The stomach that refuses to empty

Michael Camilleri

C.E.N.T.E.R., Mayo Clinic College of Medicine, Rochester, MN, USA

Disclosures
- Funding: NIH DK92179, DK 67071

The stomach that refuses to empty

- Mechanical obstruction:
  Pyloric stenosis e.g. peptic stricture
- Iatrogenic
- Neuromuscular dysfunction:
  - antral hypomotility,
  - pylorospasm,
  - chronic Intestinal dysmotility
- Cyclical vomiting
- Rumination syndrome

Figure from Nature Reviews Gastroenterology & Hepatology 10, 125 (2013)
Learning Objectives: Participants in this session will be able to

- Identify nuances in the history and examination to increase their diagnostic capabilities in the management of patients presenting with chronic nausea and/or vomiting
- Identify the main causes and clinical associations of gastroparesis
- Recognize, through case studies, conditions that are to be considered in the differential diagnosis of gastroparesis including lower GI causes of nausea, cyclical vomiting syndrome, cannabinoid hyperemesis, rumination and RED-RUM syndrome

Clinical Guideline: Management of Gastroparesis

Michael Camilleri, MD', Henry P. Parkman, MD', Mehnaz A. Shafi, MD', Thomas L. Abell, MD and Lauren Gerson, MD, MSc

Definition of gastroparesis syndrome and gastroparesis symptoms

Recommendations

1. The diagnosis of gastroparesis is based on the combination of symptoms of gastroparesis, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying.
   (Strong recommendation, high level of evidence)
2. Accelerated gastric emptying and functional dyspepsia can present with symptoms similar to those of gastroparesis; therefore, documentation of delayed gastric emptying is recommended before selecting therapy with prokinetics agents or gastric electrical stimulation (GES).
   (Strong recommendation, moderate level of evidence)

Diabetic Gastroparesis: no outlet obstruction

Gastric retention in scleroderma
Small bowel anastomotic staple line in the left lower quadrant and another in the right lower quadrant that appears to be in the distal ileum. There is marked dilatation of the small bowel, with small bowel feces in the segment proximal to the ileal staple line.

**Gastroparesis**

- Idiopathic
- Post-viral
- Iatrogenic
- Post-surgical
- Diabetic
- Neurological disease

- Others

*Soykan, McCallum et al Dig Dis Sci. 1998; 43:2398-404*

- DIABETIC GASTROPARESIS: T1 or T2DM with upper gastrointestinal symptoms
- Classical picture (-triopathy, T1DM>10y may be absent)
- Accelerated GE produces same picture: THEREFORE, MEASURE GE
Iatrogenic gastroparesis

- Post-Surgical: vagotomy or vagal injury
  - Fundoplication
  - Bariatric surgery
  - Peptic ulcer surgery: worse with vagotomy and antrectomy than PGV or vagotomy plus drainage

- Other curve balls related to Diabetes

  Type II DM Rx: Amylin analog (Pramlintide) and GLP-1 agonists (Exenatide), NOT with DPP IV inhibitors (Vildagliptin, Sitagliptin)

  In pancreas/kidney transplanted Calcineurin inhibitors: Cyclosporine A, not tacrolimus (macrolide chemistry)

- Others e.g. opiates (including tramadol and tapentadol at high doses), cannabinoid hyperemesis
Antroduodenal motility in Disease: *Fed pattern*

### Systemic Sclerosis

- Antral pressure activity in trituration of solids and in emptying of solids and liquids from stomach in humans.

### Control

- Antral pressure activity in trituration of solids and in emptying of solids and liquids from stomach in humans.

### Diabetes Mellitus

- Antral pressure activity in trituration of solids and in emptying of solids and liquids from stomach in humans.

