

Review article: gastroparesis

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SUMMARY

Background

Gastroparesis is a chronic disorder caused by stomach pump failure and characterized by profound nausea, vomiting and epigastric pain. Most often, the cause is unapparent and of the known associations, diabetes is the most common. Diagnosis is usually made using an isotope-labelled test meal. Treatment is incremental and includes education, dietary support, prokinetic and antiemetic agents. There are novel approaches including gastric neurostimulation.

Aim

To review current concepts of gastric motor function, aetiology, investigation and treatment of gastroparesis.

Methods

A systematic web-based review of the literature was undertaken using a lexicon of terms associated with gastroparesis.

Results

There are few controlled studies of this condition. Little is known about causation or underlying nerve, muscle or pacemaker pathology. Idiopathic gastroparesis occurs most commonly in women and gastric emptying is often abnormal in diabetes. Isotopic gastric scintigraphy remains the gold standard investigation, but alternative tests are being developed. Treatment is multimodal and includes education, and nutritional support. There are no adequately powered controlled trials to support a particular drug regimen. In intractable gastroparesis, gastric neurostimulation appears to offer benefit.

Conclusion

Despite a significant progress in the past decade, further controlled trials are required into the therapeutic options available for treating this intriguing condition.

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INTRODUCTION

Gastroparesis is a symptomatic chronic disorder of the stomach pump characterized by objective evidence of delayed gastric emptying in the absence of mechanical obstruction.¹ Delayed gastric emptying can be demonstrated in a third of patients with non-ulcer dyspepsia² but because gastroenterologists rarely investigate gastric pump function, gastroparesis is rarely documented in routine clinical practice. Consequently, the disorder is usually suspected, investigated and diagnosed in patients presenting with the syndrome of intense and prolonged nausea, vomiting, early satiety and epigastric pain.

Women constitute the majority of patients with a female:male ratio of 4:1 and the mean age of onset is 34 years.³ The reason for the sex ratio imbalance remains unknown, but Soykran *et al.* reported that 62% of patients with idiopathic gastroparesis revealed past history of physical or sexual abuse.³ There is also evidence of a gender difference in solid and liquid emptying between men and women with female gastric emptying slower than men.⁴

NORMAL GASTRIC FUNCTION

The gastric pump is, in many ways, a more complex pump than the heart. The two organs share many characteristics. In both organs, a pacemaker governs rhythm, and the direction of flow is controlled by a system of valves. The mitral and aortic valves of the heart are in many ways analogous to the antireflux mechanism operating at the gastro-oesophageal junction and the outflow control imposed by the pyloric valve. Just as the atria provide an elastic storage compartment for the pulmonary venous inflow, the gastric fundus provides a receptive compartment for oesophageal inflow.

However, there are important differences. Whilst throughout a lifetime the heart beats day and night, the gastric pump is carefully tuned to respond to demand, lying dormant at times, whereas pumping contents with power and rhythm at other times. In addition, the gastric pump combines the seemingly incompatible functions of storage, mixing, grinding and propelling solutes, insoluble contents, liquid and gas, into the more rapidly contracting duodenum. This complexity of functions is controlled by an amalgam of intrinsic and extrinsic mechanisms including gut hormones, the gastric pacemaker, the enteric plexus,

the extrinsic autonomic innervation and higher cerebral centres. Normal gastric emptying reflects the sum of a number of factors, including fundal relaxation, antral grinding, trituration and propulsion, pyloric control of flow into the duodenum and antro-duodenal coupling. Further influences include the physical nature of the meal (i.e. solid vs. liquids) and meal composition (fat, protein and osmolality of the liquid phase).

Just as the cardiac pump can fail because of rhythm disturbances, restrictive and dilated heart muscle disease, and valve failure, so can the stomach pump fail as a result of gastric dysrhythmias, failure of compliance, gastric muscle disease and gastric outlet obstruction. Recognition of the functional complexity of the stomach is a key to understanding, diagnosing and targeting treatment.

The proximal stomach

Normal gastric emptying reflects a complex interaction between the functionally distinct chambers of the stomach and between the stomach and duodenum. The proximal of the stomach is a capacious storage compartment. The primary function is to accommodate the meal and provide a temporary storage compartment. The fundus regulates intragastric pressure and stimulates the tonic propulsion of chyme into the distal stomach. In addition, it regulates the gastro-duodenal flow rate and provides the space and time for pepsin and hydrochloric acid to initiate digestion. The membrane potential of gastric smooth muscle exhibits a characteristic gradient decreasing from -48 mV in the fundus to -71 mV in the antrum⁵ and unlike the distal stomach, the proximal stomach membrane potential does not demonstrate phasic changes in potential. Consequently, under basal conditions, the fundus exhibits tone rather than pulsation which, in turn, can be modulated by enteric and hormonal influences.⁶

An important function of the proximal stomach is its ability to accommodate. Over a litre of nutrients can be ingested without an increased intragastric pressure. Barostat studies in human volunteers indicate that intragastric pressure falls modestly following a meal and only returns to baseline once solids have emptied from the stomach.⁷ Proximal gastric motor function is regulated by receptive relaxation and gastric accommodation reflexes. Receptive relaxation refers to the fall in proximal gastric tone that occurs with swallowing. This reflex can be demonstrated

with dry as well as bolus swallows⁸ and there is experimental evidence that nicotinic, muscarinic and nitric oxide receptors are all involved in the receptive relaxation reflex.⁹

Gastric accommodation describes reflex relaxation of the proximal stomach occurring in response to distension. Unlike receptive relaxation, the accommodation reflex does not depend on oesophageal stimulation. There is evidence that in humans, the accommodation reflex involves the release of serotonin and the activation of nitrergic motor neurones.^{10, 11} Studies in experimental animals and vagotomized humans also indicate that accommodation is also mediated by a vago-vagal reflex.^{12, 13} As might be expected, vagotomy is associated with reduced gastric distensibility and markedly increased intragastric pressure following bolus food ingestion. The complexity of proximal gastric muscle control is further illustrated by evidence for enterogastric reflexes, which also influence proximal gastric motor activity. Infusion of hydrochloric acid, protein or fat into the duodenum inhibits proximal gastric muscle activity. These enterogastric reflexes appear to be vagally mediated, with evidence that fat-induced proximal gastric relaxation is mediated by nitric oxide.^{14, 15} To add further complexity, there is evidence of enterogastric reflexes arising from the ileum where lipid has been shown to reduce gastric fundal tone creating an 'ileal brake' effect.¹⁶

