Diabetic Gastroparesis

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**The Clinical Problem**

Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating. In one tertiary referral series, diabetes accounted for almost one third of cases of gastroparesis. Other causes include previous gastric surgery and neurologic and rheumatologic disorders; many cases are idiopathic (possibly occurring after a viral infection).

Patients with diabetes in whom gastroparesis develops often have had diabetes for at least 10 years and typically have retinopathy, neuropathy, and nephropathy. Diabetic gastroparesis may cause severe symptoms and result in nutritional compromise, impaired glucose control, and a poor quality of life, independently of other factors such as age, tobacco use, alcohol use, or type of diabetes. Symptoms attributable to gastroparesis are reported by 5 to 12% of patients with diabetes.

Studies of the natural history of gastroparesis have been limited by relatively small numbers of patients, potential referral bias, or short follow-up periods. The data suggest that gastric emptying and its symptoms are generally stable during 12 years of follow-up or more. In a study of 86 patients with diabetes who were followed for at least 9 years, gastroparesis was not associated with mortality after adjustment for other disorders.

**Normal Gastric Emptying**

The proximal stomach serves as the reservoir of food, and the distal stomach as the grinder. The physical nature, particle size, and fat and caloric content of food determine its emptying rate (Fig. 1). Non-nutrient liquids empty rapidly; the rate is fastest when there is a large volume. If there are increased calories in the liquid phase of the meal, emptying is relatively constant over time, with a maximum rate of 200 kcal per hour. Solids are initially retained in the stomach and undergo churning while antral contractions propel particles toward the closed pylorus. Food particles are emptied once they have been broken down to approximately 2 mm in diameter. Thus, solids empty during two phases over 3 to 4 hours: an initial lag...
period (during which retention occurs), followed by a phase of relatively constant emptying.\textsuperscript{11}

Glucose-regulating hormones are released when food arrives in different regions of the gut. Glucagon and incretins (e.g., amylin and glucagon-like peptide 1) retard gastric emptying, allowing for the delivery of food at a rate that facilitates digestion and controls postprandial glycemia.\textsuperscript{11}

**IMPAIRED GASTRIC EMPTYING IN PATIENTS WITH DIABETES**

In patients with diabetic gastroparesis, mechanisms are deranged, largely owing to neuropathy affecting the vagus, reductions in the numbers of intrinsic inhibitory neurons that are critical for motor coordination\textsuperscript{14} and numbers of pacemaker cells (the interstitial cells of Cajal),\textsuperscript{15} and hormonal changes (e.g., increased glucagon levels). Chronically elevated blood glucose levels increase the risk of diabetic neuropathy. Increased glycated hemoglobin levels are associated with increased rates of gastrointestinal symptoms.\textsuperscript{16} Acute hyperglycemia also may contribute to motor dysfunction in patients with diabetes\textsuperscript{17}; in experiments, the time at which half of the consumed solids are emptied from the stomach (the half-time) is approximately 15 minutes longer in patients with hyperglycemia (blood glucose levels exceeding 180 mg per deciliter [10 mmol per liter]) than in subjects with euglycemia.\textsuperscript{17} Neurohormonal dysfunction and hyperglycemia reduce the frequency of antral contractions (needed to churn food) in patients with diabetes. In contrast, the emptying of liquids is usually normal in patients with hyperglycemia.\textsuperscript{18}

Delayed gastric emptying may be caused or exacerbated by medications for diabetes, including amylin analogues (e.g., pramlintide) and glucagon-like peptide 1 (e.g., exenatide).\textsuperscript{19-21} Delayed gastric emptying has direct effects on glucose metabolism, in addition to being one means of reducing the degree of postprandial hyperglycemia.\textsuperscript{19-22} In a clinical trial of exenatide, nausea occurred in 57% of patients, and vomiting occurred in 19% of patients, leading to the cessation of treatment in about one third of patients.\textsuperscript{21}

Coexisting psychiatric disorders may also contribute to symptoms of gastroparesis. In a cross-sectional study, increased states of anxiety, depression, and neuroticism were associated with an approximate doubling of the prevalence of gastrointestinal symptoms in patients with diabetes.\textsuperscript{23} However, it is unclear whether psychiatric symptoms cause the gastrointestinal complaints or result from them.

