GASTROPARESIS 2013
BACKGROUND, INVESTIGATION AND MANAGEMENT

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WHAT IS GASTROPARESIS?
Definition:
“Delayed gastric emptying in the absence of mechanical obstruction” *

“Chronic, Debilitating, Motor & Sensory disorder of the stomach that is characterized best by its Symptoms and less so by its signs”

WHAT IS GASTROPARESIS?

• Sign
  • Delayed gastric emptying

• Poor Emptying ≠ Symptoms
  • Degree of Emptying Does NOT Correlate with Degree of Symptoms

• Uncommon Disorder
  • True prevalence is unknown

BACKGROUND

• Etiologies in tertiary settings:
  • Diabetic (DGP): 29%
  • Post Surgical: 15%:
    • Fundoplication
    • Bariatric Surgery:
      • Roux-en-Y Gastroenterostomy
      • Idiopathic 36%
  • Gastroparesis in the Community Setting:
    • Type I Diabetes: 10 year incidence 5.2%
    • Type II Diabetes: 10 year incidence 1%
    • Non-diabetic controls: 0.2%

WHAT IS GASTROPARESIS?

• Symptoms
  • Chronic Nausea
  • Frequent Vomiting
  • Epigastric Pain-Under-recognized
  • Early Satiety
  • Bloating

Disease is present always but symptoms may vary widely

Prevalence of upper gastrointestinal symptoms in type 1 diabetes

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Diabetics (%)</th>
<th>Controls (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>loss of appetite</td>
<td>16.3</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>early satiation</td>
<td>26.8</td>
<td>6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>postprandial fullness</td>
<td>18.6</td>
<td>8.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>nausea</td>
<td>22.7</td>
<td>9.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>abdominal distension</td>
<td>42.3</td>
<td>24.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>vomiting</td>
<td>12.2</td>
<td>3.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*From Every Author, et al. Every Journal; 1950-2010
GASTROPARESIS
Chronic condition with delayed gastric emptying of solids in the absence of mechanical obstruction—symptoms.

Primary symptoms: 3 groups:
- nausea 92%
- post prandial emesis 84%
- early satiety 60%
- bloating 75%
- abdominal pressure
- pain 46-89%

CLINICAL MANIFESTATIONS
- Validated Patient-assessed Gastroparesis symptom severity measure
- Gastroparesis Cardinal Symptom Index (GCSI)

NATURAL HISTORY AND OUTCOMES
- Impaired gastric emptying results in mismatch of timing of food delivery to the small intestine for absorption, and the administration of anti-diabetes medication
- Erratic emptying of medications Worsens HbA1c
- Worse complications of diabetes

FUNCTIONAL ANATOMY OF THE STOMACH
- Proximal Stomach
  - Cardia, Fundus, & Proximal Body
- Distal Stomach
  - Distal body & Antrum
- Pylorus

MYOELECTRICAL BASIS FOR GASTRIC MOTILITY
- Gastric smooth muscle cells generate slow waves (mv from -60 to -40)
- Slow waves generated at 3 cpm
- As a consequence, phasic contractions only occur at a maximum of 3 cpm

GASTRIC PACEMAKER
- Resting tone provided by gastric “pacemaker”
- Located along the greater curvature in the proximal body
- Slow waves generated from the Interstitial Cells of Cajal
**TRICTURATION AND ANTRAL EMPTYING**

- Rapid emptying of liquids
- Pylorus closes to allow passage of solids < 1 mm in size
- Antrum closes and tricturation occurs
- Mediated by isolated pyloric contractions

**MEDIATORS OF GASTRIC EMPTYING**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Effect on Gastric Emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat in ileum</td>
<td>Slowing via ileal brake (Peptide Y-Y)</td>
</tr>
<tr>
<td>Nutrient Density</td>
<td>Inversely proportional to Density</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Slows</td>
</tr>
<tr>
<td>Rectal/Colonic Distension</td>
<td>Slows</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>Slower emptying of hypertonic meals</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Slows</td>
</tr>
</tbody>
</table>

**Clinical features of gastroparesis**

- Major symptoms
  - Nausea
  - Vomiting
  - Early satiety
  - Abdominal bloating/discomfort
  - Anorexia
  - Wt loss

- Complications
  - Esophagitis
  - Mallory-Weiss tear
  - Bezoar formation
  - Post-prandial hypotension