Endocrine factors also influence proximal gastric tone and volume. Hormones that relax the proximal stomach include cholecystokinin (CCK), secretin, vasoactive intestinal polypeptide (VIP), gastrin, somatostatin, dopamine, gastrin-releasing peptide, glucagon and bombesin, whilst the prokinetic gut hormone motilin increases fundic pressure.¹⁷ Rather than having a direct effect on fundic smooth muscle, these hormonal mediators act by way of neural reflexes, best demonstrated by capsaicin inhibition of CCK-induced reduction in intragastric pressure.¹⁸

The distal stomach

Unlike the fundus, the distal body of the stomach and antrum exhibits phasic rather than tonic motor activity. This is often seen on endoscopy as a powerful ring-shaped peristaltic wave, which initiates in the mid to distal body of the stomach, picking up strength as it drives towards the pylorus where it abruptly terminates.

The rhythmic activity of the distal stomach is regulated by the highly adapted myoelectrical organization of the region. The distal stomach exhibits a resting negatively charged membrane potential superimposed on which is a three cycles per minute rhythmic depolarization potential, termed the gastric slow wave. The frequency and direction of the phasic motor activity are tightly coupled with the gastric slow wave. There is evidence that the slow wave is generated by phasic depolarization of the interstitial cells of Cajal. These cells are analogous to the pacing cells of the heart and have been located at the proximal gastric body along the greater curvature of the stomach.¹⁹ Slow wave propagation is slightly faster along the greater curvature such that myoelectric coupling and activity from the greater and lesser curves reach the pylorus simultaneously.²⁰ Slow wave propagation into the fundus does not occur because of the relative reduction in the negative resting membrane potential of the fundus compared to the body and antrum.²¹ The slow wave frequency of three cycles per minute is present during both the resting and active phases of gastric motor activity. Neurohumoral activators increase the slow wave amplitude and this initiates a coupled peristaltic response^{22, 23} that grinds and triturates food into a fine particulate suspension, ready for passage into the duodenum.

Motor activity

Under the control of the gastric slow wave, the distal stomach exhibits phasic contractions with a maximal frequency of three cycles per minute. The migrating motor complex (MMC) is the fasting motility complex that clears the stomach of undigested food. The MMC consists of four phases. Phase I is characterized by motor quiescence and lasts 40–60 min of the total cycle length. Phase II, accounts for 30–50 min and is characterized by increasing but irregular contractions. Phase III is a 5- to 10-min period of intense, rhythmic, occlusive contractions, which propel and sweep all indigestible material from the stomach. In contrast to the digestive phase, the pylorus relaxes during this phase and this allows larger particles and insoluble material to pass finally into the duodenum. Phase IV is represented by a short period of transition between the barrage of contractions in phase III and the return to a period of inactivity.

The fed motor pattern appears 5–10 min after ingestion of a meal and is characterized by intermittent

phasic contractions of irregular amplitude similar to those of phase II of the MMC with approximately half the slow wave cycles coupled to contractions. Friction between the chyme bolus and the contracting wall of the antrum causes the solid material and to a lesser extent, liquids, to lag behind the velocity of antral contraction. Consequently, by the time the leading edge reaches the pylorus, the pyloric channel is contracted, only allowing liquid and triturated 1–2 mm solid particles to squeeze into the duodenal bulb.²⁴ The larger particles are repeatedly propelled and retro-pulsed between the proximal and distal stomach causing further trituration of the soluble material until all liquid and small particles have been emptied. Neuro-humoral factors control postprandial gastric motility and the distal stomach is also subject to feedback inhibition from the duodenum.

Antro-duodenal connections

The duodenum possesses a distinct electrical pacemaker generating a dominant frequency of 11–12 cycles per minute. Some conduction from the antrum across the pylorus occurs, resulting in intermittent coordination of antroduodenal electrical activity with a gastric slow wave coordinating with every three to four duodenal cycles. As a consequence of the higher duodenal slow wave frequency, additional duodenal contractions occur interspersed between coordinated antroduodenal waves.²⁵

Just as cardiac failure can result from structural, functional and rhythm disturbance, so can gastric pump failure occur as a consequence of a number of pathological pathways, most of which are still to be uncovered.

CAUSES AND PREVALENCE OF GASTROPARESIS

Functional gastrointestinal disorders are the most common reason for a patient to consult a gastroenterologist and functional dyspepsia is estimated to affect 20% of the adult population in the United States.¹ The prevalence of severe gastroparesis is difficult to assess accurately as studies usually reflect a single centre experience, and diagnostic criteria are not standardized between studies. Gastroparesis presenting as chronic nausea, vomiting and abdominal pain has been associated with a spectrum of diseases and drugs (Tables 1 and 2). In a selected series of 146 patients

Table 1. Causes of gastroparesis

Idiopathic ³
Diabetic ^{3, 26}
Upper gastrointestinal surgery ^{3, 12}
Eating disorders ^{27, 28}
Gastro-oesophageal reflux ²⁹
Iatrogenic (Table 2)
Chronic renal failure ³⁰
Portal hypertension ³¹
Intra-abdominal malignancy ³²
Systemic sclerosis ³³
Myotonic dystrophies ³⁴

Table 2. Drugs that delay gastric emptying

Alcohol
Aluminium hydroxide antacids
Atropine
β -Agonist
Calcium channel blockers
Diphenhydramine
L-Dopa
Lithium
Ondansetron
Opiates
Phenothiazines
Tricyclics

with documented gastroparesis, no cause was found in 36%, 29% were diabetic, 13% were postsurgical and miscellaneous causes were ascribed to the remaining 22%.³

There has been considerable speculation around the possible cause of idiopathic gastroparesis, which occurs mainly in young or middle-aged women. Evidence for myenteric hypoganglionosis and reduction in the interstitial cells of Cajal has been reported.³⁵ Studies of full thickness gastric biopsies indicate that in patients with idiopathic and diabetic gastroparesis, Cajal cells are absent in a third. This subgroup has more severe symptoms, gastric slow wave abnormalities on EGG, and responds poorly to gastric electrical stimulation.³⁶ In some patients, idiopathic gastroparesis presents acutely and can be dated from an acute viral-like gastrointestinal illness.³⁷ This has resulted in speculation that in some patients, damage caused by a viral gastritis might underlie the pathogenesis of idiopathic gastroparesis.

