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Grappling with Gastroparesis: Key Management Strategies

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and today we're joined by Dr. Kyle Staller, who will discuss some of the latest strategies in treating gastroparesis. Not only is he an Assistant Professor of Medicine at Harvard University, but he's also the Director of the GI Motility Lab at Massachusetts General Hospital.

Welcome back to the program, Dr. Staller.

Dr. Staller:
Thank you, Dr. Buch. Always a pleasure to be here.

Dr. Buch:
Thank you. Let's start with some background, Dr. Staller. Could you please give us an overview of gastroparesis, including common etiologies?

Dr. Staller:
Yeah. When we talk about gastroparesis, it's essential that we think about how the stomach works in general. And so, as a brief overview, food comes into the stomach, it gets accommodated in the gastric fundus, and then it gets broken down—what we call trituration—into smaller and smaller pieces until it's only 1 to 2 mm in size. And at that point, strong contractions in the gastric antrum push these things, these food particles, out of the stomach and into the duodenum. So gastroparesis is when those food particles cannot properly exit the stomach. And there can be a variety of etiologies where that happens. It can be a muscular issue where those muscular contractions are not pushing things out through the pylorus. It can be an issue where the pylorus is spasmed or tight and closed and where things are not actually able to get through because it's closed down. And when we think about bigger-picture etiologies or causes, diabetes has major impacts on the neuromuscular plexus in the GI tract, on the enteric nervous system. That's the classic cause of gastroparesis. But in fact, many of the patients we see will have idiopathic gastroparesis where we don't really know the cause. And then a smaller proportion will have postsurgical gastroparesis where the vagus nerve has been injured in something like a fundoplication or another foregut surgery.

Dr. Buch:
Thank you for that. So, with that in mind, how would you diagnose a patient with gastroparesis?

Dr. Staller:
Well, there probably are two schools of thoughts in the foregut world. One is that a lot of the upper GI symptoms people have—nausea, vomiting, dyspepsia, upper abdominal pain—can all be attributed to gastroparesis. And then the other extreme is to say that gastroparesis is not really the driver of many of these symptoms, and this should all be functional dyspepsia. But strictly speaking, we diagnose gastroparesis, generally, with a gastric scintigraphy scan. It's important that this is a very highly regulated scan in the sense that we really need people to use a standardized meal, and that's an egg sandwich with jelly, and it's radiolabeled, and then we watch over four hours. It cannot be less than four hours. Often you'll see gastroparesis called on patients who may have a delay at two hours or at 90 minutes, but really we need to see what the delay is at four hours before we definitively call it gastroparesis. And then there are breath tests that are out there as well as the wireless motility capsule, which has recently been discontinued, but there are more similar devices in the works.

Dr. Buch:
Great. Let's go down the rabbit hole. You ready?

Dr. Staller:
Ready.

Dr. Buch:
Here we go. How could gastroparesis overlap with functional dyspepsia?

Dr. Staller:
Well, this is the rabbit hole. The thing about gastroparesis is that with gastric emptying, we're looking for greater than 20 percent retention at four hours of this radiolabeled meal. That is a low bar for many people. And the stomach is an incredibly complex physiologic organ. We talked about accommodation, we talked about trituration into smaller pieces, and we talked about gastric emptying, but gastric emptying is just one thing, one measure of physiology—and in fact, the only one that we measure. And so, when someone has gastroparesis, i.e. that they have delayed gastric emptying on gastric scintigraphy, that may just be a reflection of neuromuscular dysfunction in the stomach, but maybe the driver of their symptoms is something other than gastric emptying. And so, often, these symptoms of dyspepsia, of nausea, of vomiting, and of upper epigastric abdominal pain have a lot of overlap, and we are often frustrated as treating physicians to find that no matter what we do to accelerate gastric emptying, the patient still continues to complain of pain or bloating or nausea. So it really tells us, in my view, that these are very much overlapping. There's probably one side of the spectrum where patients have pure delayed gastric emptying. If you speed up their gastric emptying, however you do it, you are likely going to have them feel better. On the other end of the spectrum, there's probably fewer functional dyspepsia. These patients probably have sensory abnormalities where they are hypersensitive to what's going on in their stomach, but the vast majority of patients that we see are going to be somewhere in the middle. They have elements of delayed gastric emptying, but they probably have elements of hypersensitivity and probably have elements of dysmotility elsewhere in the stomach too, perhaps impaired accommodation and things like that.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Kyle Staller about gastroparesis.