**ECONOMIC BURDEN**

- Healthcare Cost and Utilization Project (HCUP)
  - Nationwide Inpatient Sample (NIS) 1995-2004
    - Hospital Admissions, length of stay, cost, etc.
    - ↑ 158%
  - Hospital Charges
    - $3.5 B Gastroparesis
      - $1.3 B GERD
      - $2.2 B PUD
      - $2.1 B Gastritis
VG4102

**ETIOLOGIES**

90 known conditions present with delayed gastric emptying & Symptoms of Gastroparesis

- Idiopathic - 35%
- Diabetic - 29%
- Post-surgical - 13%
- Parkinson’s - 8%
- Vascular Disease - 5%
- Pseudo-obstruction - 4%
- Miscellaneous - 6%


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VG4103

**Causes of gastroparesis: transient**

- Drugs
  - Morphine
  - Anticholinergics
  - L-dopa
  - Nicotine
- Postoperative ileus
- Viral gastroenteritis
- Electrolyte abnormalities
  - Hyperglycaemia
  - Hypokalaemia
  - Hypomagnesaemia
- Endocrine disorders
  - Hyperthyroidism
  - Hypoglycaemia
- Herpes zoster
- Critical illness

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VG4104

**Causes of gastroparesis: chronic**

- Diabetes mellitus
- Idiopathic/functional dyspepsia
- Post-surgical ileus vasovagalism
- Atrophic gastritis
- Progressive systemic sclerosis
- Chronic idiopathic intestinal pseudo-obstruction
- Myopathy dystrophica
- Dermatomyositis/polymyositis
- Duchenne muscular dystrophy
- Amyloidosis
- Autonomic degeneration
- Spinal cord injury
- Tumor associated
- Anorexia nervosa and bulimia nervosa
- Central nervous system disease
  - Brain stem lesions
  - Parkinson’s disease
- Post-irradiation
- HIV infection
- Pernicious
- Liver disease

**PATHOPHYSIOLOGY**

- Unknown
- Autonomic Neuropathy
- Enteric Neuropathy
- ICC Abnormalities
- Psychosomatic

* I'm stumped. We'll have to wait for the autopsy.*
PATHOPHYSIOLOGY

- Motor & Sensory
- Parasympathetic
- Vagal
- Efferent & Afferent
- Sympathetic
- Splanchnic Efferents
- Spinal Afferents
- Enteric Nervous System
- Motilin, Ghrelin, NO, CCK, VIP, etc
- Inerstitial Cells of Cajal
  - 3 CPM slow wave

Diabetic gastroparesis: pathogenetic mechanisms

- Defective gastric (reservoir) accommodation
- Weakened or dysrhythmic electrical slow waves
- Weakened gastric peristalsis
- Antral hypomotility
- Disorganised antroduodenal coordination
- Pyloric sphincter dysfunction
- Disordered proximal small intestinal motility
- Poor glycemic control

Tachygastria in diabetic gastroparesis

Slow waves originate from an ectopic pacemaker and propagate in a retrograde manner in tachygastria

Gastric fundal accommodation is impaired in diabetic gastroparesis

INTERSTITIAL CELLS OF CAJAL

- Motor
  - Pacemaker
  - Enteric Nerves
  - Vagal Efferents
- Sensory
  - Spinal Afferents
  - Vagal Afferents
- Decreased in Diabetic & Idiopathic Gastroparesis

VG4135, EFFECTS OF DIABETES ON GASTRIC ICC NETWORK

VG4134, EVIDENCE THAT ICC DYSFUNCTION MAY ACCOUNT FOR DYSMOTILITY IN DIABETIC GASTROPARESIS

- ICC generate electrical slow waves
- Gastric electrical dysrhythmias may originate from ICC
- ICC provide the pathway for slow wave propagation
- Disruption of ICC networks disorganizes gastric electrical activity
- ICC mediate enteric neurotransmission
- Loss of ICC may compromise neural inputs causing:
  - Impaired gastric accommodation
  - The "epithelial and gastric phases of digestion" (e.g., antral hypomotility)
  - Increased pyloric sphincter resistance
  - Impaired gastrointestinal coordination
- These are clinically important features of diabetes mellitus

