1/28/2021

Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
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LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2021 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2022 for this activity.

MOC QUESTION
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Week 5, 2021
Cross-Sectional Imaging in IBD and Small Bowel Bleeding: What Every Gastroenterologist Should Know
Jonathan A. Leighton, MD, FACP
February 4, 2021 at Noon Eastern

Week 6, 2021
Esophageal Fistulas
Douglas G. Adler, MD, FACP
February 11, 2021 at Noon Eastern

Visit gi.org/ACGVGR to Register

Disclosures:

Speaker:
Scott L. Gabbard, MD
Dr. Gabbard has no conflicts of interest related to this talk.

Moderator:
Afrin N. Kamal, MD
Dr. Kamal has no conflicts of interest related to this talk.
Functional Dyspepsia – How to deal with the burn and the bloat

Scott L. Gabbard, MD
Section Head - Center of Neurogastroenterology and Motility
Cleveland Clinic
Cleveland, Ohio
First – A plug for the ACG

Prevalence of uninvestigated dyspepsia worldwide using Rome IV criteria

Etiology of dyspepsia

FUNCTIONAL

- Erosive esophagitis (20.0%)
- Barrett's esophagus (1.1%)
- Gastro-esophageal cancer (0.4%)
- Peptic ulcer (6.0%)
- Normal (72.5%)


Conceptual pathophysiologic basis of functional dyspepsia

Normal Gastric Motility – The stomach is pretty smart

- 0-60 minutes:
  - Fundus relaxes
  - Mediated by NO and VIP
  - Minimal emptying in first hour
- 60-240 minutes:
  - Fundus contracts
  - Gastric juice secretion
  - Peristalsis breaks down solid bolus
    - Normal peristalsis is 3 cycles per minute
  - Pylorus opens when particles <1mm and isotonic

Koch, K. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Volume 10

Typical day in motility clinic

- Complaints: bloating, satiety, epigastric fullness with meals, intermittent stabbing epigastric pain
  - Symptoms begin during meal
- Denies vomiting
- “I’m sure that I have gastroparesis, but I’ve had two scans that were normal.”
Role of delayed gastric emptying in FD

• Do symptoms correlate well with gastric emptying?
• Does delayed gastric emptying uniformly cause dyspeptic symptoms?
• Does normalization of gastric emptying improve dyspeptic symptoms?

Gastric Emptying - Diagnosis

• Gastric emptying scan
  - 4 hour solid phase GES considered the “gold standard”
  - Shorter scans or liquid phase scans are unreliable
  - Normal gastric emptying defined as less than 10-15% at 4 hours

Symptoms and Gastric Emptying

- 218 consecutive patients with dyspeptic symptoms
- Very mild correlation between symptoms and gastric emptying
  - Slight increase in post-prandial fullness with delayed emptying (30% vs. 21%), nausea (18% vs. 12%), epigastric pain (13% vs. 18%)


What happens when you intentionally slow a medical student’s stomach?

- 14 healthy volunteers (mean age 23; 6 men)
- Sumatriptan (5HT₁ agonist) before test meal
  - 5HT₁ agonists augment fundic accommodation
- Bloating, fullness, nausea and discomfort recorded
- Sumatriptan significantly delayed gastric emptying
- All symptoms significantly improved after sumatriptan

The other end of the spectrum - Rapid Gastric Emptying

- >40-70% emptying at 1 hour
- Etiologies
  - Impaired fundic accommodation
  - Increased post-prandial contractility
  - Decreased pyloric tone
- Symptoms – indistinguishable from gastroparesis
  - Symptoms immediately post-prandial (within 1 hour)
- Rapid emptying more common than delayed emptying in functional dyspepsia
- Rapid emptying most common in cyclic vomiting syndrome and POTS
- Rapid emptying more likely to present with nausea/vomiting, weight loss

Kamal A. J Clin Gastroenterol. 2020 Oct;54(9):e89-e92
Bharucha AE et al. Neurogastroenterol Motil. 2011;23:e251-e252