Hyperglycaemia can reversibly influence gastric motor function by reducing antral contractility, altering phase III of the MMC, increasing pyloric contractility, altering myoelectrical activity and influencing fundal relaxation.³⁸ Gastroparesis occurring in long-standing type 1 and type 2 diabetes mellitus most often presents in patients with evidence of other end organ complications.³⁹ Systematic study indicates that gastroparesis can be demonstrated in 25–55% of type 1 diabetics^{3, 40, 41} and 30% of patients with type 2 diabetes.⁴² Most diabetic patients with delayed gastric emptying are asymptomatic or report only mild foregut symptoms. Only a minority are troubled by classical symptoms of intense nausea and recurrent vomiting. Delayed and unpredictable gastric emptying may influence diabetic control^{43, 44} and poor blood glucose control including hypoglycaemia and hyperglycaemia should alert clinicians to the possibility of erratic, slow or even rapid gastric emptying.⁴⁵ Gastroparesis in diabetes is probably multifactorial, although neuropathic mechanisms are most likely to be a major factor.⁴² Other factors implicated in diabetic gastric pump disorders include reduction in the population of interstitial Cajal cells⁴⁶ and abnormalities of pyloric nitric oxide synthetase.⁴⁷

Abdominal surgery is the third most common cause of gastroparesis encountered in clinical practice. The vagus nerve modulates fundal accommodation and phasic antral peristalsis and is consequently thought to play a central role in postsurgical gastroparesis. Vagotomy retards solid emptying but accelerates the emptying of liquids.⁴⁸ Surgical disturbance of anatomy and physiology, including antrectomy, Roux-en-Y gastrojejunostomy and vagotomy may cause profound delayed emptying from the gastric remnant and denervated efferent limb.⁴⁹ Gastroparesis may also occur following open or laparoscopic fundoplication.⁵⁰

Gastroparesis has been reported in association with other gastrointestinal diseases including gastro-oesophageal reflux disease (GERD), chronic intestinal pseudo-obstruction, achalasia, coeliac disease, atrophic gastritis, peptic ulcer disease and chronic pancreatitis.⁵¹ In GERD, gastroparesis has been reported in 10–40% of patients studied^{52, 53} and it is important to consider whether disordered gastric function might be contributing to symptoms when patients are considered for antireflux surgery. Gastroparesis has also been associated with nongastrointestinal diseases such as anorexia nervosa, Parkinson's disease, autoimmune diseases (especially systemic sclerosis), thyroid disease

and chronic renal insufficiency. Drugs which affect gastric motility should also be considered. Commonly prescribed drugs which influence gastrointestinal motility include those with anticholinergic effects, narcotics, tricyclics and calcium channel blockers. The vomiting which occurs in severe gastroparesis needs to be differentiated from other vomiting disorders including gastro-oesophageal regurgitation, rumination, cyclical vomiting, bulimia and the superior mesenteric artery syndrome.

CLINICAL FEATURES OF GASTROPARESIS

The Rome III criteria have modified the classification of the functional gastroduodenal disorders using clinical features to define four major subtypes.⁵⁴ Patients with gastroparesis present with symptoms described within the classification of the nausea and vomiting syndromes. This distinguishes the clinical features from other functional disorders such as the epigastric pain and postprandial distress syndromes, the belching disorders and the rumination syndrome. The dominance of vomiting and nausea in gastroparesis is supported by the observation that in patients with suspected gastroparesis confirmed by gastric emptying studies, nausea occurs in 92%, vomiting in 84%, with bloating and early satiety reported in 75% and 60% respectively.³ However, delayed gastric emptying may also occur in patients with the epigastric pain and bloating syndromes⁵⁵ and asymptomatic diabetic patients,⁵⁶ indicating the overlapping clinical presentations associated with delayed emptying. The symptoms of gastroparesis also overlap with symptoms occurring in the organic disorders such as peptic ulcers, gastric and proximal small bowel obstruction, gastric cancer and biliary disease. Consequently, the diagnosis is restricted to patients with chronic nausea and vomiting who have normal foregut imaging but objective evidence of profound delay in gastric emptying.

Revicki *et al.* have devised a validated patient questionnaire to standardize documentation of symptom severity in gastroparesis.⁴³ This gastroparesis cardinal symptom index comprises patient rated scores for postprandial fullness/early satiety, nausea/vomiting and bloating and is useful for documentation and tracking of patients with diagnosed gastroparesis.

In patients with gastroparesis, physical examination may be entirely normal, or in its most severe forms,

dehydration, malnutrition and even a succussion splash may be present. Signs of associated systemic disease such as systemic sclerosis should be sought and particular care should be taken to ensure examination of the autonomic nervous system. Autonomic neuropathy might be suspected by an exaggerated postural drop in systolic and diastolic blood pressure and on ECG, vagal neuropathy is suspected if there is a loss of normal sinus dysrhythmia.

ASSESSMENT OF SUSPECTED GASTROPARESIS

Gastroparesis should be suspected in all patients with unexplained troublesome foregut symptoms. In general, an endoscopy and hepatobiliary ultrasound will have been performed in patients because of the 'alarm' features. Whilst endoscopy is often normal in patients with delayed gastric emptying, in profound gastroparesis, endoscopy often reveals food debris in the stomach. Signs of reflux oesophagitis may also be observed resulting from recurrent vomiting. Proximal small bowel obstruction should be excluded by barium follow through or CT imaging.

Gastric pump failure may reflect disorders of storage, grinding and propulsion and the key investigation is measurement of gastric emptying, which provides a summative assessment of all these functions.

Measuring gastric emptying

Scintigraphy: the gold standard. Despite its potential importance in gastrointestinal practice, the test is not widely available and standardization between laboratories is lacking. An isotope-labelled solid test meal is used to calculate the emptying time. Liquid test meals are not useful because liquid may empty normally when a solid test meal reveals evidence of quite profound gastroparesis. The solid test meal usually employs technetium-99 m [⁹⁹Tcm] sulphur-colloid bound to egg in a sandwich, or added to a uniform meal such as scrambled egg or mashed potato. The caloric and nutritional content of the test meal should be standardized.^{57, 58} When interpreting gastric emptying studies, it is important to recognize that premenopausal women have slower gastric emptying than men^{4, 59} and this should be reflected when setting normal ranges.²

Scintigraphy is performed following an overnight or fast. In advance of the test, all drugs delaying or accelerating gastric emptying should be discontinued.

