Snack Size: 100 Calorie Updates in Gastroenterology

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The Problem with Snack Size

ONE DOES NOT SIMPLY EAT THE RECOMMENDED SERVING SIZE OF ANY SNACK
Today’s Topics

- PPI-refractory GERD
- Endoscopic ultrasound and ERCP in acute pancreatitis
- Fecal Transplant: A New Frontier, and Irritable Bowel Syndrome
- Is 45 the new 50? New colon cancer screening guidelines

Refractory GERD

- Symptoms of reflux that do not respond to a double dose of PPI given for at least 8 weeks
- 10-40% of patients will have ongoing symptoms¹
- Lifestyle changes/optimize use
- Double PPI dose
- EGD with biopsies to exclude alternate dx

Next Step: pH-Impedance Monitoring

- Thin catheter passed through nose across GE junction, 24 hours
- Tests pH as well as presence of fluid
- Do test ON PPI
- Impedance portion can detect nonacid reflux

Possible Findings on Impedance pH

- Abnormal Reflux (acid or nonacid), positive symptom index (less than 25%) of patients
- Normal pH test, positive symptom index
- Normal pH test and negative symptom index
Medical Options for Ongoing Acid Exposure

- H2 blocker at night: combination of H2 plus PPI reduces nocturnal acid breakthrough only for one week¹.
- Addition of prokinetic therapy no better than PPI alone².
- Prucalopride (5-HT4 agonist) for constipation decreases acid exposure; FDA decision in Dec.
- Vonoprazan, first in class of potassium competitive acid blockers

2. Li-hua R et al. World J Gastroenterol 2014;7:20:2412-2419

Abnormal Ongoing Reflux: Due to TLESR

- Primary cause of GERD are transient lower esophageal sphincter relaxations (TLESR)
- PPI and H2 blockers do not prevent TLESR
- Baclofen, a GABA_B agonist, reduces the frequency of reflux events and inhibits TLESR

Baclofen for Refractory GERD: Meta-analysis vs placebo, 9 RCT

Incidence of GERD

Incidence of TSLER


Surgical Options For Ongoing Acid

- Fundoplication
  - High rate of satisfaction
    - Some still need acid inhibition
  - Linx device
    - Dysphagia in 68%
    - MRI ok with newer device (Up to 1.5T)
    - Similar improvement in symptoms but lower PPI elimination rate
Normal pH, negative symptom index: about 30%

- Functional heartburn/hypersensitive esophagus
- Focus on pain modulation
- Tricyclics, SSRIs
- Traditional medicine: acupuncture
- Diaphragmatic breathing/cognitive behavioral therapy
- No studies on barrier protectors (sucralfate, aluminum hydroxide)


PPI-Refractory GERD: RCT of Various Treatment Options

- 10 VA medical centers, patients with refractory GERD
- All had pH/impedance monitoring
- Normal pH and negative symptom index (functional heartburn) excluded (27%)
- Randomized the remainder who had positive symptoms and abnormal reflux or just abnormal reflux alone randomized to 1) surgery, 2) PPI plus baclofen +/- desipramine, or 3) PPI alone

Spechler S et al. Gastroenterol 2018;154:S-129, Abstract 615
VA Study: PPI refractory GERD, with abnormal ongoing acid exposure or positive symptom index

- N=78
- pH/impedance showed (+) symptom index only in 37, abnormal acid only in 15, and both symptoms and acid in 25.
- Success rates at 12 months:
  - Surgery 66.7%
  - Active medical group 28%
  - Placebo group (PPI only) 11.5%
- Conclusion: for positive symptom index or ongoing acid, surgery significantly better than medication (PPI plus baclofen +/- desipramine)

PPI-Refractory Heartburn: Summary

- Use impedance-pH monitoring (on PPI) to guide management
- Optimize PPI and lifestyle first for ongoing acid exposure; H2 blocker HS
- Prokinetic data not encouraging
- Consider baclofen (5-20 mg po tid) in addition to PPI for those with persistent acid despite BID PPI, or fundoplication
- Tricyclics, SSRI etc for functional heartburn
Pancreatitis is most commonly due to gallstones. ERCP is done for choledocholithiasis. Cholecystectomy should follow but is sometimes delayed or not done at all. How much protection does ERCP offer for recurrent pancreatitis?
Gallstone Pancreatitis

Retrospective study of 80 patients admitted over 5 years with gallstone pancreatitis at a safety-net hospital

- 40 did not have cholecystectomy prior to d/c
- 9 patients total (11.2% of entire cohort) developed recurrent pancreatitis after d/c; 8 of these (88%) were in the delayed group
- Median time to pancreatitis 4 months