**STRATEGIES AND EVIDENCE**

**DIAGNOSIS**

A history of retinopathy, nephropathy, and neuropathy, including autonomic neuropathy, is common in patients with diabetic gastroparesis,\textsuperscript{1,24} though gastroparesis may occur in the absence of other overt complications of diabetes. Vomiting in the morning before eating suggests an alternative cause (e.g., pregnancy, uremia, or a brain tumor). Heartburn, dyspepsia, or use of nonsteroidal antiinflammatory drugs suggests peptic ulcer disease, including pyloric stenosis. A careful history taking is essential to rule out the rumination syndrome — that is, daily, early postprandial, effortless regurgitation of food, which typically occurs with each meal for months. The regurgitated material is not usually bitter or sour; depending on social circumstances, the patient may spit the food out or swallow it again.\textsuperscript{25} Only the most severe gastroparesis results in daily vomiting.

The physical examination typically shows associated peripheral and autonomic neuropathy (e.g., pupils that are responsive to accommodation but not to light and peripheral sensory neuropathy), background or more advanced retinopa-
thy, epigastric distention, and the sound of liquid splashing when the abdomen is shaken from side to side. The absence of a splashing sound on abdominal succussion 1 hour after a meal suggests normal gastric emptying of liquids.

**DIAGNOSTIC TESTING**

Before evaluating a patient for gastroparesis, it is essential to rule out obstruction with the use of esophagogastroduodenoscopy or a barium study of the stomach. Food retained in the stomach after a 12-hour fast is suggestive of gastroparesis.

Measurement of gastric emptying of digestible solids is the mainstay of the diagnosis of gastroparesis (Fig. 2). Epigastric fullness, bloating, and nausea may reflect either delayed or accelerated gastric emptying; accelerated emptying is also a possible complication of diabetic neuropathy. Documentation of delayed gastric emptying is warranted before the initiation of therapy.

Scintiscanning at 15-minute intervals for 4 hours after food intake is considered the gold standard for measuring gastric emptying in detail. However, a simplified approach involving hourly scans to quantify residual gastric content is often used in practice; retention of over 10% of the meal after 4 hours is abnormal. As compared with the gold standard, the simplified approach has a specificity of 62% and a sensitivity of 93%. Since it provides the actual percentage of food emptied and requires fewer scans, the simplified approach is generally preferred. Scintiscanning requires special equipment and expertise and involves exposure to radiation (equal to about one

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**Table 2. Scintiscans of Residual Gastric Contents.**

The scintiscans were obtained after the ingestion of a standard, solid, radiolabeled meal by two patients with type 1 diabetes who had similar postprandial symptoms of nausea, early fullness, and intermittent vomiting (one patient with diabetic gastroparesis and the other with diabetes and accelerated gastric emptying) and a control subject with normal gastric emptying (middle row). The white areas represent the isotope, and the white outlines indicate the region of interest for quantification of radioactivity in the stomach. The percentage of solid food consumed that was emptied from the stomach at each time point after the meal is shown above each scintiscan.
third of the average annual exposure to radiation from natural sources in the United States).

A breath test to measure gastric emptying involves ingestion of a meal enriched with a stable isotope, followed by the collection of breath samples, which are analyzed for carbon dioxide incorporating the isotope (i.e., $^{13}$CO$_2$) at a reference laboratory. The profile of $^{13}$CO$_2$ excretion is used to estimate the half-time of gastric emptying. As compared with detailed scintiscanning over a period of 4 hours, the breath test has a specificity of 80% and a sensitivity of 86%. Gastric emptying can be evaluated with the use of radiography 6 hours after the ingestion of nondigestible, radiopaque markers. This simple test is readily available and inexpensive, but it assesses the emptying of nondigestible solids rather than digestible solids, which require a different type of contraction to be emptied from the stomach.

