Irritable Bowel Syndrome: Masqueraders Ball?
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UCSF Primary Care Medicine: Update 2012

Irritable Bowel Syndrome
Abdominal discomfort
and
Altered bowel function

• Structural and biochemical abnormalities are “absent”
  – Absent = not present OR not detectable

Rome III IBS diagnostic criteria
• Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months with 2 or more of the following:
  – Improvement of pain with defecation
  – Onset associated with change in frequency of stool
  – Onset associated with change in form (appearance) of stool

Epidemiology of IBS
• Prevalence 7-10% worldwide
  – No “gold standard”, so may be more or less
• Gender estimates range from 2:1 (female-predominating) to 1:1
• Can present at any age
  Saito, et.al. Am J Gastroenterol 2002
• Costs over $300 more/yr for IBS patients
  – Extrapolated to US: over $8 billion/yr
  Talley, et.al. Gastroenterol 1995
Who takes care of IBS?

Pathophysiology

- Altered gut motility/neuroenteric signaling
- Visceral hypersensitivity
  - Enhanced sensitivity and altered mucosal immunity
- Brain-gut dysfunction
  - Altered pain, autonomic, and stress-related pathways
- Altered gut bacterial ecology

Pathophysiology

- New directions
  - Disordered serotonin signaling in GI tract
    - Increased p11 (serotonin-related protein) mRNA in IBS patients relative to controls
      Camilleri, et.al. Gastroenterol 2007
  - Inflammatory disease?
    - Low-grade inflammation and immune activation have been identified in many subsets of IBS patients
      Tornblom, et.al. Gastroenterol 2002
      Dunlop, et.al. Am J Gastroenterol 2003
      Scully P, et.al. Am J Gastroenterol 2010

Spectrum of bowel disease?

Increasing inflammation
Inherited, learned, or both?

- IBS rates for 6060 monozygotic and dizygotic twins concordance compared to concordance with parents of twins
- Concordance:
  - Monozygotic 17.2%
  - Dizygotic  8.4%  (p=0.03)
- Greater IBS concordance with twins and their mothers than dizygotic co-twins (p=0.001)


Post-infectious IBS

- Chronic symptoms meeting IBS criteria as result of acute gastroenteritis
  - 15% persistent 8+ years after initial attack
  - Likelihood correlated to severity of bout
  - True structural abnormalities are seen:
    - Increased mucosal lymphocytic infiltration
    - Increased epithelial permeability
    - Increased inflammatory components
    - Enterochromaffin and mast cells
  - Probiotics may exert anti-inflammatory effects


Psychological stress and IBS

- Strong association found, causation hard to prove
- Psychological distress from IBS selects for those more likely to seek medical care for IBS symptoms
- IBS a key component of Gulf War syndrome
- Degree of chronic life stress associated with severity of IBS symptoms and failure to improve


Abuse and IBS

- Functional MRI on patients with hx abuse, IBS, both, or neither during aversive stimuli
- Pts with both hx abuse AND IBS had highest activation in brain regions associated with heightened pain responses

Evaluation

- CBC with differential
- ESR
- Serum chemistries
- Stool ova and parasites, occult blood
- Colonic exam (barium enema, sigmoidoscopy or colonoscopy)
- TSH

AGA Position Statement, Gastroenterol 1997
Camilleri M, Gastroenterol 2001

Evaluation

- EXTREMELY LOW YIELD
  - In patients meeting IBS symptom criteria, probability of inflammatory bowel disease, colorectal cancer, or infectious diarrhea is <1% (similar to healthy controls)
  - Standard battery of testing rarely yields any new diagnosis
  - Adds potentially unnecessary cost


Prevalence of organic disease in those meeting IBS symptom criteria

<table>
<thead>
<tr>
<th>Organic GI Disease</th>
<th>IBS Patients</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis/IBD</td>
<td>0.51-0.98%</td>
<td>0.3-1.2%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0-0.51%</td>
<td>0-6% (age-dependent)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>4.67%</td>
<td>0.25-0.5%</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>0-1.5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>6%</td>
<td>5-9%</td>
</tr>
<tr>
<td>Lactose malabsorption</td>
<td>22-26%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Cash et.al. Am J Gastroenterol 2002

Evaluation

- With classic symptoms and no alarm symptoms, routinely ordering standard “IBS tests” is NOT evidence-based
  - Diagnosis can be made on symptoms alone in most cases
- Reassurance alone not good reason for w/u
  - Measured quality of life in IBS patients unaffected by having had a colonoscopy

Spiegel BMR, et.al. Gastrointest Endosc 2005
Who with IBS should I evaluate?

