonist</td>
</tr>
</tbody>
</table>

IV indicates intravenous; SC, subcutaneous; US, United States.
many side effects. Its effectiveness and safety have been established in clinical trials, but it is not available in the United States. Domperidone can be obtained from some compounding pharmacies in the United States and from pharmacies in other countries. However, many patients may not be able to afford it because it is not usually covered by health insurance.

Erythromycin attaches to the motilin receptor and stimulates enteric contractility. Low doses can be used to treat gastroparesis (eg, 125 mg bid or tid), but its primary role is adjunctive to other prokinetic agents.

The most recently approved prokinetic agent, tegaserod, has recently been approved by the Food and Drug Administration (FDA) for treatment of women with constipation-predominant irritable bowel syndrome (IBS). This agent is a partial and selective 5-hydroxytryptamine-receptor agonist with GI stimulatory effects. Animal and human studies have shown stimulatory motor effects throughout the digestive tract, and tegaserod has been shown to accelerate orocecal transit in patients with IBS. However, there are no published data related to improved gastric emptying time, and the use of this agent in patients with gastroparesis and other GI motility disorders requires further study.

Somatostatins (eg, octreotide) are prescribed for patients with concomitant small-bowel problems such as diarrhea and bacterial overgrowth. Somatostatin works by initiating a migration motor complex that begins in the small bowel and continues down the gut. This agitates the gut, moves the bacteria further downstream, and helps to sterilize the small intestine. However, metronidazole or other antibiotics should be given during the day with octreotide treatment.

Other therapies under early investigation include sildenafil and botulinum toxin A injections aimed at relaxing the pylorus. Preliminary reports suggest that botulinum toxin A is effective for temporarily relieving symptoms of idiopathic and diabetic gastroparesis, although further study is needed. Also, the toxin must be administered frequently, so formulation and administration issues may preclude its use as a first-line therapy.

**GASTROPAESIS**

Electronic gastric pacing involves applying an electrical stimulus that either activates contractions of gastric smooth muscle or provides a stimulus to the nausea and vomiting control centers in the brain, which may decrease nausea and vomiting. The response depends on the type of electrical stimulation. A low-frequency, high-energy wave stimulates the smooth muscle at about 3 cpm. A high-frequency, low-energy stimulation appears to block nausea and vomiting. Much like a cardiac pacemaker, gastric pacing devices also may correct gastric dysrhythmias by overriding tachygastria and propelling the neuromuscular signal down the antrum.

Currently, FDA-approved gastric pacemaker devices are manufactured by Medtronic, Inc, under the trade name Enterra™. They are approximately the size of a pager and are implanted subcutaneously in the abdominal wall. Bipolar electrodes are then placed by laparotomy or laparoscopy into the peritoneal cavity and attached approximately 9.5 cm to 10 cm from the pylorus along the greater curvature of the antrum. The 2 electrodes are placed 1 cm apart, deep in the muscularis propria, and connected to the operating device. Intraoperative endoscopy is performed at the time of implantation to ensure the leads are positioned appropriately in the muscularis propria of the stomach wall and not accidentally pushed into the lumen of the stomach.

The physicians at University of Kansas Medical Center have implanted more of these devices than any other center worldwide—over 90 to date. Other centers in the United States are developing this capability. The device was approved by the FDA in 2000 as a humanitarian device, so some insurance providers now will cover the cost of implantation.

The first double-blind gastric pacemaker trial was conducted in 1998 on a total of 49 gastroparesis patients; 22 in the diabetic group, 19 in the idiopathic group, and 8 in the postsurgical group (in a conversation with R McCallum, MD [December 2002]). This international trial had a randomized, crossover design, with the device turned on for 1 month and turned off for 1 month. A follow-up evaluation was performed at 12 months. Patients included in the study had symptoms of gastroparesis for more than 1 year, were refractory to drug treatment, and had a vomiting frequency of more than 7 times per week. Gastric retention was more than 60% at 2 hours and more than 10% at 4 hours. The majority of the patients were white and female, and the mean age in each treatment group was approximately 40 years. Many had lost more than 10% of their body mass index and had been hospitalized frequently.

The results from the study show significant reductions in nausea and vomiting frequency at 6 and 12 months for all types of gastroparesis (P < .05). Overall, 90% of patients had a greater than 50% decrease in vomiting. The benefits, as measured by total symptom score (nausea, vomiting,
ing, bloating, fullness, satiety, and pain), were not as dramatic as vomiting alone, but still evident. Typically, diabetic patients had less than 10 years of (diabetic) gastroparesis symptoms prior to entering the study. And finally, weight gain of up to 8 pounds at 6 months and 15 pounds by 12 months was observed; 90% of study patients had their jejunostomy tubes out by 6 months. The investigators reported reduced hemoglobin A1C levels at 12 months in patients with diabetic gastroparesis. Overall, gastric emptying was not affected. However, gastric emptying rate was normalized in 25% to 30% of patients at 1 year. Hospital length of stay decreased dramatically, from an average of 60 days per year to 17 days per year postimplantation. The resulting cost savings were $65,000 per patient after implant in the first year. Approximately 5% of patients experienced an infection at the implant site. During the 1-year follow-up period, many of the patients ate small meals and occasionally needed prokinetic therapy after larger meals to maintain gastric emptying.

Future applications for the gastric pacemaker may include treating nausea and vomiting of any etiology (not solely gastroparesis or other gastric emptying problems); adapting the device for small-bowel and colon motility disorders and managing obesity using the 2 frequency-energy modes of stimulation. High-energy, low-frequency stimulation can cause disorganized contractions and gastric emptying. This should induce feelings of satiety and decrease interest in eating. Placing an electrode in the duodenum may cause disorganization in the contractions of the proximal duodenum, resulting in a duodenal gastric gradient against the flow and further inducing feelings of satiety.

**Conclusion**

Although gastroparesis can be difficult to diagnose, an understanding of the anatomy and physiology of digestion in the stomach can help the physician discern when common GI symptoms such as nausea and vomiting suggest gastroparesis. There are limited but effective pharmacotherapeutic options, and artificial gastric pacing, while not yet widely available, appears to be a promising novel therapy for severe gastroparesis.

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Dr M McCallum has reported he receives research support from Medtronic, Novartis, Janssen Pharmaceuticals LP, and AstraZeneca.

**REFERENCES**