146 patients with biliary pancreatitis over 10 year period (excluded severe pancreatitis)
- Only 14% had cholecystectomy same admission
- N=89 had delayed cholecystectomy; of these 53 (60%) had ERCP with sphincterotomy and 36 (40%) did not have ERCP ('no sphincterotomy')

Kulpitcharapong S, et al. GIE May 2017 supplement, AB545

**Sphincterotomy and Delayed Surgery: Recurrent Pancreatitis**

4% vs 33%, p=0.01, One death

2% vs 17%, p=0.01

Acute cholecystitis more common in never surgery group, 10% vs 5%, p = NS
### Reasons for No Surgery

<table>
<thead>
<tr>
<th>Reason for Delay</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Inpatient Surgical Consultation</td>
<td>9/40 (22.5%)</td>
</tr>
<tr>
<td>Severe pancreatitis (includes evolving pseudocyst)</td>
<td>6/40 (15%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5/40 (12.5%)</td>
</tr>
<tr>
<td>Etiology Unclear</td>
<td>4/40 (10%)</td>
</tr>
<tr>
<td>Left AMA</td>
<td>3/40 (7.5%)</td>
</tr>
<tr>
<td>Other Active Medical Issues</td>
<td>6/40 (15%)</td>
</tr>
<tr>
<td>Others (pt preference, poor surgical candidate)</td>
<td>2/40 (5%)</td>
</tr>
<tr>
<td>Pt died</td>
<td>2/40 (5%)</td>
</tr>
</tbody>
</table>

### Idiopathic Acute Pancreatitis

- 30% of cases of acute pancreatitis have no obvious cause identifiable; drops to 15-25% after extensive workup (MRCP, CT etc)
- EUS recommended after pancreatitis if no obvious source found, especially in patients > 40 or other risk factors for malignancy
- What is the incidence of cancer in patients with negative CT or MRI?
**Idiopathic Pancreatitis and Cancer**

- Retrospective 10 year study of patients with idiopathic acute or chronic pancreatiits
- All had negative imaging with CT or MRI
- n= 951 had EUS

Bartell N et al. GIE May 2017 Suppl, Abstract 114

**Results**

Patients with Idiopathic Acute or Chronic Pancreatitis that had EUS Performed

- Cancer Positive: 25
  - 22 Adenocarcinoma
  - 3 Neuroendocrine
- Cancer Negative: 926

Event Rate of pancreatic neoplasia diagnosis with EUS-FNA = 2.6%
"Idiopathic" Pancreatitis: Should the GB Come Out after One Episode?

- Retrospective study of 195 patients with idiopathic acute pancreatitis
- 33.8% underwent cholecystectomy
- Recurrence rate 19.7% vs 42.8% in those without
- Author conclusion: In patients fit for surgery, cholecystectomy should be considered to reduce the risk of recurrent episodes


Should the GB Come Out?

- RCT of 85 patients with idiopathic pancreatitis
- Randomized to cholecystectomy or watchful waiting
- Median follow-up 36 (5-58) months
- Recurrent pancreatitis higher in nonsurgical group: 30.4% vs 10%, p = 0.016)
- Subgroup followed to 24 months: 38.8% vs. 11%, p = 0.026)

Adequate hydration is mainstay of treatment in acute pancreatitis; reduces mortality
Guidelines regarding which type of fluid is best are lacking
Small studies indicate lactated ringer’s might be superior

Meta-analysis of studies comparing NS to LR
Mortality, development of systemic inflammatory response syndrome (SIRS) on admit and 24 hours, and pancreatic necrosis
5 studies; 3 were RCT, n=428
Mortality trended lower in the LR group
LR group had lower risk of SIRS at 24 hours: pooled OR 0.38, 95% CI 0.15-0.98, p = 0.05
No difference in development of necrosis

Igbal U et al. J Dig Dis 2018;19:335-341
Pancreas: Summary

- Biliary sphincterotomy is not entirely protective of future episodes of gallstone pancreatitis
- Single episode of unexplained pancreatitis: in patients over 40 with no obvious cause/negative imaging, EUS finds malignancy in very small percentage
- Single episode of completely unexplained pancreatitis: consider elective cholecystectomy
- Use of lactated ringer’s for hydration in acute pancreatitis associated with less SIRS compared to NS but no difference in mortality

Irritable Bowel Syndrome: “Disorder of Brain-Gut Axis”

- Characterized by abdominal pain with altered gut motility causing diarrhea and/or constipation
- Consumes over $20 billion in direct and indirect expenditures
- Intestinal dysbiosis (alterations in quantity/composition of GI-associated microbiota) observed in patients with IBS

2. Drossman D. Gastroenterology 2016;150:1262-1279
Probiotics (RR of persistent symptoms: 0.79, 95% CI 0.7-0.89)\(^1\)

Antibiotics (40.8% improved vs 31.2% for placebo, rifaximin for IBS-D)\(^2\)