The anti-nausea drug ondansetron has little effect on gastric emptying and in patients troubled by vomiting, this drug can be used to prevent vomiting during the test. Following ingestion of the test meal, scintigraphy should be performed over a minimum of 2 h and accuracy is improved by extending the test out to 4 h.^{60, 61} The pattern of gastric emptying is characterized by an initial lag phase followed by a linear phase of gastric emptying (Figure 1a). The test results may be reported as the per cent retention at defined time points (e.g. 2 and 4 h), or the half emptying time ($t_{1/2}$) can be calculated (Figure 1a,b). The most accurate measurement of gastric emptying is residual content at 4 h, with >10% considered abnormal. Percentage retained at time points earlier than 4 h is less predictable with false-negative results occasionally reported in patients with significantly delayed emptying.⁶¹ When scintigraphy is repeated in individual patients, it is important to recognize that there may be 20% day-to-day variation in gastric emptying. There is little standardization of liquid and solid test meals and the definition of the normal ranges varies between laboratories. Consequently, results from different laboratories cannot be readily compared.

Whilst scintigraphy remains the standard test of gastric emptying, a number of other direct imaging investigations have been developed, although currently few are in routine use.

Ultrasonography. Transabdominal ultrasound is widely available and when used to assess gastric emptying, it correlates well with scintigraphy.⁶²⁻⁶⁴ Ultrasound examination is operator dependent and it is therefore important for a single skilled operator to develop expertise in this technique. Following the test meal, serial measurements are made of the longitudinal (D_1) and anteroposterior (D_2) diameters of a single section of gastric antrum, using the abdominal aorta and the left lobe of the liver as internal landmarks.^{62, 63} By calculating the sequential change in antral area (Antral area = $[\pi \times D_1 \times D_2]/4$), it is possible to calculate gastric emptying rate (GER) from the formula: GER = $[(A \text{ area}^{90 \text{ min}}/A \text{ area}^{15 \text{ min}}) - 1] \times 100$. Another measure is to consider gastric emptying complete when, following a test meal, antral area returns to fasting size. Three-dimensional ultrasound is a newly developed technique that has recently been reported useful in determining proximal stomach function⁶⁵ and this ultrasonic technique might add a further minimally

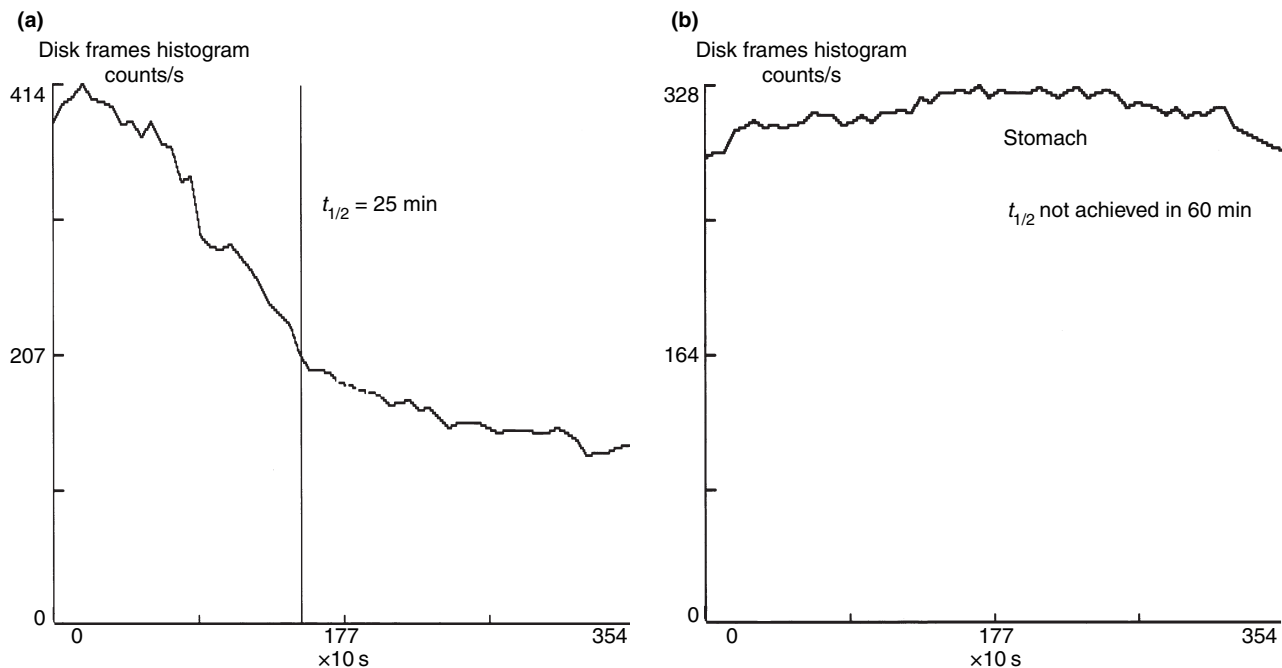


Figure 1. Scintiscans showing (a) normal gastric emptying and (b) classical gastroparesis.

invasive measurement to assess the complexity of gastric emptying.

¹³C-Breath testing. The stable, nonradioactive isotope, ¹³C, can be used to label a substrate, typically the medium chain triglyceride octanoic acid, which can then be incorporated into a solid test meal (e.g. a muffin).^{66–68} On entering the duodenum, metabolism of the octanoate releases ¹³CO₂, which is expelled in expired breath where it can be measured. Because gastric emptying is the rate limiting step, the excretion rate of breath ¹³CO₂ reflects the rate of gastric emptying and the test correlates well with scintigraphy.^{66–68} Significant lung disease and small bowel maldigestion and malabsorption may influence the test and patients with lung, small bowel, pancreatic and liver disease are considered unsuitable for this test of gastric emptying. Whilst this test is safe, accurate, convenient and can be shipped by post for analysis, ¹³C octanoic acid breath testing has not become widely available.

