Update on Rational Symptom-Based Treatment of Gastroparesis/Gastropathy
Oley Foundation Symposium on “Managing Gastroparesis Day!”
June 23, 2021
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Red Sox Fan

Main Take-Home Points
• Besides diabetes, poor glucose control, medications, abdominal surgeries, pregnancy, etc. – may lead to disorder of gastric emptying (too slow or too fast), stomach discomfort, nausea/vomit, bloating
• Measures of gastric emptying (timing/severity) poorly correlate with symptoms and overlaps with functional dyspepsia
• Mainstay of medical therapy is symptom-based:
  • Promotilides
  • Anti-nausea
  • Pain reduction
• Address coincident issues: bacterial overgrowth/dysbiosis, malnutrition/food aversion, neuroinflammation, anxiety/depression
• Non-medical treatments include:
  • Herbs/acupuncture (Complementary Medicine)
  • Electrical stimulators vs. pacers
  • 5-G-POEMs, jejunostomy/venting G tube

Importance of Gastropathy in Diabetes Care
• Doctors generally screen for renal, ophthalmic, podiatry, cardiac and neurological problems in diabetic patients, but gastrointestinal (GI) problems are commonly under-recognized because patients do not volunteer information or are not directly asked by doctors
• Symptoms that can be confused with reflux disease, ulcers, gallstone, pancreas, irritable bowel, etc.
• Can manifest by poor oral glycemic control
• Review medications: anticholinergics, antihistamines, antidepressants, narcotics; diabetes medicines such as amylin analogs and GLP-1 may worsen
• 19-76% patients in a diabetes clinic reported significant GI symptoms, most commonly:
  • Early satiety
  • Reflux (e.g., heartburn)
  • Abdominal pain
  • Nausea/vomiting
  • Diarrhea
  • Constipation

Gastroparesis: Definition
delayed gastric emptying in the absence of a fixed mechanical obstruction of the pylorus or duodenum

Spectrum of Gastric Dysmotility in Diabetics
Dysrhythmia
Antral hypomotility
Stomach paralysis
Gastropathy
bloating
nausea
pain

Gastropathy in Diabetics:
potential other causes besides autonomic neuropathy
• Metabolic and endocrine: DKA, pregnancy, hypothyroidism, electrolyte imbalance, renal failure, neoplastic (breast/small cell/pancreas)
• Medications: anticholinergics, antipsychotics, Ca2+ channel blockers, glucagon, levodopa, trospium, THC, alcohol, tobacco, etc.
• Postsurgery: vagal nerve injury, partial gastrectomy, fundoplication, Whipple
• Infectious: acute viral gastrointestinal, EBV, varicella, parvovirus-like, Chagas, C. botulinum
• Gastritis: atrophic, pernicious anemia
• Rheumatologic: scleroderma, SLE, polymyositis/dermatomyositis
• Pseudo-obstruction: idiopathic, secondary (amyloidosis, MS, paraneoplastic)
• Electrical dysrhythmia: tachy, brady, or gastroduodenal dysynchrony
• Central nervous system: tumor, bulbar poliomyelitis, depression, CVA, head trauma, labyrinthe disorders, seizures, abdominal migraine
• Peripheral nervous system: Parkinson’s, Guillain-Barre, MS, dysautonomia
• Idiopathic

Important Emerging Key Concepts

- Stomach is not a simple bag
- Different areas have different function
- Solid food emptied differently from liquids
- Relation of muscle and nerves to allow coordinated emptying
- Inflammation and altered sensory understanding important for rational treatments

Functional Parts of the Stomach

- Esophagus
- Fundus
- Cardia
- Antrum
- Incisura
- Angularis
- Pyloric Sphincter
- Body

DISTINCT REGIONAL DYSFUNCTION IN DIABETES

- Esophagus
- Fundus
- Cardia
- Antrum
- Incisura
- Angularis
- Pyloric Sphincter
- Body

Liquids and Solids Empty Differently!

- Solids 
  - Trituration
  - Requires churning by retropulsion and coordinated pyloric closure

Feedback from Nutrients in Intestine

- Delays Gastric Emptying Through Vagally Mediated Hormonal Inhibitory and Excitatory Reflex
- CCK, gastrin, GLP-1, etc.
- Hormone and stretch receptors along duodenal/jejunal segments
Yin - Yang of motor neurons in the stomach: underappreciated importance of relaxation

Excitatory Motor Neurons

Inhibitory Motor Neurons

Muscle

CONTRACTION

Muscle

RELAXATION

Genetic Mouse Model Reveals Importance of Nitric Oxide

Deficiency of neuronal nitric oxide leads to gastroparesis

Wild type  nNOS(-)  eNOS(-)

Bezoar in nNOS(-)

Gastroparesis in nNOS-deficiency

Selective decrease in inhibitory pathway in major gastrointestinal motility disorders:

Examples:
- Diabetic gastropathy
- Achalasia
- Pyloric stenosis
- Pseudo-obstruction
- Chronic constipation
- Hirschsprung Disease

Severity of Dyspeptic Symptoms Correlate Poorly with Delay in Gastric Emptying in Type I Diabetes
suggestive symptoms and potential pathogenesis

- Early satiety/anorexia/food avoidance
- Bloating/postprandial fullness
- Heartburn
- Epigastric pain
- Nausea
- Postprandial vomiting
- Weight loss

EVALUATION

Gastroparesis: Definition

This refers to delayed gastric emptying in the absence of a fixed mechanical obstruction of the pylorus or duodenum.