Diet

Fecal Transplant

\(^1\) Ford A et al. Am J Gastroenterol 2014;109:1547-1561


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FODMAP diet associated with reduced global symptoms (RR 0.69, 95% CI 0.54-0.88)

Meta-analysis: Gluten Free Diet vs Placebo

**Conclusion:** FODMAP has modest effect on reduction of global symptoms in IBS. Gluten-free diet, not worth it.

### Fecal Transplant

- Transfer of distal gut microbial communities from a healthy individual to a patient’s intestinal tract to cure a disease
- Colonic instillation of donor stool results in cure of C. diff infection in around 90% (flex sig, colonoscopy, retention enema)
- Upper tract instillation not as effective; risk of regurgitation/aspiration
Fecal Transplant: A Cure for Everything? Treatment of Ulcerative Colitis

-Hepatic encephalopathy: benefit in small study
-Metabolic syndrome: trials ongoing

Narula N et al. Inflamm Bowel Dis 2017;23:1702-1709
Fecal Transplant for IBS: RCTs

<table>
<thead>
<tr>
<th>n</th>
<th>Type of IBS</th>
<th>Weeks followup</th>
<th>Outcome met</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>IBS unspecified</td>
<td>2,4,8</td>
<td>IBS score decreased at 8 weeks</td>
</tr>
<tr>
<td>90</td>
<td>IBS-D, IBS-mixed</td>
<td>12</td>
<td>65% FMT vs 43%, p = 0.049, large lasting placebo effect</td>
</tr>
<tr>
<td>64</td>
<td>IBS-nonC</td>
<td>12</td>
<td>49% FMT vs 29%, p = 0.004</td>
</tr>
<tr>
<td>48</td>
<td>IBS-D</td>
<td>12</td>
<td>No difference at 12 weeks; placebo better at 24 weeks</td>
</tr>
<tr>
<td>52</td>
<td>IBS unspecified</td>
<td>4, 12, 24</td>
<td>No difference in symptom scores; QOL better in placebo</td>
</tr>
</tbody>
</table>

Schmulson M et al. Curr Opin Pharmacol 2018; 43:72-80

Fecal Transplant for IBS

- RCT of 52 adults with IBS, with moderate to severe disease (based on symptom score)
- Randomized to FMT or placebo capsules x 12 days; followed for 6 months
- FMT patients had an increase in biodiversity and became indistinguishable from donors; placebo pt stool remained the same
- No significant difference in symptom score at 6 mo
- IBS QOL data showed significant difference in improvement...favoring the placebo arm

Halkjaer S et al. Gastroenterol 2018;14:S-181, abstract 914
**FMT: Many Unanswered Questions**

- No long term safety data (reassuring data for recurrent CDI)
- Uncertainty about most effective method of delivery (enema vs colonoscopy), and protocol
- Pretreatment antibiotics? Bowel prep?
- Ideal method of preparation of transplant?
- Fecal Microbiota Transplant National Registry will follow 4,000 patients for 10 years

**Biofeedback**

- Therapeutic strategy designed to target factors that maintain IBS
- Faulty processing of information that dysregulates brain-gut interactions
- Increased rates of anxiety, specifically “visceral anxiety” and catastrophizing
- Misinterpret normal digestive processes as dangerous
- Not commonly used
NIH RCT, 3 arms, 436 pts: 4 session home-based CBT, 10 session clinic-based CBT, 4 session IBS education
- Home based CBT produced larger percent of responders (‘substantially or moderately improved’) than education only group (61% vs 43.5%, p < 0.05)
- Similar response for standard CBT
- Low decline in gains: 57% at 3, 6, and 9 mo, and 61% at 12 mo

Lackner J et al. Gastroenterol 2018; 154:S-105, Abstract 455

Underutilized; major barriers are knowledge of its existence, patient acceptance, and availability of trained psych professionals
- Internet based therapy seems to be as effective
- Suspect will be most helpful for difficult/refractory cases Primary care and GI clinics might consider employing a psychotherapist
Summary: IBS

- FODMAP diet: modest benefit
- Gluten free diet: no benefit
- Fecal transplant: Doesn’t seem to work, but need more standardization of methods, and studies to identify subgroups
- Large placebo effect with IBS in all studies: exploit this with CBT, which does work

Colon Cancer

- Second leading cause of cancer death in the U.S.
- 1 in 3 who get it will die of it
- 20% of colon cancer in US diagnosed when it has already metastasized
- Colonoscopy most used screening test (61%)
### Risk Factors

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>Decreased Risk</th>
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<tbody>
<tr>
<td>Lack of physical activity</td>
<td>Multivitamin with folate</td>
</tr>
<tr>
<td>Obesity</td>
<td>Aspirin and other NSAIDS</td>
</tr>
<tr>
<td>Consumption of red meat</td>
<td>Postmenopausal hormone use</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Calcium, selenium</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Consumption of fruits, vegetables, and fiber</td>
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</tbody>
</table>