Magnetic resonance imaging. Magnetic resonance imaging (MRI) can measure gastric emptying and accommodation using sequential transaxial abdominal scans.⁵⁸ MRI provides an excellent spatial

resolution with a high sensitivity.⁶⁹ A semisolid meal is enhanced with dilute gadolinium to brighten the stomach lumen and fast acquisition sequences allow direct visualization of regional gastric movement giving information on intragastric distribution of a test meal.⁷⁰ Antral propagation waves can be observed and their velocity calculated. MRI can differentiate gastric meal volume and total gastric volume, allowing gastric secretory rates to be calculated. In gastroparesis, there is a significant reduction in the velocity of these waves.⁷¹ Currently, use of this minimally invasive technique is limited by availability and cost.

Swallowed capsule telemetry. The ingestible telemetry capsule (SmartPill Corporation, New York, NY, USA) offers a promising new method for assessing gastric emptying. The telemetry capsule broadcasts in real time, intraluminal pH, phasic gastric pressure activity and ambient temperature. The time taken for the pill to be expelled from the stomach into the duodenum is readily measured by monitoring the time point at which the acid readings of the stomach are replaced by the dramatic increase in pH as the capsule enters the duodenum. Although this

method utilizes an insoluble capsule rather than a physiological test meal, the telemetric approach has been shown to correlate well with scintigraphy.⁷² The frequencies and amplitudes of antral contractions can also be measured and have been shown to be significantly different in gastroparetic patients from those of normal controls.⁷³

Antroduodenal manometry. Stationary or ambulatory antroduodenal manometry provides simultaneous information on gastric and duodenal motor activity. The information is helpful in building a full motor picture of the stomach and duodenum. Distinct patterns characterize the fasting (interdigestive) and fed (digestive) phases. During the interdigestive phase, the MMC recurs every 2 h. The MMC consists of phases and in phase III, an integrated peristaltic wave, initiated in the stomach, sweeps indigestible solids from the stomach into the duodenum and beyond. Ingestion of food triggers a more regular antral and duodenal rhythm, which is responsible for antrograde pumping and mixing of liquids and soluble solids. In the fed state, the stomach is paced at a mean frequency of three cycles per minute, whereas the duodenal rate is 12 cycles per minute.

Abnormal antroduodenal manometry has provided important information on the abnormalities occurring in gastroparesis. There is manometric evidence for two mechanisms that can contribute to gastric pump failure.⁷⁴ Some patients exhibit antral hypomotility, whereas others reveal evidence of increased resistance to gastric emptying because of duodenal, rather than antral, dysmotility. These two patterns are reflected in different shapes to the gastric emptying curves measured by scintigraphy.⁷⁴ Antroduodenal manometry can also distinguish between neuropathic and myopathic diseases. In neuropathic disorders, contractions are of normal amplitude, but propagation is abnormal with loss of phase III of the MMC, random bursts of activity and failure to switch between the fasting and fed state. Myopathic disorders, like those occurring in systemic sclerosis or amyloidosis, are characterized by low amplitude contractions.

In diabetic gastroparesis, tonic and phasic pylorospasm has been observed, as well as an abnormal pattern of small intestinal contraction.⁷⁵ Additional findings indicate that in some patients, the phase III complexes of the MMC initiate in the duodenum rather than in the stomach.⁷⁶

Measuring myoelectrical activity

Electrogastrography. The rhythm of the gastric pacemaker can be measured using the electrogastrogram. The EGG measures the myoelectrical slow wave, which triggers the antrograde antral peristaltic wave and regulates its frequency. Cutaneous electrodes are positioned along the long axis of the stomach and a 45–60 min preprandial recording is captured. Patients are then given a 500 kcal cheese or turkey sandwich and an equivalent postprandial recording is captured. The recorded signals are amplified and filtering to exclude artefact signal from surrounding organs and patient movement. Raw EGG signals are transformed and a three-dimensional plot is produced. The normal slow wave frequency is 2.4–3.6 cycles per minute. Abnormality of the EGG is defined by >30% abnormality of slow wave frequency and/or failure of meal ingestion to increase the signal amplitude.⁷⁷ Gastric dysrhythmias include preprandial and/or postprandial tachygastria (3.6–9.9 cycles per minute), bradygastria (0.9–2.4 cycles per minute) or tachy-brady-gastria.

A range of dysrhythmias have been described in patients with both idiopathic and diabetic gastroparesis⁷⁸ and up to 75% of patients with gastroparesis have an abnormal EGG.⁷⁷ Patients with an abnormal EGG have also been found to have more severe symptoms.⁷⁹ The value of the EGG in patients with gastroparesis remains to be defined, but it is possible that the test identifies a particular patient subgroup that, in turn, might require a treatment regimen targeting the rhythm disturbance.

TREATMENT OF GASTROPARESIS

Treatment of gastroparesis is focused on patient education and explanation, dietary modification, management of any underlying cause and symptom treatment (Figure 2).

Patient education

The disabling chronic symptoms of gastroparesis impact profoundly on the patient's sense of well-being, mental state, behaviour and social life. Anxiety and depression almost always complicates this clinical disorder, and in addition to sensitive caring from the clinical team, professional counselling might be necessary to help the patient cope with the disability.