Intraluminal pressure and surface electrical profiles can be used to assess the motor function of the stomach. However, these assessments are not recommended in routine practice; the results do not add clinically relevant information to that gained from an accurate gastric emptying test.

### MANAGEMENT

Key principles in the management of diabetic gastroparesis are the correction of exacerbating factors, including optimization of glucose and electrolyte levels; the provision of nutritional support; and the use of prokinetic and symptomatic therapies. Management can be tailored to the severity of the condition, which is classified according to the ability to maintain adequate nutrition and the responsiveness to therapy. Mild gastroparesis is characterized by symptoms that are easily controlled by maintaining weight and nutrition on a regular diet or by making minor dietary modifications. Compensated gastroparesis is associated with moderately severe symptoms, partially controlled with medications; nutrition is maintained with the use of dietary and lifestyle adjustments, and treatment in the hospital is rarely required. In gastroparesis with gastric failure, symptoms are refractory despite medical therapy, nutrition cannot be maintained through the oral route, and emergency room visits or hospitalizations are required. Table 1 summarizes recommendations for management that are based on consensus recommendations, available data, and clinical experience.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Severity of Disease (typical gastric retention at 4 hr)</th>
</tr>
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<tr>
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* The severity of gastroparesis, types of drugs listed, and recommendations for nutritional support are based on guidelines of the American Motility Society and the American Gastroenterological Association. The priorities for treatments in each category are based on clinical experience. In general, management progresses from the top down, according to the patient’s response to treatment. PEJ denotes percutaneous endoscopic jejunostomy. Typical gastric retention of solid food at 4 hours correlates with the severity of gastroparesis and provides some guidance on selection of treatment but should not be used alone to guide treatment.

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Table 1. Management of Diabetic Gastroparesis.

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Exacerbating Factors
Medications such as antihypertensive agents (calcium-channel blockers or clonidine), anticholinergic agents (e.g., antidepressants), and exenatide or pramlintide (used to control postprandial hyperglycemia) should be discontinued whenever possible. Although there is a lack of clinical trials showing that the restoration of euglycemia or correction of electrolyte derangements normalizes gastric emptying or ameliorates symptoms, clinical experience and observational data suggest that improved metabolic control is beneficial. For example, in one study, patients with uremia due to diabetes who underwent kidney and pancreas transplantation had significant improvement in gastric emptying and associated gastrointestinal symptoms.33

Pharmacologic Therapy
Prokinetic Agents
Prokinetic agents most commonly used to treat gastroparesis include metoclopramide and erythromycin. Randomized clinical trials have shown a symptomatic benefit of these agents, as well as of cisapride and domperidone.31,34-42 In general, as compared with placebo, these agents have increased gastric emptying by about 25 to 72% and have reduced the severity of symptoms (typically measured with the use of Likert scales) by 25 to 68%. However, many of these trials were small, some were not blind, and some included patients with gastroparesis due to causes other than diabetes. In addition, data from head-to-head comparisons of these agents are limited. In one such trial, involving children with diabetes, domperidone was found to be superior to cisapride.42 In another trial, metoclopramide and domperidone were equally effective in reducing symptoms, but side effects on the central nervous system (somnolence, mental function, anxiety, and depression) were more pronounced in patients receiving metoclopramide.36 Domperidone is not currently approved by the Food and Drug Administration (FDA) but is available, with approval by local institutional review boards, through an FDA investigational new drug application. Cisapride is associated with an increased risk of cardiac arrhythmia, including torsades de pointes; therefore it is currently available in the United States only through a compassionate-use limited-access program and is used only if other medications fail. Intravenous erythromycin (3 mg per kilogram of body weight every 8 hours by infusion) is more effective than placebo in relieving acute gastroparesis in hospitalized patients41,43,44; however, no trials have compared erythromycin and another agent.