VG4136, EFFECTS OF DIABETES ON GASTRIC SLOW WAVES

VG4143, DIABETIC GASTROPARESIS: IMPACT OF GLYCEMIC CONTROL

- Acute hyperglycemia delays gastric emptying
- Reduces proximal gastric tone
- Inhibits antral pressure waves
- Particularly propagating pressure waves
- In fasted and fed states
- Stimulates isolated pyloric pressure waves ("pylorospasm")
- Acute hypoglycemia accelerates gastric emptying
- Responses probably vagally-mediated
- Implies a degree of reversibility of gastrointestinal dysmotility in chronic hyperglycemia

VG4144, HYPERGLYCEMIA IMPAIRS ANTRAL MOTILITY AFTER A MEAL

ETIOLOGIES

- Idiopathic
  - Symptoms fluctuate, spontaneous resolution
  - Patients are frequently young or middle-aged women, otherwise healthy
- Viral? (25% h/o gastroenteritis or viral syndrome)
- Diabetic
  - 40-50% of Type 1
  - 30-40% of Type 2
- Post-Surgical
  - Post-Vagotomy / PUD, Nissen, lung and heart-lung transplantation, bariatric

DIAGNOSTIC TOOLS

- History and physical
- Exclude mechanical obstruction
  - UGI SBFT or EGD
- Tests
  - AntralDuodenal Manometry
  - Electrogastrography (EGG)
  - Smart Pill
  - EGD
  - Gastric emptying

EVALUATION

- Barium study  (as an adjunct maybe…)
  - Rule out gastric outlet obstruction

GASTRIC SCINTIGRAPHY

- Consensus Statement
- American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine
- Abell TL et al. AJG 2008

GASTRIC EMPTYING TEST

- Scintigraphy is the gold standard
- Hospitals have their own test methods
  - Meal (composition, volume, energy density)
  - Protocol and analysis ($T_{50}$, slope, lag phase, retention)
  - “Normals” - small series

GASTRIC SCINTIGRAPHY (CONSENSUS GUIDELINES)

- 4 hour study
- Test meal should consist of low fat meal
  - Two large egg whites (Eggbeaters)
  - Two pieces of white toast (120 kcal)
  - Strawberry Jam (30 g, 70 kcal)
  - Water (120 cc’s)
- Liquid GES: Increased sensitivity; Glucose makes bigger impact on liquid than solids


EXPERIENCE WITH A SIMPLIFIED, STANDARDIZED 4-HOUR GASTRIC-EMPTYING PROTOCOL

- 175 pts with symptoms of gastroparesis
  - Compared results of 1hr, 2hr, 3hr, 4hr retention
  - Increased sensitivity, specificity with 4hr study
    - 60% (2hr) → 80% (4hr)
Consensus Recommendations for Gastric Emptying Scintigraphy: A Joint Report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine

- Morning after overnight fast
- Low fat egg white meal (Egg Beaters)
- Sitting erect during images
- Ambulatory between images
- % Retention @1, 2, 3, and 4 hrs

GASTRIC SCINTIGRAPHY

- Recommended to obtain images at 2 hours and 4 hours

<table>
<thead>
<tr>
<th>Time</th>
<th>Threshold Value for Delayed Gastric Emptying</th>
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<tbody>
<tr>
<td>2 h</td>
<td>90%</td>
</tr>
<tr>
<td>3 h</td>
<td>60%</td>
</tr>
<tr>
<td>4 h</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

- 4-hour protocol increases the diagnostic yield for delayed gastric emptying


OPTIMIZE RESULTS OF GE SCINTIGRAPHY

- 8 h fast, off TPN 12 h
- Euglycemia in diabetics
  - check sugar prior to test and record in report, consider cancel < 75, > 275.
- Medications – Hold 48 h
- Consider outpatient test
  - avoid in hospital – multiple medications
  - severity of illness

SMARTPILL

- Alternative method for measuring gastric emptying
- Wireless capsule with pH and pressure sensors
- Provide a test meal (Clif Bar)
- Must perform test off of PPI therapy

SMARTPILL TRACING

pH >4 & at least 3 points above baseline by 4 hours

83% Sensitivity and 83% Specificity

FREQUENCY OF ANTRAL CONTRACTIONS

- Gastroparesis: 0.6 cpm in the 1 hour prior to gastric emptying
- Normal Controls: 1.2 cpm
- Idiopathic Gastroparesis: Decreased CPM 20-40 min prior to emptying
- Diabetic Gastroparesis: Decreased CPM 40-60 min prior to gastric emptying