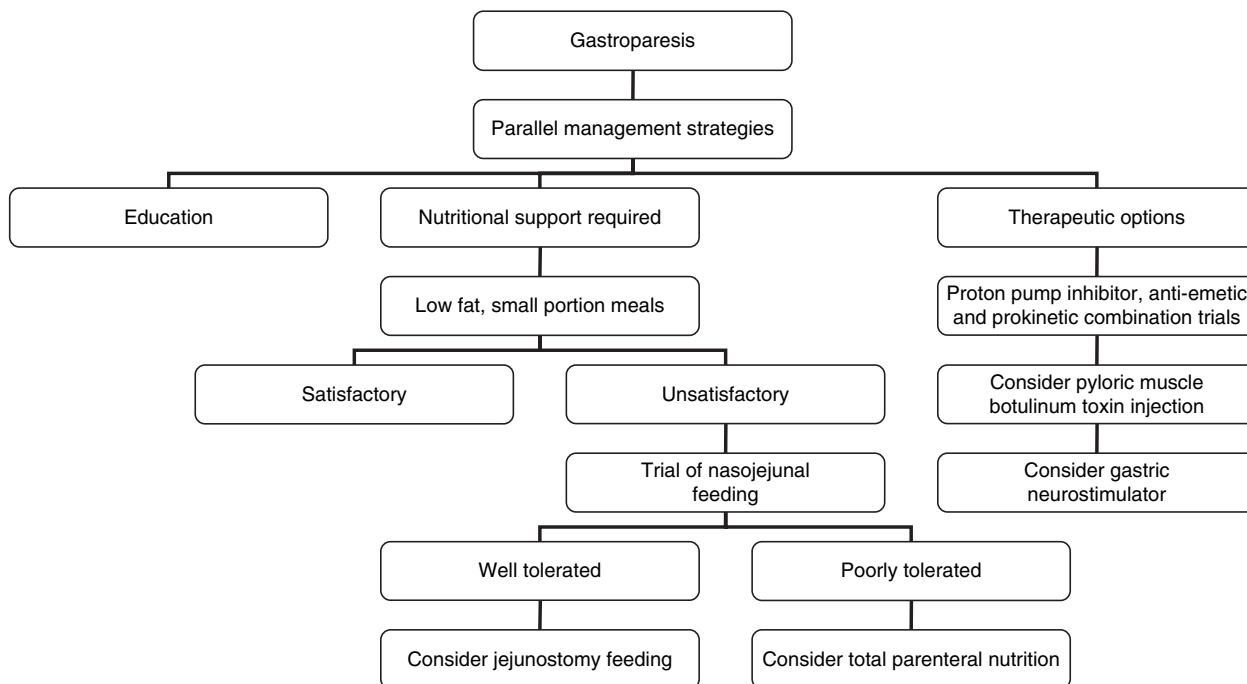


Figure 2. Gastroparesis management strategies.

Partners, close associates and even employers are affected by the patient's poor health and impaired social functioning and time and effort should be set aside for explanation and counselling all those affected by the patient's illness. Patients will generally have no grasp of gastric anatomy and physiology and the complexity of the gastric pump should be discussed using illustrations and animations laced with appropriate analogies. It might also be helpful to demonstrate a video clip of a normal gastroscopy, illustrating the fundus, the region of the gastric pacemaker, the antrum, pylorus and duodenum. A clip showing the dramatic sweeping action of a powerful peristaltic contraction might also be helpful in explaining gastric emptying and its pathophysiology. At the outset, it is important to set realistic expectations of treatment. Patients should be informed that a number of drugs may be tried in an attempt to discover the optimal therapeutic regimen and that the aim of the treatment is to control rather than cure the disorder.

Dietary manipulation

Diet is a central concern to patients and their families and adjustment needs to be tailored to symptom severity and the patient's particular needs. At the

outset, it is advisable to introduce an experienced dietician who can discuss and explore the patient's tolerance of solids, semi-solids and liquids as well as dietary balance, meal size and timing of meals. High fibre foods, animal fats and vegetable oils delay gastric emptying and a low fibre, low fat diet usually constitutes a basis for manipulating the quality and consistency of meals. Alcohol and smoking delay gastric emptying and these should be discouraged. Liquid emptying is often satisfactory when solid emptying is abnormal and the use of liquid supplements or pureed foods might underpin the diet. Low fibre, low fat caloric supplements containing iron, folic acid, calcium and vitamins D, K and B₁₂ are commercially available in a number of flavours and formulae. Appropriate meal size and frequency need experimentation and it is useful to define portion size by the size of an egg.

If simple dietary measures and drug treatment fail to improve the patient's symptoms, and if the patient is unable to sustain his weight, artificial enteral nutrition should be considered. Initially, it is worth experimenting with a trial of slow, pump-driven nasogastric infusion, to assess whether a steady liquid drip feed is tolerated. Where patients are intolerant of intragastric feeding, a trial of nasojejunal feeding

should follow.⁸⁰ This route bypasses the stomach, and the small bowel challenge provides nutrition, indicates whether jejunal feeding is tolerated and establishes whether there is symptom relief. A satisfactory response to a trial of nasogastric feeding is an indication to consider direct feeding through a percutaneous endoscopically placed gastrostomy (PEG), which can be used for both liquid feeding and stomach venting.⁸¹ Where nasojejunal feeding is helpful, an endoscopic or surgically placed jejunostomy might be indicated.⁸² At the outset, dilute liquid iso-osmolar enteral feeds are started at low infusion rates (e.g. 10–20 mL/h) and the intake is steadily increased every 12 h (by 10 mL/h) until the calculated nutritional intake is achieved. In rare instances when enteral nutrition is poorly tolerated because of pain, bloating or recurrent abdominal wall infection, long-term parenteral nutrition might be necessary.

Metabolic control

Hyperglycaemia delays gastric emptying in the absence of end-organ damage^{83–85} and there is evidence that high blood sugar levels interfere with the effects of prokinetic agents like the motilin agonist erythromycin.⁸⁵ It is therefore desirable to strive for knife edge control in diabetics with gastroparesis. Achieving this is usually difficult because of unpredictable gastric emptying and in these patients, the use of a portable insulin pump might be helpful in achieving optimal control.

Drug treatment. The pharmacotherapy of gastric pump failure is stepwise, incremental and long-term. The most commonly used drug classes include prokinetic and antiemetic agents. There have been few adequately powered drug trials in patients with gastroparesis and no study has attempted to stratify the different subtypes (i.e. myopathic, neuropathic, dysrhythmic and mixed). Consequently, a selection of drugs is used empirically. The aim of therapy is to improve the efficiency of the gastric pump and relieve symptoms, including nausea, bloating, vomiting and pain.

Although prokinetic drugs have powerful pharmacological properties, prokinetic treatment is often disappointing, especially in more severe gastroparesis. This probably reflects failure of the drug to target selectively the muscle, nerve and rhythm disturbances, all of which can singly, or in combination, cause gastric

pump malfunction. The importance of selective drug targeting is suggested by the observations that certain prokinetics such as metoclopramide, domperidone and cisapride improve gastric dysrhythmias, whereas other drugs, such as erythromycin, can aggravate gastric dysrhythmias.⁸⁶ Other differences might equally apply to drugs that act by increasing the frequency of antral peristalsis, coordinate antroduodenal coupling or relax or increase the tone of the fundus.