Muscarnic cholinergic agents (e.g., bethanechol), anticholinesterases (e.g., pyridostigmine), and the 5-hydroxytryptamine 4 (5-HT4) agonist tegaserod may accelerate gastric emptying, but data from trials assessing effects on symptoms of gastroparesis are lacking. The doses and side effects of various agents proposed for use in treating gastroparesis are summarized in Table 2.

Other Agents
Antiemetic agents are helpful for the relief of symptoms. Although few trials have compared different classes of antiemetic agents in patients with gastroparesis, it is reasonable to try the less expensive therapies (e.g., dimenhydrinate or meclizine) first; if these are ineffective, a 5-hydroxytryptamine 3 (5-HT3) antagonist may be tried, though this class has not been explicitly studied for use in treating gastroparesis.

Pain relief is sometimes required. There are no data from controlled trials to guide the choice of agent for use in patients with gastroparesis. Agents used in clinical practice include antidepressants (e.g., low-dose tricyclics or duloxetine) and pregabalin (approved for patients with diabetic neuropathy). Nonsteroidal agents are typically avoided because of the potential for renal damage in patients with diabetes. Tramadol and opiates should be avoided because of their inhibiting effects on motility as well as the risk of addiction.

Nutritional Support
The choice of nutritional support and its route of administration depend on the severity of disease (Table 1). The indications for supplementation of enteral nutrition33 include unintentional loss of 10% or more of the usual body weight during a period of 3 to 6 months, inability to achieve the recommended weight by the oral route, repeated hospitalization for refractory symptoms, interference with delivery of nutrients and medications, need for nasogastric intubation to relieve symptoms, and nausea and vomiting resulting in a poor quality of life.31 The degree of gastric retention at 4 hours may help guide decisions regarding nutritional support (Table 1) but should not be used in isolation in the decision making.
Endoscopic or operative placement of gastrostomy tubes (for decompression, not feeding) or jejunal feeding tubes is reserved for patients with severe gastroparesis. A potential disadvantage of gastrostomy is that it might interfere with subsequent electrode placement for gastric electrical stimulation (see below). Permanent percutaneous placement of a jejunal tube should be preceded by successful nasojejunal feeding. In appropriate patients, enteral feeding through the jejunum maintains nutrition, relieves symptoms, and reduces the frequency of hospital admissions for acute exacerbation of symptoms. In one case series, direct percutaneous endoscopic jejunostomy was feasible in 68% of 307 consecutive attempts, though 10% of patients had complications; in 2% of patients, serious complications occurred: bowel perforations, jejunal volvulus, major bleeding (including one episode of fatal mesenteric bleeding), and aspiration.

Nonpharmacologic Therapy

Endoscopic Injection of Botulinum Toxin

The results of several uncontrolled studies have suggested that endoscopic injection of botulinum toxin into the pylorus is efficacious. However, a controlled trial showed no efficacy.

Gastric Electrical Stimulation

Gastric electrical stimulation involves the use of electrodes, usually placed laparoscopically in the muscle wall of the stomach antrum, connected to a neurostimulator in a pocket of the abdominal wall. Limited data suggest that this approach may control symptoms of gastroparesis. The device (Enterra, Medtronic) has been approved by the FDA through a humanitarian device exemption. In the only controlled trial (crossover, with each treatment administered for 1 month), involving 33 patients with idiopathic or diabetic gastroparesis, electrical stimulation had no significant effect on symptoms overall but reduced the weekly frequency of vomiting (P<0.05). Among the 17 patients with diabetes in the study, the median frequency of episodes of vomiting per week was 6.0 with the stimulator on and 12.8 with the stimulator off (P=0.16). Long-term open-label studies of gastric stimulation, with mean follow-up periods of 3.7 and 4.3 years, have reported relief of symptoms and a reduced need for nutritional support, but no long-term randomized trials have been conducted. The mechanism by which electrical stimulation improves symptoms is unclear. The use of different electrical settings for stimulation may improve clinical efficacy, but this suggestion requires further study.

Surgery

Surgery is rarely indicated for the treatment of gastroparesis, except to rule out other disorders or to place decompression or feeding tubes. A systematic review concluded that the data are insufficient to provide support for gastric surgery in the treatment of patients with diabetic gastroparesis. Concomitant denervation of the small intestine may result in persistent symptoms in patients with diabetes, even after gastrectomy.