---

**Camilleri, Dig Dis Sci, Vol 38, 1993**

**Camilleri M et al Am J Physiol 249: G580-5, 1985**

**ACG 2014 Annual Postgraduate Course**

**Copyright 2014 American College of Gastroenterology**

---

\[ R = 0.64, \quad P = 0.013 \]

**FIG. 4.** Relation between duration of lag phase and average antral motility during lag phase.

\[ R = 0.56, \quad P = 0.036 \]

**FIG. 5.** Relation between solid emptying and antral motility during emptying period.
Postprandial pylorospasm ? Narcotic-induced

Distal antrum 1
Distal antrum 2
Pylorus

Pylorospasm usually with antral hypomotility


An accurate gastric emptying test is required to exclude gastroparesis

- Society (ANMS, SNM) recommended scintigraphic gastric emptying test 300kcal, 2% fat: >10% retained at 4h
- Well validated Mayo Clinic gastric emptying test: 320kcal, 32% fat, scintigraphy: >23% retained at 4h
- Wireless motility capsule: retention at 5h
- Future in some countries, already available in Europe: stable isotope gastric emptying test
Treatment algorithm for gastroparesis

1. Suspected Gastroparesis
   - Confirm Diagnosis Testing for Cause
   - Restoration of Fluids and Electrolytes
   - Dietary Modifications Glucose Control
   - Prokinetic Therapy qac Anti-emetics pm
   - Consider Feeding Jejunostomy, Decompressive Gastrotomy, Gastric Electrical Stimulation OR Surgical Therapy

2. "Gastroparesis" diet
   - Metoclopramide 5–10 mg ac b.i.d.-t.i.d.

3. Clinical Response
   - Maintain at Lowest Effective Dose
   - Side effects
     - Start Domperidone 10 mg ac t.i.d.
     - Dose Titration
   - Incomplete Response
     - Increase to 10–20 mg t.i.d–q.i.d. as tolerated

4. Persistent Symptoms
   - Re-evaluation of Diet
   - Nutritional Support
   - Consider Short-Course Erythromycin 250–500 mg ac t.i.d.

**CASE #1** 72 year old man with weight loss food intolerance, stool incontinence, never smoker

- Back DJD and pain, unable to walk, peripheral weakness
- Macrocytic anemia, normal B12, ferritin
- Albumen 3.1g/dL, Creatinine 1.8mg/dL, sTSH 6.5u/L, glucose 118mg/dL, urine 236 protein mg/24h
- SPEP, immunofixation –ve
- Sed Rate 23 mm 1st h
- Paraneoplastic screen serology, syphilis, urine heavy metals –ve
- CXR, bone survey for myeloma -ve
**Delayed gastric emptying, other transit normal**

<table>
<thead>
<tr>
<th>Gastric Emptying</th>
<th>0</th>
<th>24%</th>
<th>33%</th>
<th>76%</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>C-SC:0</th>
<th>C-SC:1</th>
<th>C-SC:2</th>
<th>C-SC:4</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
</tbody>
</table>

- **Colonic filling**
  - At 6h: 94%

- **Colonic transit**
  - At 24h: GC 2.0

---

**Thermoregulatory Sweat Test**

- **Desk:** G08S  **Age:** 72  **Sex:** M  **Date/Time:** 2/23/2007 12:00

**Indication:** GI MOTILITY DISORDER; PERIPHERAL & TRUNCAL NEUROPATHY

**RESULTS:**
- Oral temperature before: 36.7°C  after: 38.0°C
- Body surface anhidrosis: 91%
- Distribution: GLOBAL

**IMPRESSION:**
- The patient was essentially anhidrotic, with relative sparing of the hands, thighs and distal feet. Such pattern can be seen in widespread autonomic neuropathies or central autonomic disorder.
HEART RATE RESPONSES

<table>
<thead>
<tr>
<th>Test</th>
<th>Parameter</th>
<th>Result</th>
<th>[Normal Range for age, gender]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva Maneuver</td>
<td>Valsalva Ratio</td>
<td>1.14</td>
<td>&gt; 1.29</td>
</tr>
<tr>
<td>Deep Breathing</td>
<td>Heart Rate Range (bpm)</td>
<td>1.3</td>
<td>&gt; 7</td>
</tr>
</tbody>
</table>