Podoloff et al. A 1247 ACG 2008
Diabetic Gastroparesis: symptoms correlate poorly with rate of emptying

Strategy & Goals of Therapy

- Relieve symptoms
- Improve QOL & minimize side effects
- Temper treatment based on symptom severity
- Multiple levels of interaction lead to symptoms
- Lots of overlap - eg gastroparesis, functional dyspepsia
- Only limited repertoire of medical treatments
- Multifaceted, team approach for complex cases
- How can we best help our patients with what is available

General Principles of Treatment

- Treatment = diet + prokinetics + antiemetics
- Diabetics: optimize treatment,
  Hyperglycemia → gastric motor abnormalities
  Anti-Emetics
  Prokinetics
- Role of antidepressants: symptom and or pain relief
- Ancillary measures: Chinese herbs, ginger, acupuncture
  (J Trad Chin Med 2004;24:1633-5)

Proposed classification of gastroparesis severity

Grade 1: Mild gastroparesis
Symptoms relatively easily controlled
Able to maintain weight and nutrition on a regular diet or minor dietary modifications

Grade 2: Compensated gastroparesis
Moderate symptoms with partial control with pharmacological agents
Able to maintain nutrition with dietary and lifestyle adjustments
Rare hospital admissions

Grade 3: Gastroparesis with gastric failure
Refractory symptoms despite medical therapy
Inability to maintain nutrition via oral route
Frequent emergency room visits or hospitalizations

Diet Modification:
Low Fat, Low Fiber or Residual
Frequent Smaller Volumes

- Diet modifications:
  - adjustments in composition, consistency, size, and frequency of meals
  - Low Fat and Low Fiber
  - Low residual
  - Promote gastric emptying
  - Decrease Bezoars
  - Blenderized food
  - A liquid diet supplemented with vitamins and minerals
  - Stand up/Walk after meals

Dietary

- Small meals: Stomach empties about 1-2 kcal/min 4-5 times per day
- Liquid emptying usually preserved so increasing liquid nutrient portions helps
- High calorie, high frequency liquid diet can be beneficial
- Failure of a liquid diet carries a poorer prognosis
**DRUG THERAPY FOR GASTROPARESIS**

- Anti-Emetics alone (Zofran, Compazine, etc)
- Anti-Depressants (Mirtazapine (Remeron, Avanza, Zispin))
- Combination of prokinetic agents and antiemetics:
  - Metoclopramide (3 months)
  - Erythromycin (Loss of action over time)
  - Cisapride and Zelnorm (off the market in US)
- Domperidone (from Canada and some compounding pharmacies)
- Narcotics!!? Stop them…!
- Newer Agents
  - Motemcinal (Motilin Receptor Agonist)*
  - 75% improvement in Emptying
  - No symptomatic improvement compared to placebo
  - Ghrelin
- **Ghrelin**

**ANTI-EMETIC THERAPIES**

**ANTI-EMETIC PLUS PROKINETIC**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>D$_2$ &amp; 5HT$_3$ antagonist</td>
<td>10-30 mg tid</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>5HT$_4$ receptor facilitation of acetylcholine release from enteric nerves</td>
<td>10-20 mg tid</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Peripheral dopamine D$_2$ receptor antagonist</td>
<td>10-30 mg tid</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Motilin receptor agonist</td>
<td>10-20 mg tid</td>
</tr>
<tr>
<td>Zelnorm</td>
<td>Motilin receptor agonist</td>
<td>10-20 mg tid</td>
</tr>
<tr>
<td>Zoleclonium</td>
<td>Acetylcholinesterase inhibitor</td>
<td>10-20 mg tid</td>
</tr>
</tbody>
</table>

**METOCLOPRAMIDE : FDA 90 DAY LIMITATION**

Prokinetic + Antiemetic

- Prokinetic effect down over time unlike antiemetic effect
  - D$_2$ & 5HT$_3$ antagonist, 5HT$_4$ agonist
  - Several studies: all short term symptom improvement and gastric emptying increase compared to placebo.
  - Start at liquid 5 mg PO dose tid before meals increasing up to 10 mg tid ac; 7 OTD = Liquid formulation
  - Periodic dose reduction or holidays
  - Side effects and risks: Always document discussions
    - CNS SE up to 40%
    - Acute dystonias: 0.2%
    - 15 year: 95% of SE dystonias, 4% parkinson’s; 1% TD

