

ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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Highlights From the New ACG Clinical Guideline for Gastroparesis



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G&H Why did the American College of Gastroenterology recently update its clinical guideline on gastroparesis, and what is the main focus of the updated guideline?

MC The American College of Gastroenterology (ACG) published a new clinical guideline on gastroparesis in the August 2022 issue of *The American Journal of Gastroenterology*. This is an update of the previous guideline, which was published in 2013. Since then, a number of new directions have emerged in the management of gastroparesis that the ACG believed were worthy of an update. In addition, gastroparesis is regarded among clinical gastroenterologists as an area that requires further advances to help in the management of patients.

The main focus of the new guideline is to review the risk factors for gastroparesis and to update clinicians and other readers regarding recommendations for the diagnosis and treatment of patients with gastroparesis. Specifically, the guideline discusses the best diagnostic approaches and, in particular, the ways in which new devices and new endoscopic procedures have been evaluated since the prior guideline.

G&H In the new guideline, how was the evidence assessed, and how was the strength of the recommendations graded?

MC Four participants in the guideline development were content experts—that is, gastroenterologists and researchers who work on understanding the risk factors, diagnosis, and treatment of gastroparesis. In addition, 2 librarians

conducted an extensive literature search and brought to the attention of the content experts approximately 200 to 250 papers regarding gastroparesis, particularly those involving risk factors, diagnosis, and treatment.

The strength of the recommendations was based on assessment of the evidence by 2 specialists in the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, Dr Rena Yadlapati and Dr Katarina Greer, who independently adjudicated the evidence regarding each Patient, Intervention, Comparison, and Outcomes (PICO) question that was tabulated by the content experts. As much as possible, the specialists were given an opportunity to independently assess the evidence and to make the recommendations, as well as adjudicate the strength of those recommendations.

G&H According to the new guideline, how should gastroparesis be diagnosed, and are there any updates or changes in the diagnosis or testing for gastroparesis?

MC There are 2 very positive statements that could be made regarding diagnosis. The gold standard for the diagnosis of gastroparesis is a scintigraphic study of gastric emptying of a solid meal, typically an egg or egg/protein-based meal. Imaging of the abdomen needs to occur for at least 3 hours and preferably 4 hours after the meal. It is the proportion or percentage of the radioisotope associated with that meal that is retained in the stomach at 4 hours that is the gold standard for the diagnosis of gastroparesis. Using an egg/protein-based meal, for instance, greater than 10% retained in the stomach is often used as

the diagnostic criterion for the presence of delayed gastric emptying.

Importantly, since the 2013 guideline, the US Food and Drug Administration (FDA) has approved a stable isotope gastric-emptying breath test using carbon-13 (¹³C) spirulina, in which the patient ingests a meal containing this stable isotope, and then breath samples are taken for enrichment of ¹³C CO₂ for approximately 4 hours. The samples are sent to a centralized laboratory, and a report can then be provided to the clinician who has requested the gastric-emptying test.

Those are the 2 gold standard measurements of gastric emptying to make a diagnosis of gastroparesis. The diagnosis of gastroparesis depends on 3 things: the symptoms of gastroparesis, the objective measurement of delayed gastric emptying of solids, and the exclusion of obstruction in the stomach or in the small intestine.

Two points were also made regarding other diagnostic tests that are sometimes used. The first is that measurement of emptying of radiopaque markers from the stomach was not recommended. The reason for that is radiopaque markers do not empty with solid food from the stomach. In addition, a wireless motility capsule, which provides accurate measurement of small bowel and colonic transit, is not as accurate for the measurement of gastric emptying because, as with radiopaque markers, the nondigestible capsule does not empty with the solid meal from the stomach. Therefore, it could give an erroneous, often false-positive, result regarding the delay in gastric emptying. Those are the 2 most important recommendations of tests not to be conducted.

G&H What are the most important dietary recommendations for patients with gastroparesis, according to the new guideline, and are there any changes or updates included in the new version?

MC A very important randomized controlled trial by Olausson and colleagues from Sweden is highlighted in the guideline. It involved comparison of a diet consisting of small particles with a diet containing food of varying particle size, as in ordinary food. This trial demonstrated that the patients who were taking a small-particle diet had marked improvement in virtually all of their gastroparesis symptoms.

Another general recommendation regarding gastroparesis is to avoid nondigestible fiber in vegetables and fruits. I often tell patients that any food that crunches under their teeth cannot be digested easily by their stomach. That food needs to be cooked, put in a blender, and consumed as a soup. Similarly, a very high-fat diet generally slows down stomach emptying. To summarize,

a small-particle diet is recommended whenever possible, and nondigestible fiber and a high-fat diet should be avoided.

G&H What are the best pharmacologic treatments available, and are there any changes in the new guideline?