BLOOD PRESSURE & HEART RATE RESPONSES TO TILT

Values with subject to 70 degree tilt up

<table>
<thead>
<tr>
<th>Supine</th>
<th>1 min</th>
<th>5 min</th>
<th>7 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mmHg)</td>
<td>134/78</td>
<td>108/64</td>
<td>80/54</td>
</tr>
<tr>
<td>Pulse</td>
<td>74</td>
<td>78</td>
<td>83</td>
</tr>
</tbody>
</table>

QUANTITATIVE SUDOMOTOR AXON REFLEX TEST (QSART)

<table>
<thead>
<tr>
<th>Site</th>
<th>Current (mA)</th>
<th>Duration (min)</th>
<th>Output (uL/cm²)</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Forearm</td>
<td>2</td>
<td>10</td>
<td>4.76</td>
<td>[M 0.84-5.42; F 0.12-4.39]</td>
</tr>
<tr>
<td>L Proximal Leg</td>
<td>2</td>
<td>10</td>
<td>2.11</td>
<td>[M 0.76-3.91; F 0.20-2.36]</td>
</tr>
<tr>
<td>L Distal Leg</td>
<td>2</td>
<td>10</td>
<td>0.19</td>
<td>[M 0.93-4.98; F 0.20-2.98]</td>
</tr>
<tr>
<td>L Foot</td>
<td>2</td>
<td>10</td>
<td>0.50</td>
<td>[M 0.70-5.39; F 0.16-3.03]</td>
</tr>
</tbody>
</table>

Widespread autonomic and peripheral neuropathy

- **Autonomic**: Cardiovagal, cardiovascular adrenergic, and postganglionic sympathetic sudomotor dysfunction
- **EMG, Nerve conduction**: a length-dependent axonal sensorimotor neuropathy
- **Anal sphincter pressure**: rest 54mmHg; squeeze 83 mmHg *(pudendal nerve dysfunction)*
Neuro and other consults

- Macroglossia; dysgeusia
- Special urine studies: small monoclonal κ light chain
- Fat aspirate +ve for amyloid protein
- NOTE SPEP does not exclude monoclonal gammopathy and AMYLOIDOSIS
- Cardiac Echo: left ventricular wall thickness, diastolic dysfunction, bi-atrial enlargement
- Bone marrow: Systemic amyloidosis, AL type, comprised of κ Ig light chains
- NOTE GI diagnosis aided by autonomic tests
- Unfortunately, patient died 4 months later

CASE #2 42 year old male diabetic patient diagnosed with cyclical vomiting syndrome

- Transit, accommodation and MRI brain: all normal 5 yr previously at Mayo Clinic (another GI staff).
- 7 year history of morning sickness,
- Acute attacks occurring approximately once every month for past 6 years, requiring multiple admissions to hospital for 24 to 48 hours after presentation to the emergency room.
- Experiences excessive heat and sweating during acute emesis.
- In the past year, i.m. Compazine and Versed to abort the episodes of severe nausea and vomiting.
  - Denies history of retinopathy, neuropathy, or nephropathy in association with diabetes,
  - Onset of nausea /vomiting very soon after onset of diabetes.
- Rx: Metformin 500mg b.i.d. and Exenatide 5μg b.i.d.
CASE #2 42 year old male diabetic patient diagnosed with cyclical vomiting syndrome

- The patient acknowledges that he may use marijuana in order to control the nausea, and that if available, he would use daily.
- He acknowledges exposure to marijuana in his late teens.
- Scintigraphic gastric emptying:
  - 1 hr 22% (normal 11-39%)
  - 2 hr 56% (normal 40-76%)
  - 4 hr 87% (normal 84-98%)
- Gastric accommodation test 432 mL (normal >428 mL).
- **Diagnosis**: Probably cannabinoid hyperemesis
- **Refer**: Psychiatry for withdrawal of cannabinoids.

