Question #1: How is Gastroparesis defined?
Gastroparesis Defined

• “Paresis” (Gr) – weakness of movement
• A combination of:
  – symptoms
  – absence of gastric outlet obstruction
  – delayed gastric emptying


Question #2: What are the Typical Symptoms of Gastroparesis?
Symptoms of Gastroparesis

- Abdominal pain – 89-90%
- Early satiety – 80-85%
- Nausea – 90-95%
- Vomiting – 68%
- Bloating
- Gastroesophageal reflux
- Anorexia and weight loss

Question #3 FD & GP: 1 Disease or 2?

Functional Dyspepsia

Gastroparesis
Symptoms of Functional Dyspepsia

- Epigastric pain/discomfort – 90%
- Post-prandial fullness – 75-79%
- Bloating – 68-96%
- Nausea – 50-85%
- Early satiation – 50-82%
- Belching – 45-85%
- Vomiting – 20-31%
- Weight loss – 58%


Functional Dyspepsia with/without disordered gastric emptying

- Rapid gastric emptying
- Normal gastric emptying
- Mild delay in gastric emptying
- Severely delayed gastric emptying

Lacy, Am J Gastroenterol 2013
Question #4: What is the Pathophysiology of Gastroparesis?

Gastroparesis: Pathophysiology

- GP is not a single disorder
- A gastric neuropathy (gastropathy)
- Rarely a myopathy
- Typically involves injury to the ENS
- Vagal injury may rarely be present, but is not the cause in all patients
- ? a sensory disorder or motor disorder or both?
Question #5: What is the Etiology of Gastroparesis?

- DIABETES
- POST-SURGICAL
- POST-VIRAL
- NEUROLOGIC
- ISCHEMIA
- METABOLIC
- RADIATION
- VACCINATIONS
- (IDIOPATHIC)
- PSEUDO-OBSTRUCTION
- COLLAGEN-VASCULAR
- INFLAMMATORY
- MEDICATIONS
- INFLTRATIVE
- PRIOR TRANSPLANT
- CIRRHOSIS
- PARANEOPLASTIC
- ANOREXIA

Gastroparesis: Differential Diagnosis

- Functional dyspepsia
- Mechanical obstruction
- Rumination syndrome
- CVS
- Hyperemesis due to cannabis use
- Anorexia & Bulimia
- Medication-induced
- Celiac artery compression syndrome (MALS)
- SMA syndrome
- Munchausen’s
**Question #6: What Diagnostic Studies are available/required?**

- Abdominal x-ray
- UGI series +/- SBFT
- Upper endoscopy
- Gastric emptying scans - liquid or solid
- Wireless motility capsule
- Ultrasound
- Breath tests
- Electrogastrogram (EGG)
- Antroduodenal Manometry
- MRI, PET scans

**Required Tests to Diagnose GP**

- Rule out obstruction
  - EGD or UGI series
- Evaluate possible etiologies
  - Stop medications that slow gastric emptying
  - Control blood sugar (< 275 mg/dl)
- Laboratory tests
  - CBC, TSH, HgbA1c, fasting glucose
  - Consider: autoimmune/CTD labs
- Assess the degree of delay in emptying
  - 4-hour solid phase gastric emptying scan
- Rarely, more esoteric tests are useful
Placement of ADM catheter

Gastric Motility – Fasting State
ElectroGastroGraphy (EGG)

- Non-invasive measure of gastric myoelectrical activity
- Evaluates the gastric slow wave (3 cpm)
- Assesses the dominant frequency and measures the increase in amplitude (power) after a meal
- Safe, easy to perform
- Best used as an adjunct to other tests

EGG – Diabetic gastropathy
Question #7: What is the role of Dietary Therapy?

- Small frequent meals - 5 to 6 per day
- Low fat & low fiber
- Restore electrolytes & hydration
  - Emphasize liquids (bouillon, Gatorade)
- Supplement diet with egg whites, protein powders, and nutritional drinks (Enlive, Breeze, low fat Ensure)
- Control serum glucose
- Consider referral to a nutritionist

Question #8: What is the role of prokinetic therapy?
**Metoclopramide**

- A substituted benzamide derivative
  - Chemical structure similar to procainamide
- Available since 1979
- Increases ACh release from intrinsic neurons
- A dopamine D2-receptor antagonist
- Inhibits DA receptors centrally and peripherally
- Increases the amplitude of antral contractions
- Relaxes the pyloric sphincter
- FDA approved for diabetic GP

**Metoclopramide:**
Side Effects & Tardive Dyskinesia

- 30-40% of patients have side effects
  - Anxiety, depression, insomnia, “skin crawling”, acute dystonic reaction, akathisia, Parkinsonism
- 37 cases of NMS; 8 deaths
- Black box warning (FDA – 2-26-09)
- TD - an extrapyramidal disorder characterized by irreversible involuntary movements
  - Some reports state risk is as high as 15%
  - Real risk: likely < 1%
- FDA: chronic use should be avoided
Domperidone

- A benzamidazole derivative
- Acts peripherally to block D2 receptors
- Increases local release of ACh
- Antiemetic activity is due to DA receptor blockade in the CTZ
- Side effects due to elevated prolactin levels
- PO form only; IV form may lead to arrhythmias
- Not FDA approved for treatment of GP
- Check EKG first; don’t use if QT >450 ms in women, and 470 ms in men

Domperidone: What’s the data?