Areas of Uncertainty

Randomized clinical trials are needed to guide decisions about the optimal drug, device, and nutritional management of diabetic gastroparesis. Few medications or nonpharmacologic therapies have been studied rigorously for this indication. Agents such as the 5-HT₄-receptor agonist tegaserod (which is approved for the treatment of patients with the irritable bowel syndrome in whom constipation is predominant and patients with chronic constipation) and acetylcholine inhibitors (e.g., pyridostigmine) have been used off-label in patients with gastroparesis, but data from clinical trials providing support for their use are lacking. The use of gastric electrical stimulation is based largely on open-label experience, and its mechanism of action is unclear. An observational study suggested a benefit of acupuncture for diabetic gastroparesis, but controlled trials have not been performed.

Guidelines

Guidelines for management have been published by the American Gastroenterological Association and the American Motility Society; these guidelines predominantly reflect expert opinion, since there are only limited data from randomized trials to guide management. The recommendations in this article are generally consistent with the guidelines.

Summary and Recommendations

In the patient described in the vignette, the diabetic complications and gastrointestinal symptoms suggest the diagnosis of gastroparesis. After
Table 2. Prokinetic and Antiemetic Medications Proposed in Consensus Guidelines for the Treatment of Gastroparesis.*

<table>
<thead>
<tr>
<th>Class of Agent†</th>
<th>Examples</th>
<th>Usual Dose‡</th>
<th>Main Side Effects and Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokinetic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dopamine D2-receptor antagonists (I)</td>
<td>Metoclopramide (Reglan)§, domperidone (Motilium)¶</td>
<td>Start with 5 mg thrice daily; usual dose is 10–20 mg thrice daily, 15 min before meals</td>
<td>Anxiety; depression; galactorrhea; extrapyramidal symptoms; rarely, tardive dyskinesia</td>
<td>Antiemetic action also contributes to symptom relief; metoclopramide (10 mg) also can be used intramuscularly, intravenously, and subcutaneously</td>
</tr>
<tr>
<td>Motilin-receptor agonists (II)</td>
<td>Erythromycin (e.g., E-mycin), clarithromycin (Biaxin), azithromycin (Zithromax)</td>
<td>Erythromycin, 40–250 mg thrice daily, 15 min before meals; clarithromycin, 125–250 mg daily; azithromycin, 250 mg daily</td>
<td>Abdominal cramping, loss of appetite</td>
<td>Tolerance reached rapidly; erythromycin useful for acute gastroparesis (3 mg/kg by intravenous infusion every 8 hr); clarithromycin and azithromycin not formally tested in diabetic gastroparesis</td>
</tr>
<tr>
<td>5-HT₄-receptor agonists (III)</td>
<td>Tegaserod (Zelnorm), cisapride (Propulsid)</td>
<td>Tegaserod, 2–6 mg twice daily, 15 min before meals; cisapride, 10–20 mg thrice daily, 15 min before meals</td>
<td>Diarrhea, abdominal pain, potential for cardiac dysrhythmia with cisapride</td>
<td>Tegaserod efficacy unclear; cisapride only available through a compassionate-use or limited-access program, when other drugs fail</td>
</tr>
<tr>
<td>Muscarinic-receptor agonists (III)</td>
<td>Bethanechol (Urecholine)</td>
<td>10–20 mg thrice daily before meals</td>
<td>Cholinergic side effects (e.g., sweating or bladder dysfunction)</td>
<td>Stimulates gastric emptying; side effects are dose limiting; efficacy against symptoms unclear</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitors</td>
<td>Pyridostigmine (Mestinon), neostigmine methylsulfate (Prostigmin)</td>
<td>Pyridostigmine, 30 mg four times daily; neostigmine methylsulfate, 0.5–1 mg intramuscularly</td>
<td>Cholinergic side effects (e.g., sweating or bladder dysfunction)</td>
<td>Unclear efficacy</td>
</tr>
</tbody>
</table>
## Antiemetic