CASE #3: 43 year old female with recent history of breast cancer (will require chemo and radiotherapy) referred for chronic vomiting

- Extensively evaluated elsewhere, including negative upper GI endoscopy, gastroduodenal manometry, esophageal manometry and impedance, Bravo pH testing, etc…
- Cholecystectomy for a small stone in the gallbladder
- **What is the appropriate NEXT STEP?**
  - CT/MRI of brainstem
  - Other?
CASE #3: 43 year old female with recent history of breast cancer (will require chemo and radiotherapy) referred for chronic vomiting

• TAKE A HISTORY
• Past three years:
  • daily, effortless vomiting occurring after every meal starting within one hour of eating, typically immediately after breakfast.
  • The food tastes just like the food she has just eaten as it regurgitates back in the throat.
  • Sometimes she does have acid or burning food coming back into her throat.
  • She does not swallow food back down but expels it from the throat and mouth.

Rumination Syndrome
• Repetitive regurgitation of gastric contents occurring within minutes after a meal
• Episodes often persist for 1 to 2 hours.
• Regurgitant: partially recognizable food
• Regurgitation is effortless or preceded by a sensation of belching immediately before the regurgitation or arrival of food in the pharynx
• No retching or nausea precedes regurgitation.
• Conscious decision: swallow or spit
• A "meal in, meal out, day in, day out" behavior

"You cannot be serious, doc!
You have got to do more tests"

GE may be modestly delayed in Rumination syndrome as food moves back and forth, up and down in the stomach.
**SPECT Method to Measure Gastric Volumes**

SPECT camera to measure gastric volume

**Abdo perimeter**

**REGION OF INTEREST AROUND STOMACH**

**Transaxial images** reconstruction with ANALYZE

- **I.V. 10mCi 99mTcO4**
- **Abdo Abdo**
- **p**
- **\( \text{REGION OF INTEREST} \)**
- **\( \text{AROUND STOMACH} \)**

**Gastric Volume, mL**

- **Fasting**
- **Postprandial**

- **Fast**
  - **PP 3-12 min**
  - **PP 12-21 min**

- **Normal Gastric Accommodation**

- **Proximal Stomach Volume (cm³)**
  - **Fasting**
  - **0-9 Min Postprandial**
  - **9-10 Min Postprandial**
  - **Average Postprandial**
  - **Average Fasting**

- **Whole Stomach Volume (cm³)**
  - **Fasting**
  - **0-9 Min Postprandial**
  - **9-10 Min Postprandial**
  - **Average Postprandial**
  - **Average Fasting**

- **Normal >428mL**

**Rx**: Behavioral therapy with diaphragmatic breathing
Meal-related "reflux" with no supine pH drops = Rumination

Meal-related and supine pH drops = TRUE GE reflux

Rumination syndrome with complications

• Iatrogenic
• RED-RUM syndrome
CASE #4:
F, 21y “Past 5 y, my stomach does not allow food to digest”

- Effortless regurgitation
  - Daily, immediately after every meal
  - Several hours
  - Solids and liquids
  - Non-acid $\rightarrow$ acid and bitter
  - Re-swallowing

- Other symptoms
  - Abdominal bloating
  - Nausea, no vomiting
  - Weight fluctuation
  - Burning retrosternal sensation
  - Constipation

Past Medical History

- Anorexia nervosa – bulimia
- Bipolar disorder
- ADHD (attention deficit, hyperactivity disorder)
- EGD: grade C esophagitis (Los Angeles)
- Esophageal manometry
  - abnormal GE junction + hypotensive LES
- Laparoscopic Nissen fundoplication (01-2008); “leak” leading to localized gastric resection; G tube feeding for 3 months
Physical examination

- BMI 18.3 kg/m²
- Abdomen
  - multiple scars, nl bowel sounds, no succussion splash/organomegaly/mass
- Rectum
  - no signs of evacuation disorder

Gastric Emptying of Solids: Markedly delayed:
Note the esophagus
Gastric Accommodation: Markedly reduced 290mL

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>0-9 Minutes Postprandial</th>
<th>9-18 Minutes Postprandial</th>
<th>Average Postprandial</th>
<th>Average - Fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal Stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>214.40</td>
<td>303.26</td>
<td>405.19</td>
<td>307.20</td>
<td>172.07</td>
</tr>
<tr>
<td>Fasting Ratio</td>
<td>1.00</td>
<td>1.72</td>
<td>1.69</td>
<td>1.51</td>
<td></td>
</tr>
<tr>
<td>Whole Stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>425.00</td>
<td>600.50</td>
<td>701.96</td>
<td>725.44</td>
<td>299.76</td>
</tr>
<tr>
<td>Fasting Ratio</td>
<td>1.00</td>
<td>1.54</td>
<td>1.79</td>
<td>1.67</td>
<td></td>
</tr>
</tbody>
</table>