Evaluation

Gastroparesis: Definition

- Scintigraphy
- Endoscopy/UGI-SBFT

Evaluating Gastric Dysmotility

- REVIEW MEDICATIONS!
- Endoscopy/UGI-SBFT - rule out mucosal disease and obstruction
- Gastric Emptying Tests
- Gastr-duodenal Manometry
- Electrogastrography
- Barostat
- PP for vagal integrity
- Smart Pill

Gastric Emptying Tests: Indications

To evaluate:
- Unexplained nausea/vomiting
- "Nausea-like" non-ulcer dyspepsia (bloat, early satiety, anorexia)
- Severe gastroesophageal reflux disease refractory to medications
- Suspected gastroparesis in diabetics
- Suspected dumping/stasis after gastric surgery
- Suspected chronic intestinal pseudo-obstruction
- Possible re-evaluation in known gastroparetic in clinical trials of promotility agents

Not necessary if overt retention of food (on xray or endoscopy) after reliable fast.

Camilleri et al., Gastro 1995 115:747
Other Gastric Emptying Tests

- Gastric Emptying Breath Tests (GEBT, Advanced Breath Test Diagnostics) – C13-Spirulina Breath Test – FDA-approved
  - Intubation/aspiration
  - 375ml saline via ngt, check read after 30 min, nl <375ml
  - Acetaminophen absorption
  - Noninvasive measure of liquid emptying
  - Not extensively validated, need multiple blood samples, limited accuracy
  - Single-photon-emission CT (SPECT) imaging of gastric accommodation
  - SmartPill

Gastroduodenal Manometry

Electrogastrography and Manometry

EGG

Pressure transducer
Surface electrodes
Electrodes can be mucosal, serosal, or cutaneous

Gastric dysrhythmia in patient with diabetic gastroparesis:
12 month treatment with domperidone


EGG interpretation

• Evaluation of frequency and power
• may define abnormality in a different subset of patients than those with emptying or manometry
• positive predictive value of abnormal EGG is estimated at 60%–90%
• suggested that dysrhythmias may be better indicators of symptoms such as nausea and early satiety than gastric emptying, and may better correlate with symptomatic responses to medications

Barostat: measuring gastric volume with controlled bag pressure

Azpiroz F. et al Gastroenterology 1987;92:934-43

TREATMENT

Current Treatment of Gastroparesis
• Correct underlying condition
• Review medications; control hyperglycemia: "7 tod P/S check
• Insulin pump therapy in diabetics
• Hydration and nutrition, check dentition
• Dietary changes:
  • small frequent meals, low residue, low fat
• Psychological measures: empathy/education, support groups, relaxation/hypnosis
• Medical treatments
• Botulinum toxin
• For failures, decompression (PEG-J) and nutrition (PEJ) only after trial of NG and NJ tubes
• Surgery - g-POEMs? rare except outlet obstruction from PUD or CaUNHMAG - generally disappointing
• Gastric Electrical Stimulation/Pacing
Medications that Slow Gastric Emptying

- anticholinergic agents
- antidepressants
- beta-adrenergic agonists
- calcium channel blockers
- ganglion blocking agents
- levodopa
- nicotine
- octreotide
- opiates
- tricyclics
- vincristine

Diabetes drugs that cause or worsen gastroparesis:

- amylin analog pramlintide (Symlin), both Type 1 and 2
- GLP-1 agonist
- short acting: exenatide (Byetta), exenatide (Advinex), lixisenatide (Adlyxin)
- long acting: exenatide (Bydureon), liraglutide (Victoza), dulaglutide (Trulicity), semaglutide (Ozempic)

- May need to switch to DPP 4 inhibitors: vildagliptin (Galvus), sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta)

For example, in clinical trials:
- Nausea was 39% for exenatide vs. 5% for sitagliptin
- Vomiting was 19% for exenatide vs. 5% for sitagliptin

Three-step Dietary Treatment

**STEP 1: rehydration Day 1-2**
- sip Gatorade or salty bouillon solution to ingest goal 1.5L over 24 hours, multiple vitamin
- avoid citrus or highly sweetened drinks

**STEP 2: diet advance to soups**
- soups with noodles/rice and crackers, 6 small-volume meals per day, goal 1500 cal/day and maintain/gain weight
- avoid fatty foods

**STEP 3: introduction of more solid foods**
- stanches (require less electrocontractile work), white meat
- avoid red meat, fresh vegetables, fiber

Pharmacological Treatment

- prokinetics
- antimetics
- pain control
- antibiotics (bacterial overgrowth)