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug(s)</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D2-receptor antagonists (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine (Compazine), trimethobenzamide (Tigan)</td>
<td>Prochlorperazine, 5–10 mg by mouth thrice daily or 5–25 mg as required every 12 hr as rectal suppository; trimethobenzamide, 300 mg thrice daily as required</td>
<td>Extrapyramidal effects; rarely, jaundice</td>
<td></td>
</tr>
<tr>
<td>Serotonin 5-HT3-receptor antagonists (II)</td>
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<tr>
<td>Ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzamet), tropisetron (Novoban)</td>
<td>Ondansetron, 4–8 mg thrice daily as required; granisetron, 1 mg twice daily; dolasetron, 50–100 mg as required only; tropisetron, 2–5 mg intravenously</td>
<td>Constipation with regular use; Unclear efficacy as compared with D2-receptor antagonists; also available intravenously</td>
<td></td>
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<tr>
<td>Muscarinic M1-receptor antagonists (III)</td>
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<tr>
<td>Scopolamine (Scopoderm HS) patch</td>
<td>1 mg every 3 days</td>
<td>Drowsiness, headache, dry mouth (may be worse on withdrawal); Contraindicated with glaucoma or bladder-emptying problems</td>
<td></td>
</tr>
<tr>
<td>Histamine H1-receptor antagonists (II)</td>
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<tr>
<td>Dimenhydrinate (Dramamine), meclizine (Antivert), promethazine (Phenergan)</td>
<td>Dimenhydrinate, 50 mg thrice daily as required; meclizine, 12.5–25 mg thrice daily as required; promethazine, 12.5–25 mg intramuscularly as required</td>
<td>Drowsiness, blurred vision, headache or dry mouth; Contraindicated with glaucoma or bladder-emptying problems</td>
<td></td>
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<tr>
<td>Benzodiazepines (III)</td>
<td></td>
<td></td>
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<tr>
<td>Lorazepam (Ativan)</td>
<td>0.5–1 mg as required</td>
<td>Sedation; Unclear efficacy for gastroparesis</td>
<td></td>
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<tr>
<td>Neurokinin-1–receptor antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprepitant (Emend)</td>
<td>125 mg</td>
<td>Weakness, bowel dysfunction, reduced efficacy of oral contraceptives; Contraindicated with astemizole (Hismanal), cisapride, and pimozide (Orap); Unclear efficacy for gastroparesis</td>
<td></td>
</tr>
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</table>

* Recommendations are based on guidelines of the American Motility Society and the American Gastroenterological Association. These guidelines also list antidepressants and cannabinoid agonists. However, these two classes of drugs may retard gastric emptying and are of unclear efficacy for gastroparesis; cannabinoids may cause problems with memory and learning, distorted perception, anxiety, or panic attacks.

† Roman numerals refer to the line of therapy, from first (I) to third (III), recommended on the basis of drug efficacy, cost, ease of administration, and adverse effects.

‡ Dose is by mouth, unless otherwise indicated.

§ Metoclopramide is the only medication approved by the FDA for gastroparesis.

¶ Domperidone is not approved by the FDA for gastroparesis.
obstruction has been ruled out with the use of gastroduodenoscopy, the diagnosis should be confirmed. I would confirm it by measuring gastric emptying using scintigraphy hourly for 4 hours (alternatively, a breath test could be performed). I would then initiate therapy with a prokinetic agent (I start with metoclopramide, 10 mg three times daily before meals) and an antiemetic agent (either prochlorperazine, 10 mg, or dimenhydrinate, 50 mg, every 12 hours). A dietitian should advise the patient on the use of liquid or homogenized meals to supplement oral nutrition, and control of diabetes should be optimized. If symptoms persist and weight loss increases despite medical therapy, nasojejunal feeding should be attempted; if such feeding is tolerated, a percutaneous endoscopic jejunostomy tube should be placed for enteral nutrition.

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REFERENCES


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