So, now that we have an understanding about gastroparesis, Dr. Staller, how do you use metoclopramide?

Dr. Staller:
So metoclopramide—we should remind our listeners—really is the only FDA-approved treatment for gastroparesis, but the issue with metoclopramide is it has been associated with both reversible and irreversible tardive dyskinesia, and that has really dampened some of the enthusiasm for using this medication even though it's been around for many years. In reality, our experience is that the risk of tardive dyskinesia is probably quite low among selected patients. So the risk of tardive dyskinesia with metoclopramide gets higher for older patients. It gets higher for cumulative usage. And there are some of those in the field who would say that using liquid metoclopramide may have a benefit over using pills. So often, I use metoclopramide as a diagnostic and therapeutic trial. If a patient has significant improvement on metoclopramide, that may be someone where we know that gastric emptying is at least playing some part of their physiology and their symptoms. And then metoclopramide really shouldn't be used for beyond 12 weeks in a stretch, so when we see patients who are on continuous metoclopramide, we really try to get them on to something else that may accelerate gastric emptying.

Now, the other side of metoclopramide that I should mention is that, in addition to being a prokinetic, in that it helps the stomach empty, it's also an antiemetic, and so it has strong antiemetic effects that may provide some of the benefit as well. So in reality, metoclopramide is something that we'll often use first, we'll use it in a younger population, and then we may reserve it for many of our patients to use on special occasions or perhaps when symptoms are more severe, but generally, we are not using it continuously because we don't want to exceed that 12-week mark.

Dr. Buch:
Perfect. Thank you. And when do you consider off-label medications for treating gastroparesis, like 5-HT4 agonists, labeled prucalopride?

Dr. Staller:
Often, I would say. So this is one of those cases where the FDA-approved treatment metoclopramide has some potential serious side effects, and those side effects are going to become more likely with cumulative use over time and as people age, so we're really looking for something alternative. So I am frequently using prucalopride, which is a 5-HT4 agonist, which is known to accelerate gastric emptying, small bowel transit and colonic transit. And, in fact, its label is for chronic idiopathic constipation, so any patient with delayed gastric emptying, symptoms that are compatible with delayed gastric emptying, and constipation is automatically going to get prucalopride as the first pass. It's a little bit more difficult from an insurance approval perspective to get someone who doesn't have

constipation prucalopride, but we know it's an incredibly safe drug, and unlike it's forebearers that were also 5-HT4 agonists but were less selective and had some cardiac effects, prucalopride does not appear to have any of those, and it's been in long use outside of the US before it was approved in the United States.

Otherwise, for off-label drugs, I use a lot of erythromycin. Erythromycin is an antibiotic. It's also a motilin agonist, and that's why it has impact on gastric delay. One sort of user-unique feature of erythromycin is that likely at higher doses, the pill form, which generally comes in capsules or tablets at 250 to 500 mg, will accelerate gastric emptying, but it's probably going to inhibit small bowel emptying. And I had spoken before to say functional dyspepsia and gastroparesis exist on a spectrum, and I would say probably delayed gastric emptying and small bowel dysfunction exist on a spectrum as well and can have, actually, the same symptoms. So you can imagine if you're using high-dose erythromycin and you are accelerating gastric emptying into a small bowel that then you are slowing down and you may develop some issues, so I actually will use lower-dose erythromycin—40 to 50 mg—before meals and at bedtime. And that's available in a liquid formulation in lieu or instead of using the pill form.

Dr. Buch:
Thank you. And moving on from medications to a more aggressive approach, when should we consider gastric electric stimulation or G-POEM, also known as gastric peroral endoscopic myotomy?