Dyspepsia: Diagnosis

- Thorough history and physical examination
- Evaluate for warning signs/features
  - Anemia, odynophagia, or dysphagia
  - Previous gastrointestinal bleeding or ulcer disease
  - Evidence of malnutrition
  - Evidence of CTD
  - Evidence of a bowel obstruction on examination
  - Abdominal bruit
- Evaluation of the upper GI tract (EGD)
Rome IV criteria

FD Symptom Cluster Analysis

- Post-prandial distress (dysmotility-like)
  - Disruption of fundal accommodation or delay in gastric emptying
  - Nausea, vomiting, early satiety and weight loss cluster together as one factor
- Epigastric pain syndrome (ulcer-like)
  - Mediated by visceral hypersensitivity
  - Epigastric pain and epigastric burning
Do all patients with dyspepsia require EGD?


**Endoscopy – ACG Guidelines**

- **A few points**
  - Alarm symptoms in patients < 60 had limited value
    - Risk of GI malignancy with alarm symptom = <1%
    - Exception would be dysphagia, GI bleeding, concern for biliary source, etc.
  - Dyspepsia and age > 60 -> EGD
  - Dyspepsia and age < 60
    - Alarm Symptoms = EGD not indicated for excluding malignancy
    - Test (non-invasive) and treat for *H. pylori*

Dyspepsia: Diagnostic testing

- **H. pylori**
  - High-prevalence of low-prevalence *H. pylori* area?
    - CDC: HP prevalence is 20-25% in US
  - Diagnostic tests
    - Serology: Sens = 90%, Spec = 76%
    - Stool Ag: Sens = 94%; Spec = 97%
    - UBT: Sens 90-95%; Spec = 95%
    - Urease test: Sens/Spec 90-95%
    - Pathology: Sens/Spec 95-98%


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**H. pylori** tips

- Epidemiology
  - Worldwide prevalence = 50%
  - US prevalence = 20-25%
  - Reinfection rare
- Testing (ACG Recommendations)
  - Testing is indicated in patients with gastric MALT lymphoma, active peptic ulcer disease, dyspepsia or a past history of documented peptic ulcer, ITP
  - When endoscopy is indicated, the test of first choice is a urease test on an antral biopsy
  - UBT – high false negative rate in PPI use (33%)
  - Serology – high false positive rate in US
  - Stool test – most cost-effective test

FD Treatment

Step 1

- Make a confident diagnosis
  - Use Rome IV criteria
  - Show the Rome IV papers to your patient
- What not to do
  - “We don’t know what you have”
  - “It’s probably just IBS, here’s the door”
Step 2

- **What to say**
  - “Functional dyspepsia is a NERVE DISORDER of the stomach/duodenum”
    - Nerves are overly sensitive to physiologic events

- **What not to say**
  - “We don’t know what functional dyspepsia is”

Vanner, et al. Gastroenterology, 150, 6, 2016, 1280–1291

Step 3

- **Patient: “Why did I get functional dyspepsia?”**
  - “We think that many factors are at play”
    - Genetics
    - Inflammatory/post-infectious event
    - Sensitization of the visceral nerves
    - Central sensitization

Step 4

• “Will this ever go away”
  - 10 year data (IBS – but FD is likely comparable)
    • 67% will continue to have IBS at 10 years
    • 1 in 3 will have spontaneous resolution of IBS


Step 5

• “Does this affect my long-term survival?”
  • No
  • Presence of dyspepsia did not impact survival
    • 8,300 individuals
    • > 84,000 years of follow-up

Step 6

• “How do we treat this?”
  - Medications
    • Neuromodulators
      • “We are not using this because you are anxious or crazy. We are using this medication because it regulates the signaling chemicals in your gut – serotonin, norepinephrine, etc.”
  - Behavioral Therapies
    • I tell patients that it modulates the interface between the ENS and CNS.