Prokinetic drugs

This class of drug is used as first-line medical treatment. They stimulate peristalsis and may specifically improve gastric pump function by influencing antral contractility and rhythm as well as antroduodenal coordination. Unfortunately, symptom response to prokinetic drugs correlates poorly with impact on gastric emptying.^{87, 88} There is also a powerful placebo effect and a meta-analysis has questioned the validity of positive clinical trials because of evidence of publication bias.⁸⁹

Metoclopramide. Metoclopramide is a substituted benzamide with prokinetic activity, which is localized to the proximal gastrointestinal tract. In addition, the drug has antiemetic properties. Metoclopramide is a 5-HT₄ receptor agonist, which releases acetylcholine from the myenteric plexus. The net effect is to increase lower oesophageal sphincter pressure and fundal tone, as well as increasing the amplitude of antral contractions and facilitating antroduodenal coupling. Metoclopramide also has dopamine receptor antagonist properties, and is a weak 5-HT₃ receptor antagonist; these actions, together with the effect on motility, provide the drug with its antiemetic properties. Small controlled trials have been reported, suggesting that metoclopramide does have some benefit in idiopathic and diabetic gastroparesis.^{83, 90}

Metoclopramide is available in tablet form, liquid and suppository, and can be administered intravenously. The usual dose of metoclopramide is 10 mg before meals and an additional bedtime dose. Side effects occur in up to 30% of patients and result from antidopaminergic effects on the CNS. These include restlessness, agitation, dizziness, drowsiness and hyperprolactinaemia with breast engorgement and galactorrhoea. All patients should be forewarned of the rare instance of dystonic reactions characterized

by facial spasm, trismus, torticollis and oculogyric crises occurring within 48 h of starting treatment. With chronic use, a Parkinsonian syndrome may appear, characterized by tardive dyskinesia.

Domperidone. Domperidone is a benzimidazole derivative and is a specific dopamine (D₂) antagonist with similar physiological effects on the upper gastrointestinal tract as metoclopramide. The blood-brain barrier is relatively impermeable to domperidone and consequently, it has fewer central side effects, whilst still offering some antiemetic effect. Controlled trials have shown efficacy in gastroparesis^{90, 91} and in diabetics, the effect is similar to metoclopramide but with fewer side effects.^{90, 91} The symptom improvement associated with domperidone^{92, 93} cannot be directly linked to improved gastric emptying and it is suggested that its effect on the gastric slow wave might be more important.⁹⁴ There is also evidence of tachyphylaxis.⁹²

The usual dose of domperidone is 10 mg before meals and an additional bedtime dose. Because of the lower incidence of central side effects, the dose can be increased more readily than with metoclopramide. However, hyperprolactinaemia, menstrual disturbance, breast engorgement and galactorrhoea may still occur because of its antidopaminergic effect.

Erythromycin. Erythromycin is a macrolide antibiotic, which coincidentally has motilin receptor agonist activity. Motilin is a 22 amino acid polypeptide hormone present in the endocrine cells of the distal stomach and duodenum. This gut hormone increases lower oesophageal sphincter pressure and is responsible for initiating the MMC. In line with its motilin-like effect, erythromycin has been shown to increase the amplitude of antral peristalsis, trigger premature MMC phase III activity and stimulate gastric emptying.⁹⁵ Its main symptomatic effect appears to be on bloating rather than early satiety or nausea⁹⁶ and its effect diminishes with time.⁹⁷⁻⁹⁹ This tachyphylaxis is believed to be caused by downregulation of motilin receptors and there is evidence that loss of efficacy may be overcome by using erythromycin at low dose (e.g. 50-100 mg four times daily).¹⁰⁰ The drug is most rapidly absorbed when administered as a suspension¹⁰¹ and the liquid presentation offers the additional benefit of allowing dose manipulation. The evidence base for dosing and long-term symptom improvement remains wanting, but many clinicians use erythromycin as part

of an escalating or changing prokinetic regimen. A reasonable approach might be to introduce erythromycin suspension at a low dosage (e.g. 50 mg taken 30 min before meals and a further dose before retiring at night) and depending on response, increasing the dose in 25-50 mg increments every few days to a maximum dose of 250 mg. The most common erythromycin side effects are skin rashes, nausea, cramping and abdominal pain. There is concern about complications of long-term treatment, especially torsades de pointes. All these factors need consideration when deciding whether or not to add erythromycin to the treatment of gastroparesis.

Tegaserod. This is a 5-HT₄ receptor partial agonist used in the treatment of women with constipation-predominant irritable bowel syndrome. The drug stimulates small intestinal motility and in healthy volunteers, there is evidence both for¹⁰² and against¹⁰³ gastric prokinetic activity. The potential to influence gastric pump activity has been used to recommend its trial in gastroparesis, but currently there is no good evidence to support its use.

Antiemetic agents

Nausea and vomiting are the most disabling symptom of gastric pump failure and antiemetic may be used either alone, or in conjunction with prokinetics. There is little evidence from clinical trials to support the use of specific antiemetic regimens in gastroparesis, but clinical experience suggests that a range of antiemetics might be helpful in controlling nausea and vomiting. Like prokinetics, the choice of antiemetic is empirical and it is common practice to prescribe initially a phenothiazine such as prochlorperazine, or an antihistamine such as cyclizine. If both these classes of antiemetics fail to control symptoms, the 5-HT₃ receptor antagonists such as ondansetron and granisetron might be tried.

Phenothiazines. Prochlorperazine is a potent neuroleptic with antiemetic properties and a potency 10-20 times that of chlorpromazine. It is the phenothiazine most commonly used for the treatment of nausea in patients with gastroparesis. The drug is a dopamine receptor antagonist, which acts centrally on the vomiting centre. Prochlorperazine can be administered in tablet form, liquid suspension, suppository and by

injection, allowing adaptation of the formulation to the patient's condition. Onset of action is rapid following intramuscular injection and buccal treatment, with a more delayed but more sustained action when given in tablet form. Side effects include drowsiness, dry mouth, constipation, skin rashes and Parkinsonian-like tardive dyskinesia. These side effects are similar to those exhibited by all phenothiazines, but the incidence is much less commonly encountered than with chlorpromazine.

Antihistamines. Cyclizine is a piperazine derivative with histamine H1-receptor antagonist and anticholinergic activity. This is the most commonly prescribed antihistamine antiemetic and is available as a 50 mg tablet and also in injectable form. The drug is used to treat nausea and vomiting associated with motion sickness. The mechanism of action is poorly understood but is likely to involve both a labyrinthine and chemoreceptor trigger zone. Dimenhydrinate, another antiemetic antihistamine, has been shown to improve the EGG abnormality (tachygastria) occurring in motion sickness¹⁰⁴ and it is possible that in gastroparesis, this effect might be responsible for an antinausea effect. Side effects include drowsiness, dry mouth, blurred vision, difficulty urinating, constipation, palpitations, dizziness, insomnia and tremor.