(Normal > 428mL)

Plasma pancreatic polypeptide response to modified sham feeding: test of abdominal vagus

Δ < 25pg/mL, Flat response
Treatment strategy

• Rumination syndrome
  • Diaphragmatic breathing
• Severe gastroparesis
  • Homogenized solids
  • Liquid formula metoclopramide 5mg 4x/d
  • Buspirone 5mg 2x1/d
• Bile acid reflux
  • Al-Mg 30ml 3x/d

CASE #5: 18y, F with 10 year history of

• Abdominal pain: sharp, epigastric, without radiation, relieved by lying down, curling up in bed, or stooping forward.
• Vomiting worse with fast foods and red sauces: worse with anxiety, and associated with nausea, loss of appetite
• Food would regurgitate easily in an effortless manner, almost on its own without any straining, retching, or contraction of the abdominal muscles. The effortless regurgitation of food consisted of material that was containing unchanged food, but subsequently it also occurred repeatedly and the subsequent regurgitant was bitter or acid to taste.
• Started on domperidone 10 mg tablets on awakening.
• 3 EGDs and colonoscopy elsewhere: essentially negative.
CASE #5: 18y, F with 10 y vomiting and abdo pain

- **EXAMINATION**

- Abdomen: palpable stool in RLQ and LLQ.
- Rectum: 2/4 maneuvers to evacuate the examining finger paradoxical contraction of the puborectalis and anal sphincter.
GI Transit

<table>
<thead>
<tr>
<th>Protocol Time</th>
<th>Region Of Interest</th>
<th>Imaging Time</th>
<th>% Enter</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Hr</td>
<td></td>
<td>03:01</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1 Hr</td>
<td>Stomach</td>
<td>09:57</td>
<td>6</td>
<td>4 - 31% 17%</td>
</tr>
<tr>
<td>2 Hr</td>
<td>Stomach</td>
<td>11:02</td>
<td>20</td>
<td>25 - 71% 43%</td>
</tr>
<tr>
<td>4 Hr</td>
<td>Stomach</td>
<td>12:59</td>
<td>80</td>
<td>76 - 100% 92%</td>
</tr>
<tr>
<td>6 Hr</td>
<td>Small bowel</td>
<td>15:01</td>
<td>46</td>
<td>0 - 100% 44%</td>
</tr>
</tbody>
</table>

Colonic Transit

24 Hr Colonic Geometric Center = 2.3
48 Hr Colonic Geometric Center = 3.2
Anorectal Manometry

Resting Anal Pressure 160mmHg
Squeeze Anal Pressure 289mmHg
R-A pressure differential -30.6mmHg
Balloon expulsion 94g

Results in 57 patients with this syndrome

Diagnosis: Rumination syndrome, Rectal Evacuation Disorder (Anismus), RED-RUM syndrome
Reduced gastric accommodation

Diagnosis: RED-RUM syndrome

- Rumination syndrome + Rectal Evacuation Disorder
- Of 438 patients evaluated for RED over the 19 years, 57 (13%) had concomitant rumination syndrome:
  - 95% F, 89% Caucasian
  - Mean 30.3 ± 1.6 y (8 being <18 years)
  - BMI 20.8 ± 0.5 kg/m² (15 BMI <18.5 kg/m²)

Vijayvargiya, Iturrino, Camilleri et al
UEG Journal 2014:2:38-46
Take Home: Chronic Nausea and Vomiting

- Inquire about constipation and rumination
- Examine the whole patient (especially rectum)
- Consider iatrogenic disease
- Measure whole GI and colonic transit
- Have a low threshold to evaluate rectal emptying
- Ockham’s razor or law of parsimony (used in logic and problem-solving: “among competing hypotheses, the hypothesis with the fewest assumptions should be selected”) does not work