H. pylori treatment

• Treatment (NNT = 7 for dyspepsia)
  - First Line
    • PPI, amoxicillin (1 g twice daily), and clarithromycin (500 mg twice daily) for 14 days – 80% efficacy
      • Only if no previous macrolide exposure
    • Bismuth subsalicylate 525 mg QID, metronidazole 250 mg QID, tetracycline 500 mg QID, PPI for 10-14 days – 85% efficacy
    • Levofloxacin, amoxicillin, PPI for 10-14 days – 90% efficacy
  - Confirm eradication
    • All patients receiving treatment
    • UBT or stool test 4 weeks after treatment (off PPI for 2 weeks)

Moayyedi P, et al. AJG 2017
### Treating FD - beyond *H. pylori*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>0.49 [0.36, 0.69]</td>
</tr>
<tr>
<td>TCAs</td>
<td>0.71 [0.58, 0.87]</td>
</tr>
<tr>
<td>Mitrazapine</td>
<td>0.73 [0.48, 1.10]</td>
</tr>
<tr>
<td>H2RAs</td>
<td>0.81 [0.73, 0.90]</td>
</tr>
<tr>
<td>Standard dose PPIs</td>
<td>0.84 [0.77, 0.91]</td>
</tr>
<tr>
<td>Domperidone</td>
<td>0.86 [0.69, 1.05]</td>
</tr>
<tr>
<td>Low-dose PPIs</td>
<td>0.88 [0.79, 0.94]</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>0.87 [0.77, 0.99]</td>
</tr>
<tr>
<td>Tagatremil</td>
<td>0.99 [0.75, 1.36]</td>
</tr>
<tr>
<td>Acetanside</td>
<td>0.99 [0.79, 1.29]</td>
</tr>
<tr>
<td>High-dose PPIs</td>
<td>0.89 [0.79, 1.01]</td>
</tr>
<tr>
<td>Misoprostil</td>
<td>0.92 [0.79, 1.06]</td>
</tr>
<tr>
<td>SNRIs</td>
<td>1.02 [0.81, 1.26]</td>
</tr>
<tr>
<td>E6RIs</td>
<td>0.99 [0.81, 1.21]</td>
</tr>
<tr>
<td>L-687,162 agonists</td>
<td>1.03 [0.87, 1.26]</td>
</tr>
</tbody>
</table>


### Antipsychotics

- Sulpiride/levosulpiride – not available in US
Neuromodulation: TCAs

- Reserved for moderate to severe symptoms
- Tricyclic antidepressants (TCAs)
  - Visceral and somatic perception are altered with TCAs.\(^1\)
  - Study in 7 patients found that amitriptyline improved symptoms but did not alter sensation of gastric distention.\(^2\)
  - Meta-analysis in patients with FGIDs found improvement of global symptoms (OR = 4.2; NNT = 3.2) and pain.\(^3\)
- NIH Functional Dyspepsia Treatment Trial\(^4\)
  - 292 patients with FD (Rome II criteria)
  - Response rate for amitriptyline 50mg significantly higher than for citalopram or placebo (53%, 38%, 40%, p <0.05)
  - Improvement seen more in patients with epigastric pain, than for patients with post-prandial distress (67% response rate in epigastric pain syndrome)


• Buspirone
  - 5HT-1\(_A\) receptor agonist
  - 10 mg TID 15 min before meals in FD patients
  - Increased gastric accommodation by 62%
  - Improved
    - Postprandial fullness (41% compared to baseline)
    - Bloating (28% compared to baseline)
  - May also work in patients with rapid gastric emptying

But didn’t you say 5-HT\textsubscript{1A} agents don’t work??

**Table:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison: Treatment vs. Placebo (Random-effects model)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
<td>0.49 (0.36, 0.69)</td>
</tr>
<tr>
<td>TDPs</td>
<td></td>
<td>0.71 (0.59, 0.87)</td>
</tr>
<tr>
<td>Mianserin</td>
<td></td>
<td>0.73 (0.68, 0.78)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td>0.61 (0.53, 0.70)</td>
</tr>
<tr>
<td>Standard dose PPIs</td>
<td></td>
<td>0.64 (0.57, 0.73)</td>
</tr>
<tr>
<td>Comparisons</td>
<td></td>
<td>0.48 (0.40, 0.57)</td>
</tr>
<tr>
<td>Low dose PPIs</td>
<td></td>
<td>0.66 (0.57, 0.79)</td>
</tr>
<tr>
<td>H2-blockers</td>
<td></td>
<td>0.60 (0.57, 0.64)</td>
</tr>
<tr>
<td>Tagamet</td>
<td></td>
<td>0.60 (0.54, 0.66)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td></td>
<td>0.68 (0.59, 0.79)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
<td>0.60 (0.54, 0.66)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td></td>
<td>0.68 (0.60, 0.79)</td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
<td>0.60 (0.54, 0.66)</td>
</tr>
<tr>
<td>SERT blockers</td>
<td></td>
<td>0.60 (0.54, 0.66)</td>
</tr>
<tr>
<td>5-HT\textsubscript{1A} agonists</td>
<td></td>
<td>1.05 (0.87, 1.26)</td>
</tr>
</tbody>
</table>