- NOT octreotide (actually decreases postprandial antral motility index), however phase II augmentation of small bowel
- NOT mesanotents agonists alone (actually just disordinated contractions)
- Sumatriptan, bupropion, tramadol - relax fundus for dyspepsia but may delay gastric emptying

From: Mashimo, May; O'Shaughnessy, Havlin, Alim in Joslin's Diabetes Mellitus 2011 1:165

Prokinetic Therapy

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<tr>
<th>Prokinetic Agent</th>
<th>Other Mechanism</th>
<th>Dosage</th>
<th>Comments</th>
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<td>Bethanechol</td>
<td>Motilin receptor agonists</td>
<td>25mg qid</td>
<td>The only medication presently FDA-regulated for gastroparesis; all others off-label use</td>
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Antiemetics

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<tr>
<th>Antiemetic</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>1-20mg qid</td>
<td>Off-label use in gastroparesis</td>
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<tr>
<td>Domperidone</td>
<td>10-20mg qid</td>
<td>Off-label use in gastroparesis</td>
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<tr>
<td>Hyoscine</td>
<td>10-100mg</td>
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<td>Atenolol</td>
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<tr>
<td>Prochlorperazine</td>
<td>5-50mg</td>
<td>Off-label use in gastroparesis</td>
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<tr>
<td>Meclizine</td>
<td>5-25mg</td>
<td>Off-label use in gastroparesis</td>
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<tr>
<td>Trimethobenzamide</td>
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<tr>
<td>Promethazine</td>
<td>10-50mg</td>
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<tr>
<td>Thiethylperazine</td>
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* The only medication presently FDA-regulated for gastroparesis; all others off-label use.
Pain Control

• Pain from autonomic neuropathy? But more severe forms of diabetic neuropathy had LESS pain.
• Indomethacin and ketorolac may resolve slow wave abnormalities in DM and dyspeptic patients.
• Caution ulcers and renal function in DM.
• TCAs at low doses.
• SSRIs:
  - Paroxetine accelerate small intestinal transit.
  - Methadone or transderm fentanyl - less constipation.
• NaSSA - mirtazapine (Remeron).
• Other drugs for neuropathic pain: gabapentin, topiramate, clonidine - but uncertain role in gastroparesis.
• Avoid narcotics.
  - Tramadol - less µ-agonist action.
  - Methadone or transderm fentanyl - less constipation.
• Methylbetalactone (s.c.)

Upcoming/Newer Drugs Potential for Gastropathy

• Other 5HT agents: alosetron (re-approved for IBS-d), Aryx (MYD-206), Teraparase, olsaparax, I-510B (velusetrag), T249.
• Dopaminergic: TAP106.
• COX antagonist: doslumide, belumidime.
  - Increase gastric and colonic motility, reduce visceral perception.
• Motilin receptor agonist: mithracin (GM 611-05), ABT229.
• No antibacterial properties, and resistant.
• Opioid receptor modifiers: methylmaltrexone.
• Neurotrophin-3 (BDNF).
• Guanylyl cyclase agonist: linaclotide.
• Ghrelin: Reamlorrelin, TZP101, pentapeptide.
• Neurokinin/tachykinin analogues.
• Amylin antagonists.

Potential Non-Drug Treatments

• Ginger - weak 5HT-3R antagonist.
• Acupuncture point P6 (Neiguan point) - reduction of nausea.
  - Postoperative nausea and vomiting (Dawson, T.W., et al. 1988).
• Reliefband (Valedo Medicals, CA).
• Gastric electrical pacing (Biliuchuk, K. et al. 1998).
  - Free 20% above baseline, pulse width 300ms for entrainment.
• Gastric electrical stimulation (GEMS study group, 1998).
• Entera therapy (Medtronics).
• Gene therapy?

Refractory Patients

1. Switching prokinetic and antiemetic agents.
2. Combining prokinetic agents.
3. Gastrostomy/jejunostomy tubes.
4. Injecting botulinum toxin into the pylorus - matter of patient selection, and presently not advocated unless part of clinical trial.
5. Gastric-POEM?
6. Implanting a gastric electric stimulator?

Distinct Regional Dysfunction in Diabetes

GEMS: Stimulation System

| Equipment | Medtronic 7425
| Intermuscle lead 1300-14 cm |
| Procedure | Laparotomy 1-3 day Laparoscopy 1.5-3 day |
| Time | 2-7 days |
| Recovery | 5-7 days |
| Measurements | Rate: 5-6 Hz |
| Pulse width: 500 µs |
| Current | 5 mA |
| (Desired) Cycle time | 5-6 sec |
SUMMARY

• Gastropathy commonly under-recognized
• need to ask patients
• suspect in patients with nausea/vomit, dyspepsia, early satiety, poor appetite, poor glycemic control
• Diagnose by scintigraphy, rule out mucosal disease/obstruction by endoscopy and barium small bowel follow-through
• Review culprit medications: anticholinergics, antihistamines, narcotics; amylin analogs and GLP-1 may exacerbate
• Correct underlying metabolic disorders, initiate three-step dietary progression
• Treatment: prokinetics, antiemetics, and pain control