**DOPERIDONE-NOT FDA APPROVED NOR READILY AVAILABLE IN US**

Dopa D2 antagonist, doesn’t cross blood brain barrier

- Increased solid and liquid emptying.
- Largest study 260 patients 1998, 80% responders (> 30% Sx reduction)
- Vs Metoclopramide equally effective, ↓ side effects AJG, 1999
- Increased prolactin (same as MCP) Often Rx in US
- Can be used in Parkinson’s Disease patients
- Check QT interval baseline, serum K’, repeat yearly
DOMPERIDONE
Dosage:
• Start 10 mg ac & hs; then ↑ 20 mg ac/hs, max dose is 120 mg/day (30 mg ac/hs)
• need 1 month to assess efficacy
No IV form – rare reports fatal cardiac arrhythmia
??Need IRB OK for institution, IND (Investigational New Drug), approval FDA to prescribe
FDA 2004 – No Compounding but it is available.....
Available internet from other countries, e.g., Canada but much more difficult....., New Zealand

ERYTHROMYCIN-PURE PROKINETIC
• Most potent prokinetic acutely - useful IV
• Motilin agonist - induces phase III MMC’s → antral duod contractions.
• IV and oral forms improve emptying
• Reviewed → symptomatic relief: AJG (2003) 98, 259-263
  • Examined 35 trials, only 5 using symptoms as end point
  • DM, idiopathic, post surgical, PSS
• Overall > 25% improvement symptoms in 48% of patients.
• Problem outlined with these studies – open label, small size, treatment < 4 weeks. Authors conclude all weak, subject to bias

ERYTHROMYCIN
Dosage: lower dosages recommended
Tachyphylaxis: down regulation of the motilin receptor
3 weeks on, 1 week off proposed
Range 50-250 mg 2-4 x daily. Trial 2 weeks
• Liquid syrup form absorbed better
• Side effects: abdominal cramp and nausea, antibiotic effects.
  ↓ accommodation
• Use with MCP ? – No data
• Important precaution: increase in sudden cardiac death, 2 fold
  • Concurrent use with strong inhibitors CYP3A enzymes should be avoided
  • e.g. calcium channel blockers, verapamil, diltaizem (NEJM 2004;551:1089)

GHRELIN—IN THE FUTURE??
• 28 amino-acid peptide
• Synthesized mainly in the gastric mucosa
  • Secreted into the Blood Stream
• CNS - Crosses Blood Brain Barrier
  • Stimulate Appetite
  • ↑ Fat Deposit
• Gastric Acid Secretion
• Gastric Motility

GHRELIN??
• Dogs
  • Laparotomy
  • Ghrelin vs Saline
• 5 pts with DM Gastroparesis
  • Improved Emptying
  • Tack, et al 2009
  • 6 idiopathic patients
• IV Ghrelin vs Saline
• Improvement in emptying and Symptoms
• TZP-101 & TZP-102
• Phase II & III
ALTERNATIVE TREATMENTS

- Anti-Emetic therapy
- 5HT3 Antagonist: Ondansetron
- Prochlorperazine and Thiethylperazine
- Antihistamine: Promethazine (warnings QTc, venous injury)
- TCA (tricyclic anti-depressant agents)
- Amitriptyline and Noratriptyline at low doses
- 5HT2 Agonist: Mirtazapine

BOTOX?? INITIAL ENTHUSIASM....

- 4 Quadrant Injections (100-200 units) into the Pylorus
- Uncontrolled Studies
  - Philadelphia
    - 63 patients
    - 43% symptomatic improvement
    - 5 Months duration
  - Belgium**
    - 23 patients (placebo vs botox)
    - No difference in Symptoms or Emptying

BOTOX-DIDN'T REALLY PAN OUT...

- Prospective, Double Blind RCT
- 4 Quadrant Injections of Pylorus
  - 16 Botox
  - 16 Saline
- No Difference in emptying or symptoms

ENDOSCOPIC

- Pyloric Balloon Dilation
- No published evidence
OTHER OPTIONS? DRUG-REFRACTORY PATIENTS

- Total parenteral nutrition (TPN)
  - The cost is at least ten times greater than enteral feeding. Over $200,000 annually in healthcare costs

- Enteral feeding access
  - Gastrostomy tube
  - Jejunostomy tube
  - G-J Tube

- Gastroscopy-partial or total
- Gastrostimulation (not pacing...)
- Enterra Procedure