Dr. Staller:
In some ways, the procedural world in gastroparesis is a little bit the wild west. And I mentioned earlier that not only do gastroparesis and functional dyspepsia exist on a spectrum, but even within gastroparesis, you can have a failure of the gastric contractions to coordinately move food into the duodenum; you can have pylorospasm, where the pylorus does not open up appropriately. And so you can imagine that with varying degrees or varying problems that are driving the underlying pathophysiology, that some of these interventions may work for one group of patients and not the other.

So to speak to G-POEM first, because that's a bit of a simpler story, G-POEM is likely effective for those patients where there is pylorus spasm, and that's why many people identify the best candidates for G-POEM by doing a trial of Botox injections to the pylorus. Now, Botox was very popularly done, and I'm still seeing it done in the pediatric population, but two clinical trials showed that it actually was not effective in the larger gastroparesis population. However, for those people who have pylorus spasm, perhaps those who do well with a trial of Botox injection—just one because you don't want to create too much fibrosis for whoever is going to be doing your G-POEM—they may be good candidates for G-POEM.

Now, on the other end of the spectrum, gastric electrical stimulation has not been adopted with as much enthusiasm; and in fact, where I practice in the Boston area, none of the academic centers are placing gastric stimulators right now. That's probably because the gastric stimulator may have an impact on a different population. It may not be that delayed-emptying population or that pylorospasm patient. Maybe it's more someone where there are some neurosensory issues and chronic nausea is more of an issue. And indeed, some of the data would suggest that chronic nausea is better treated with gastric electrical stimulation than some of the other symptoms of gastroparesis. So in general I'm not putting in a lot of stimulators, and, in fact, I don't have a way to put in stimulators.

G-POEM, because it is relatively noninvasive, is a third-space procedure in the sense that there is no surgical recovery, the procedure is performed through the stomach, and the stomach has an incredibly thick lining. We're not necessarily seeing a lot of complications from G-POEM, but I have rarely seen a G-POEM patient who is 100 percent better. I see some who have significant improvement in their symptoms, but that probably speaks to the fact that there are other things going on aside from pylorospasm in many of these patients.

Dr. Buch:
Thank you. And Dr. Staller, in the last few moments of our discussion, are there any additional insights you'd like to share?

Dr. Staller:
Yeah. I think I mentioned this earlier on in the podcast. Gastric scintigraphy is only one way to measure the complex physiologic function of the stomach, and we tend to hang our hats on that. And I'll have patients who are referred to me with delayed gastric emptying and refractory gastroparesis, and in reality, their symptoms are more compatible with a sensory issue, and they just need some neuromodulation. To put an exclamation point on this, the Gastroparesis Consortium, which is an NIH-funded consortium that looks at patients with gastroparesis, did a cohort study over 12 years where they followed 981 patients at baseline and at 48 weeks. What they found is that about 41 percent of the cohort would shift their diagnosis over time, meaning they initially had delayed gastric emptying, a good chunk of those patients—despite having no difference in the severity of their symptoms—and when you checked them at 48 weeks, they did not have any delay in gastric emptying. And at the same token, those people who did not have a delay in gastric emptying but had severe symptoms and would be classified as functional dyspepsia, over 48 weeks, many of them switched to have delayed gastric emptying. So I just want to warn the listeners not to be too dependent on gastric emptying as the be-all end-all.

Again, the physiology of the stomach is complex, and so we need to think about it more in a more complex manner. So take caution when you have a patient with gastroparesis. Do not be overly aggressive. And really, the patients with delayed emptying probably should have 20 percent emptying at four hours, or 80 percent, and should have symptoms compatible with delayed emptying, particularly nausea and vomiting. If you have someone who has delayed stomach emptying but they're not vomiting, that should raise some red flags—not that they don't have anything wrong, but that perhaps prokinetics or other things like G-POEM that are designed to help the stomach empty better may not necessarily be what this patient needs.

Dr. Buch:
With those key impacts in mind, I want to thank my guest, Dr. Kyle Staller, for joining us today to share his important insights on gastroparesis.

Dr. Staller, it was a pleasure speaking with you today.

Dr. Staller:
Thank you. As always, Dr. Buch, always a pleasure to be here.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening, and see you next time.