- 11 studies performed to date in Pts with GP
- 4 = open label; 1 single-blind
- Subjects: 3 to 287
- Doses: 10 mg TID to 20 mg QID
- Study length: 4 weeks to 2 years
- Outcomes: Symptoms and/or gastric emptying
- Results: Symptoms improved in 36% - 94%
- Gastric emptying improved in 0 – 64%
- Similar or better than metoclopramide
Erythromycin

- A macrolide antibiotic
- Mimics the action of motilin
- Induces Phase III of the MMC
- Increases the amplitude of antral contractions and increases antro-duodenal coordination
- Ideal dose is 3 mg/kg Q 8 hrs
- Tachyphylaxis is common & expected
- Not FDA approved for gastroparesis

Question #9: What is the role of Antiemetic Therapy?

- Phenothiazines (compazine)
- Antihistamines (meclizine)
- Anticholinergics (scopolamine)
- DA antagonists (metoclopramide)
- 5HT-3 antagonists (ondansetron)
- Others: marinol, tigan, lorazepam, prednisone, haldol

No controlled studies to support use in gastroparesis patients
Question #10: What is the role of surgery?

Gastrectomy and gastroparesis

- All studies are retrospective, unblinded, or uncontrolled
- 60 patients with near total gastrectomy¹
  - follow-up of >5 years
  - 67% noted improvement in symptoms
- 52 patients with near total or completion gastrectomy²
  - follow-up at 4.5 years
  - 78% noted improvement in symptoms
- No good studies in diabetic patients

¹Forstner-Barthell et al, J Gastrointest Surg 1999; 3: 15
²Eckhauser et al, Am Surg 1998; 64: 711
Gastric Stimulation: Theoretical MOA

- Entrainment (pacing) of gastric slow waves can be achieved with low frequency/long duration pulses. But….
- Increases gastric emptying. No.
- Vagal nerve stimulation with modulation of CTZ and nausea and vomiting center.
  - Very appealing
  - PET study – GES increases activity in thalamus
  - But, why does it work in some patients who have had a vagotomy?

Port Placement

- 3-4 Ports
- Typically utilize 5mm ports
- Upper right port becomes stimulator pocket
**Lead Fixation**

- Abdominal pocket placement
- Utilize port placement site
- Leads pulled through port to site
- Snug fit

**Stimulator Pocket**
Gastric stimulation

- FDA approved in 2000 as a HUD
- 14 studies published to date; only 1 = blinded
- 6 different publication groups total
- Study size: 5-214 (most = 18-33)
- Most are mixed groups (DM and idiopathic)

Gastric Stimulation

- Bottom line:
  - Improves nausea and vomiting in 50% of Pts
  - 76% of Pts were able to stop TPN/PPN
  - Some improvement in glycemic control
  - Not helpful for pain or bloating
  - Less helpful for those on narcotics
  - Doesn’t improve Gastric emptying time
  - Doesn’t change gastric electrical rhythm
  - Better in diabetics than non-diabetics
  - Appears to improve Patients’ quality-of-life
Question #11 What about Botox?

Botox & Gastroparesis: A Systematic Review

• 15 trials to date
  – only 2 were R, PC trials
• Arts (2007; Europe) – 100 U Botox; 4 week FU
  – 23 Patients: 19 idiopathic; 2 DM; 2 post-op
  – no change in symptoms using GCSI or GES
• Friedenberg (2008; USA) – 200 U Botox; 4 week FU
  – 32 Pts: 18 DM, 13 idiopathic; 1 post-op;
  – no change in symptoms using GCSI or GES
Question #12: What about CAM?

- Acupressure
- Acupuncture
  - Single-blinded, R; n = 19; type 2 DM
  - 2 week study; 2 week follow-up
- Ginger
- Hypnotherapy

Question #13: What’s in the future?

- TZP-101 (ghrelin agonist; i.v.)
- TZP-102 (ghrelin agonist; oral)
- RM-131 (ghrelin agonist; s.c.)
- GSK962040 (motilin agonist)
- RQ-00-20194 (motilin agonist)
**TZP-101**

- Multicenter, R, DB, PC study
- Single infusion; 20-600 ug/kg
- 57 Diabetics (75% Type 1; mean age 41-48)
- GES and GCSI scores: pre- & post-infusion
- Results:
  - GES time improved 25% vs. placebo (8%; n.s.)
  - At 30 days follow-up, frequency of vomiting was improved compared to placebo for 80 ug/kg (p = 0.024)
  - No other symptom differences noted

Ejskjaer et al, Neurogastro & Motil 2010;22:1069-281

**RM-131**

- Ghrelin agonist
- Double-blind, randomized, single-dose, cross-over study
- 10 Pts (Type 1 DM; mean age = 46); all with delayed GE
- 100 ug s.c. vs. placebo
- Gastric emptying improved at 1 & 2 hours, but not at 4 hours
- Symptom improvement noted using GCSI

Gastroparesis: Summary

- Significant impact on patients’ quality of life
- Symptoms do not correlate with gastric emptying
- Symptoms correlate poorly with underlying pathophysiology
- Blood sugar control is paramount in diabetics
- Treat the predominant symptom
- Avoid narcotics
- Avoid surgery