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**Figure 3:**

Proportion of responders in patients treated with trandolapirone: a comparison of the primary end point with placebo. The primary end point was assessed at week 4. The difference of proportions (95% confidence interval) and P-values are shown in the figure. P-values were calculated by Cochran-Mantel-Haenszel test adjusted for the quartiles of baseline total score. Two patients in trandolapirone arm and four patients in the placebo arm with no data throughout weeks 1-4 were excluded. On assuming these six patients as responders, or as to make the difference between the two arms conservative, P-values were found to be 0.009 and 0.004 at weeks 2 and 4, respectively.


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American College of Gastroenterology
**Neuromodulation - Mirtazapine**

- **Mirtazapine**
  - 5-HT2c antagonist, 5-HT3 antagonist
  - Studied in FD patients - 15mg QHS
    - Early satiety (43% improvement)
    - Nausea (33% improvement)
    - 4 kg weight gain at 8 weeks


**Post-fundoplication dyspepsia**

- ACG 2020 Poster 1161 (Gabbard, Singh): **Role of Neuromodulators for Patients With Dyspepsia Post-Fundoplication: A Case Series of Three Patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>76</td>
<td>74</td>
<td>64</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td>Nissen fundoplication</td>
<td>Nissen fundoplication</td>
<td>Nissen fundoplication</td>
</tr>
<tr>
<td><strong>Dyspepsia subtype</strong></td>
<td>Epigastric pain syndrome and Post-prandial distress syndrome</td>
<td>Epigastric pain</td>
<td>Post-prandial distress syndrome</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Buspirone 10mg TID</td>
<td>Buspirone 10mg TID</td>
<td>Buspirone 10mg TID + mirtazapine 30mg QHS</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Complete resolution</td>
<td>Could not tolerate due to side effects</td>
<td>Resolved by 90%</td>
</tr>
<tr>
<td><strong>Weight changes</strong></td>
<td>Gained 16 pounds</td>
<td>Gained 3 pounds</td>
<td>Gained 17 pounds</td>
</tr>
</tbody>
</table>

American College of Gastroenterology
Table 11. Endoscopic findings and disease characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clavulanate (n = 30)</th>
<th>Metoclopramide (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Erosion in gastric corpus</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Large non-scarring ulcerations</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Pyloric deformation</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Reflux ileus</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Belching</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Heartburn</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>9.7 ± 6.3</td>
<td>5.6 ± 4.3</td>
</tr>
</tbody>
</table>

* Organome disease was excluded at trial entry, with the exception of hemorrhagic perforation.

† One of the following symptoms was present, but noted mild to lower abdominal pain, distention, diarrhea, constipation, patients having severe antacid bowel syndrome-like symptoms were excluded.

* Mean ± standard deviation; significantly different between the two groups (P < 0.05).

Fig. 1: Global therapeutic outcomes after 2 and 4 weeks of treatment with 5mg clavulanate three times daily (CL) or 10mg metoclopramide three times daily (MCL) and after 2 weeks of drug-free follow-up. Respondents = patients with no or mild symptoms, non-responders = patients with severe symptoms requiring drug treatment or with recurrence of severe symptoms after cessation of treatment (P > 0.05).
CAM for FD

- STW 5
  - 9 herbs
    - bitter candytuft, angelica root, milk thistle fruit, celandine herb, caraway fruit, licorice root, peppermint herb, balm leaf and chamomile flower
  - Significant improvement compared to placebo in dyspeptic symptoms after 8 weeks
    - 20 drops before meals
  - Can be obtained online
    - $32 per bottle (100 doses), $58 for 2 bottles