MC The guideline notes that its recommendations on treatment have been somewhat compromised by the fact that there is only 1 pharmacologic treatment that is approved in the United States for gastroparesis, and that is metoclopramide. At the same time, the FDA has a black box warning regarding the duration of the prescription of metoclopramide, which should be 3 months or less. The reason for this concern about metoclopramide is that the FDA determined there is an approximately 4% risk of tardive dyskinesia, which is an irreversible disorder with involuntary movements. Because of that risk, the FDA recommended, first, not to exceed a total dose of approximately 40 mg per day (ie, 5-10 mg before meals and 5-10 mg before bedtime) and, second, that the prescription should be for 3 months or less.

Patients with gastroparesis have symptoms and problems that last more than 3 months; therefore, the guideline includes opportunities for off-label treatment with other medications to try to enhance the emptying of food from the stomach and also to relieve patients' symptoms. There are recommendations not only for the use of metoclopramide in accordance with the FDA recommendations but also recommendations regarding other treatments that are not approved specifically for gastroparesis.

For example, domperidone is available in some countries and under certain conditions within the United States, and can be used mainly for its antiemetic effect. Other medications stimulate the nerves and muscles of the stomach, such as prucalopride, which is a prokinetic 5-HT₄ receptor agonist approved for the treatment of chronic constipation, and pyridostigmine, which is used in the treatment of neurologic disorders. Pyridostigmine is an acetylcholinesterase inhibitor and increases the amount of acetylcholine in the wall of the stomach to help the stomach empty better. Also, erythromycin can be used for a short period before tachyphylaxis occurs and its efficacy is lost. I often remind physicians that intravenous erythromycin at the dose of 3 mg/kg every 8 hours can be used to help jump-start the stomach if the patient is admitted to the hospital because of dehydration, inadequate nutrition, and the stomach not emptying well enough to support hydration and nutrition. Those are just some of the examples.

In addition, emphasis was made on the importance of antiemetic medications. These could be antihistamine

medications such as promethazine or 5-HT₃ receptor antagonists such as ondansetron. Some of the experimental trials that show potential to treat gastroparesis were also highlighted in the guideline, and these include medications such as aprepitant, which is approved for chemotherapy-induced emesis. However, according to a large, well-designed trial by Parkman and colleagues in the United States, the central neuromodulator nortriptyline was not efficacious; therefore, the guideline recommends that central neuromodulators not be used for gastroparesis. Some experimental therapies not yet approved anywhere in the world appear to be promising, including tradipitant, which is a neurokinin-1 receptor antagonist, and relamorelin, which is a ghrelin receptor agonist. There is much promise if these medications can be followed through to phase 3 trials and approved by the FDA.

G&H What are the best nonpharmacologic treatment options available, and are there any changes in the new guideline?

MC I have already discussed the importance of diet. Other nonpharmacologic treatments, such as gastric electrical stimulation, have been approved in the United States. There is some evidence that, particularly for patients with refractory vomiting, gastric electrical stimulation might be beneficial, and that was proven in a randomized controlled, crossover study by Ducrotte and colleagues in France.

Gastric peroral endoscopic myotomy (G-POEM) of the pylorus is a newer treatment option. A large amount of evidence, mostly based on open-label studies, has suggested that G-POEM is efficacious for the treatment of symptoms and for improvement of gastric emptying. Importantly, in April of this year, the first pilot, sham-controlled study of G-POEM was published by Martinek and colleagues, who demonstrated that G-POEM was superior in the treatment of gastroparesis compared with a sham control in which patients underwent an endoscopy but the pylorus was not cut. That is very promising, and it was included in the guideline as something that also needs to be followed through with further studies.

G&H What future areas of research in gastroparesis are most needed?

MC As I indicated previously, there is only 1 approved medication (metoclopramide), and it is associated with a black box warning and a risk that the FDA estimated was approximately 4%. More recent literature from Al-Saffar

and colleagues suggests that it is closer to 0.1% or less; that is, 1 in 1000 to 1 in 10,000 patients actually develop tardive dyskinesia. There is still an opportunity to try to help patients by using relatively low doses of metoclopramide without the risk of an irreversible neurologic syndrome. Nevertheless, there is a need for better pharmacologic therapies than metoclopramide, which is a relatively weak prokinetic and a weak antiemetic. Hopefully, some of the other medications that I mentioned will continue to be pursued to provide additional treatments for patients. Because of the excitement and the opportunity to help patients with endoscopic pyloromyotomy, hopefully there will be more sham-controlled studies of the G-POEM procedure for patients with gastroparesis. Finally, basic science studies are being conducted to try to understand the molecular pathogenesis and the deficiencies in the intrinsic or enteric nervous system within the wall of the stomach in patients with gastroparesis. I am hoping that those 3 approaches—pharmacology, sham-controlled studies of G-POEM, and also translational research on animal models and biopsies taken from the stomach—will enhance the diagnosis and treatment of gastroparesis in the future.

Disclosures

Dr Camilleri has participated in single-center research studies for Allergan, Takeda, and Vanda and has been a consultant with compensation to his employer for Takeda and Alpha Sigma Wasserman. He was the first author of the new ACG guideline for gastroparesis.

Suggested Reading

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