**Nonmodifiable risk:** Male gender, age > 50, AA race, genetics/family history

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#### Table 4. Multi-Society Task Force ranking of current colorectal cancer screening tests

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy every 10 years</td>
<td>CT colonography every 5 years</td>
<td>Capsule colonoscopy every 5 years</td>
</tr>
<tr>
<td>Annual fecal immunochemical test</td>
<td>FIT-fecal DNA every 3 years</td>
<td>Available tests not currently recommended</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 10 years (or every 5 years)</td>
<td></td>
<td>Septin 9</td>
</tr>
</tbody>
</table>

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### Performance Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity for cancer</th>
<th>Sensitivity for large polyps</th>
<th>False positive rate</th>
<th>Cost</th>
<th>Sensitivity for SSPs &gt; 1 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT</td>
<td>73.8%</td>
<td>30%</td>
<td>5%</td>
<td>$22</td>
<td>none</td>
</tr>
<tr>
<td>Cologuard (includes FIT)</td>
<td>92%</td>
<td>42%</td>
<td>12%</td>
<td>$502 (Medicare rate)</td>
<td>40%</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>&gt;95%</td>
<td>95%</td>
<td>0%</td>
<td>$1-3K</td>
<td>92-93%</td>
</tr>
</tbody>
</table>


### FIT Screening: Poor Compliance?

<table>
<thead>
<tr>
<th></th>
<th>Screening round (number eligible)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Round 1 (n=8,237)</td>
</tr>
<tr>
<td>FIT completion</td>
<td>4,820 (26.4%)</td>
</tr>
<tr>
<td>Positive FIT</td>
<td>209 (4.3%)</td>
</tr>
<tr>
<td>Follow-up with colonoscopy</td>
<td>123 (58.9%)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>8</td>
</tr>
<tr>
<td>Adenoma (advanced)</td>
<td>63 (36)</td>
</tr>
</tbody>
</table>

Murphy C et al. Gastroenterol 2018;154:S-29 (abstract 96)
American Cancer Society released new guidelines with a 'qualified' recommendation to begin screening at 45 rather than 50 for average risk individuals.

How strong are the findings of increasing CRC incidence in people < 50, and life years gained with earlier screening?

By 2030, incidence rate will increase by 90% in 20-34 year old age group
- Compared with adults born around 1950, those born in 1990 have *double* the risk of colon cancer and *quadruple* the risk of rectal cancer
- Young patients more commonly have symptomatic, later stage, mucinous, and poorly differentiated tumors

Life-years gained starting screening at 45 (blue) vs 50 (grey)

Starting at age 45 results in 6.2% more life years gained, and 17% more lifetime colonoscopies versus age 50.
Colorectal Cancer in the Young: WHY?

- 114 cases of early-onset CRC documented (median age, 45 years, interquartile range, 41-47 years)
- RR 1.37 (95% CI 0.81-2.30) for overweight women (BMI 25-29.9) and 1.93 (95% CI, 1.15-3.25 for obese women (BMI > 30)
- RR of early onset CRC 1.65 for women gaining 20-39.9 kg since age 18) and 2.15 (95% CI 1.01-4.55) for women gaining 40 kg or more (p = 0.007 for trend)

The Role of Obesity

- National Inpatient Sample, 2002-2013
- Identified 91,116 obese and 1,181,127 nonobese who had resection for colorectal cancer
- Rate of obese pts undergoing resection for colon cancer increased across all age groups
- Steepest rise in 18-49 year old age group: annual percentage change 13.1%, p< 0.001

Rates in women increasing more quickly than men

![Graph showing gender differences in colorectal cancer hospitalizations for age group 41-50 yrs: 2010-2014.](image)

Desai R et al. Am J Gastroenterol 2018;113: abstract 150

Screening Conclusions

- Reasons for colon cancer increase in younger patients: not known at this time
- Age 45-50 screening: controversial
- Offer colonoscopy first, FIT as alternative
- Cologuard adds minor amount of sensitivity at increased cost and higher false positive rate
- Continue screening through age 75
- Age 76-85: individualize
- Age 86 and up: discontinue screening
Other Snacks: Honorable Mentions

- Eosinophilic esophagitis: each year of untreated disease increases risk of stricture by 9%¹
- Chronic cannabis users: Abdominal pain (25% vs 8%, p < 0.002), heartburn (15% vs 9%), nausea and vomiting (7% vs 1%)²
- Four new drugs on the horizon for NASH


Hot Snack: Flamin’ Hot Cheetos, and a visit to the ER

Rapper Lil Xan
Questions?