Serotonin 5-HT₃ receptor antagonists. Serotonin (5-HT₃) receptor antagonists are effective treatments for chemotherapy and radiotherapy-induced nausea and vomiting. This class of drug is thought to act on the chemoreceptor trigger zone as well as afferent vagal nerves. Whilst ondansetron and granisetron are expensive, and there are no clinical trials to support its use in gastroparesis, these drugs may be helpful when all other drugs have failed to provide symptom relief.

Management of complex gastroparesis

There is a substantial subgroup of patients with troublesome gastroparesis in whom explanation, education, dietary manipulation and sequential or incremental trials of prokinetic drugs and/or antiemetics fail to provide adequate relief. Those most refractory to treatment are likely to include markedly symptomatic patients with evidence of profound delay in gastric emptying. Additional strategies might be considered in these complex patients.

Low-dose tricyclics antidepressants. Whilst in general, tricyclics antidepressants impair gastrointestinal motility through their anticholinergic activity, there are reports that low-dose tricyclics (amitriptyline, desipramine, nortriptyline, doxepin and imipramine) may relieve nausea, vomiting and pain occurring in functional dyspepsia.¹⁰⁵⁻¹⁰⁷ Efficacy does not appear to differ between tricyclics preparations and the starting dose is usually 10 mg, taken 2 h before bedtime. If the patient tolerates this dose, there is scope for progressively increasing the dosing to 25 mg or even 50 mg. Whilst side effects with low-dose tricyclics are uncommon, excessive sedation and dry mouth occasionally limit use. Switching between tricyclics might be helpful and nortriptyline and desipramine are thought to have a lower incidence of side effects.¹⁰⁶

Pyloric injection of botulinum toxin. Botulinum toxin A is a bacterial toxin that inhibits acetylcholine release causing muscle paralysis. Following intramuscular injection, the effect lasts months and function gradually returns requiring repeat injection. Pylorospasm has been shown to occur in diabetic gastroparesis¹⁰⁸ and in uncontrolled series of between three and 63 patients with both idiopathic and diabetic gastroparesis, injection of 25 units of Botox into each of four pyloric quadrants has been reported to improve both symptoms and gastric emptying.¹⁰⁹⁻¹¹⁴ The largest series reported 63 highly selected patients with primarily idiopathic gastroparesis, 43% of who responded symptomatically with mean response duration of 5 months. Male gender, but not the presence of vomiting, predicted response.¹¹¹ However, a recent double-blind controlled crossover study found no improvement over the use of placebo in a group of predominantly idiopathic gastroparesis patients.¹¹⁵ Intraspincteric Botox is therefore currently not advocated unless in the context of a controlled clinical trial, or occasionally, when all other treatments have failed.

Gastric neurostimulation. Paced gastric neurostimulation using an implantable stimulator (Enterra therapy, Medtronic, Minneapolis, MN, USA) has been approved by the FDA. The device has not received NICE approval in the UK. Electrical stimulation is delivered by two electrodes implanted laparoscopically¹¹⁶ or at laparotomy, onto the serosal surface overlying the pacemaker area on the greater curve of the stomach

and approximately 2 cm apart. Leads from the electrodes connect to a neurostimulator, which resembles a cardiac pacemaker that is implanted in the anterior abdominal wall. Enterra generates a high frequency (12 cycles per minute), low energy, short duration pulse. A wireless remote controller allows settings to be adjusted to optimize symptom control. A landmark study by Abell *et al.* reported on 33 patients, half of whom had idiopathic, and the other half diabetic, gastroparesis. Both patients and clinicians were blinded to whether the device was switched on or off. Overall, 79% of patients had a 50% or greater decrease in vomiting. The benefits, measured by a symptom score of nausea, vomiting, bloating, fullness, satiety and pain, were significant, but less so than for vomiting alone.¹¹⁷ A reduction in medication use with fewer hospital admissions has been reported^{118, 119} and other uncontrolled series have reported benefit.^{120–122} Gastric electrical stimulation is reported to enhance nutritional status, reduce the requirement for supplemental feeds¹²³ and improve glycaemic control in diabetics.¹¹⁹

The effect of Enterra on gastric emptying is controversial with different outcomes reported in the literature.^{124, 125} However, there is general agreement that symptom relief is disproportionate to any effect on gastric pump function. Symptom improvement is probably because of another action and there is speculation that electrical stimulation of vagal afferents might suppress the vomiting centre in the brain. Electro-stimulation has, however, also been reported in patients with postsurgical gastroparesis who have undergone vagotomy.¹²¹ Infection is the major complication associated with neurostimulator implantation resulting in removal of the device in 5–20% of patients. Despite its apparent value in refractory gastroparesis, most authorities recommend that neurostimulators should be implanted in the context of long-term controlled trials.

Gastrectomy. Gastrectomy has been reported in a final attempt to manage severe, intractable and refractory

gastroparesis.^{81, 126} The procedure carries a substantial morbidity and mortality and there is little experience to guide practice. Highly selected small case series suggest that the procedure is more likely to succeed in postsurgical and diabetic^{127, 128} gastroparesis. There have also been reports of symptom improvement in diabetics following pancreatic transplantation.^{129, 130} As there are no prospective controlled trials of gastrectomy, this treatment should only be considered in rare instances in expert tertiary referral centres.

CONCLUSION

Whilst delayed gastric emptying is common in patients with functional dyspepsia, the diagnosis of gastroparesis is usually considered in patients presenting with profound vomiting and nausea and no cause on fore-gut imaging. Gastroenterologists should recognize that the gastric pump is complex and investigation of the structures beyond the mucosa is more likely than endoscopy to reveal the diagnosis. Diagnosis is usually made by gastric scintigraphy, which provides a composite measure of gastric pump function. Treatment should focus on education, nutritional support, control of blood glucose in diabetics and sequential trials of prokinetics and antiemetics used either alone or in combination. If medical treatments fail to relieve symptoms and in particular vomiting, intrapyloric botulinum toxin might be tried. The gastric neurostimulator is helpful in some patients with intractable and refractory gastroparesis, although the mechanism by which it reduces vomiting remains uncertain. It is likely that gastroparesis results from a range of muscular, neural or rhythm disorders of the stomach and progress in the treatment of the syndrome awaits a better understanding of pathogenesis.

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