CAM for FD

- Duodenal release menthol and caraway oil
- 2 capsules BID (~$0.70 per pill)
- EPS and PDS both significantly improved
- Patients with more severe symptoms had greater response

CAM for FD

- **Capsaicin**
  - Selectively inhibits activity of nociceptive C-type fibers
  - 30 patients with functional dyspepsia
    - Dyspeptic symptoms improved by 60% (30% in placebo)
      - 2.5g red pepper powder per day ($0.04 per pill)
      - 500mg before breakfast, 1000mg before lunch/dinner
      - Symptoms worsen after the first day, then improve

Bortolotti et al. Aliment Pharmacol Ther 2002

- **Acupuncture**
  - Significant improvement in dyspeptic symptoms compared to sham
    - 5 sessions per week – all acupuncture meridians beneficial
    - Group A: ST42, ST40, ST36, and ST34 – stomach meridian points
    - PDS symptoms and epigastric pain responded best
      - Epigastric burning had lowest response

Behavioral Therapy for Functional Dyspepsia

- NNT = 3

Moayyedi P, et al. AJG 2017;112:988-1013

ACG and CAG Clinical Guideline: Management of Dyspepsia

Table 1. Summary and strength of recommendations

1. We suggest dyspepsia patients aged 60 or over have an endoscopy to exclude upper gastrointestinal neoplasia. Conditional recommendation, very low quality evidence.
2. We do not suggest endoscopy to investigate alarm features for dyspepsia patients under the age of 60 to exclude upper GI neoplasia. Conditional recommendation, moderate quality evidence.
3. We recommend dyspepsia patients under the age of 60 should have a non-invasive test for H. pylori and therapy for H. pylori infection if positive. Strong recommendation, high quality evidence.
4. We recommend dyspepsia patients under the age of 60 should have an empirical PPI trial if they are H. pylori-negative or who remain symptomatic after H. pylori-eradication therapy. Strong recommendation, high quality evidence.
5. We suggest dyspepsia patients under the age of 60 not responding to PPI or H. pylori-eradication therapy should be offered TCA therapy. Conditional recommendation, very low quality evidence.
6. We suggest dyspepsia patients under the age of 60 not responding to PPI or H. pylori-eradication therapy should be offered TCA therapy. Conditional recommendation, very low quality evidence.
7. We recommend FD patients that are H. pylori positive should be prescribed therapy to treat the infection. Strong recommendation, high quality evidence.
8. We recommend FD patients who are H. pylori-negative or who remain symptomatic despite eradication of the infection should be treated with PPI therapy. Strong recommendation, moderate quality evidence.
9. We recommend FD patients not responding to PPI or H. pylori-eradication therapy (if appropriate) should be offered TCA therapy. Conditional recommendation, moderate quality evidence.
10. We suggest FD patients not responding to PPI or H. pylori-eradication therapy or ticlopidine antispasmodic therapy should be offered psychological therapies. Conditional recommendation, very low quality evidence.
11. We recommend FD patients not responding to drug therapy should be offered psychological therapies. Conditional recommendation, very low quality evidence.
12. We do not recommend the routine use of complementary and alternative medicines for FD. Conditional Recommendation, very low quality evidence.
13. We recommend against routine motility studies for patients with FD. Conditional recommendation, very low quality evidence.
14. We suggest motility studies for selected patients with FD when gas-bloat is strongly suspected. Conditional recommendation, very low quality evidence.
Gabbard Tips – Functional Dyspepsia

- Post-prandial distress
  - Bloating/epigastric fullness/early satiety
    - Buspirone 10mg before meals
    - Augments relaxation of the fundus
    - Mirtazapine 7.5-15mg QHS
    - Especially if weight loss
- Epigastric pain
  - Stabbing or burning pain
    - Amitriptyline 10mg QHS, increase as tolerated
- Adjuncts (for either)
  - Menthol/caraway preparation
  - STW 5 – 20 drops before meals
  - Cayenne – 2500mg daily, split doses
  - Behavioral therapy
  - Acupuncture
- Print
Questions?

Speaker: Scott L. Gabbard, MD

Moderator: Afrin N. Kamal, MD

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ACG Functional GI Health and Nutrition Circle
ACG GI Circle
ACG Women in GI Circle

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