- Over age 50 for colon cancer screening
- Alarm symptoms
  - rectal bleeding
  - weight loss >10 pounds
  - family history of colon cancer, IBD, or celiac dz
  - recurring fevers
  - nocturnal symptoms
  - anemia
  - chronic severe diarrhea

Treatment

- Since the pathophysiology of IBS is complex, diverse and still not elucidated, and there is no cure, treatment is still SYMPTOM-BASED
- Subgroups to assist therapy:
  - Diarrhea-predominant (IBS-D)
  - Constipation-predominant (IBS-C)
  - Alternating diarrhea/constipation (IBS-M)
  - "Gas/bloat IBS" (IBS-GB)

Most effective: placebo?

- Placebo effect tends to be large (20-50%) in IBS medication trials
  - This increases the number needed to treat (NNT) for improvement over placebo in all trials
- Hard to trust results of anything short of double-blinded randomized placebo-controlled trials
**IBS: General approaches**

- Identify and offset psychological stressors
- Avoid common dietary triggers
  - Lactose-containing foods
  - Gas-promoting foods
  - Fructose/fructans (fruits, honey, corn syrup)
    
- Encourage healthy eating HABITS
- Exercise

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**IBS: General approaches**

- Bulking agents: fiber
  - Non-digestible carbohydrates transformed by colonic bacteria into gas & fluid
  - Improves water content of stool
  - Improves stool frequency
  - Trials: most small, poor quality
  - Found to be effective for constipation
  - No controlled trials have demonstrated improvements in pain, diarrhea, or global IBS symptoms
  - May make diarrhea and bloating worse


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**IBS: General approaches**

- Antispasmodics
  - Induce smooth muscle relaxation
    - Anticholinergic/antimuscarinic
    - USA: only available agents hyoscyamine & dicyclomine
  - Trials: All small, short duration, poor quality
    - Only 1/3 improved global IBS symptoms significantly over placebo
    - Atropinic side-effects limit dosing


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**IBS: General approaches**

- Probiotics: Theory
  - Suppress overgrowth of urease-producing strains of bacteria that follow acute gastroenteritis
  - Alter composition of gut flora
  - Inhibit activities of pathogenic bacteria
  - Exert favorable influences on immune system
    - Promote favorable IL-10/IL-12 ratio
**IBS: General approaches**

- **Probiotics:** practice
  - 2 randomized trials\(^1\,^2\) with *Bifidobacterium infantis* ("Align") showed improvement in symptoms
  - Other smaller studies with various *lactobacillus* and other *bifidobacterium spp* show mixed results
  - Overall role remains unclear (but little risk)
  - Post infectious IBS results most promising

\(^1\)O’Mahony L et.al. Gastroenterol 2005
\(^2\)Whorwell PJ et.al. Am J Gastroenterol 2006

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**Anti-diarrheals**

- **Loperamide, diphenoxylate/atropine, bismuth subsalicylate**
  - Delay intestinal transit, promoting water removal from stool
  - Only loperamide studied in randomized controlled trials, all low-quality
  - Efficacy for diarrhea but not for pain or global IBS symptoms

Efskind PS, et.al. Scand J Gastroenterol 1996
Antidepressants

- Tricyclic antidepressants and SSRIs
  - Decrease nociception
  - Treat concomitant depression/anxiety
  - Anti-cholinergic side effects of TCAs result in smooth muscle relaxation and slowed transit
- Meta-analysis:
  - RR of IBS on therapy: 0.66 (95% CI 0.57-0.78)
  - TCAs and SSRIs equally effective
  - NNT 4 for 1 improvement


Laxatives

- Usually critical element in treating IBS-C
- Most classes of laxatives effective for short-term use
- Preferred agents for long-term use:
  - Emollient laxatives (eg. Docusate)
  - Osmotic laxatives (eg. polyethylene glycol)

Alosetron (Lotronex)

- Serotonin 5HT3 antagonist
  - Slows colonic transit
  - Decreases distension-induced discomfort
  - 4 large, short trials showed improvement in stool frequency and pain (10-27% over placebo)
    - NNT 7.6 for 1 improvement over placebo
  - Removed from market for 2 years: ischemic colitis and severe constipation
  - Now only FDA approved for women with severe IBS-D who have failed other therapies


Tegaserod (Zelnorm)

- 5HT4 receptor agonist
  - Stimulates peristalsis
  - Increases intestinal transit
  - Decreases visceral hypersensitivity
  - Large major trials: 42% improved global IBS sx vs. 32% placebo
  - NNT: 10.7 for 1 improvement over placebo
  - Taken off market 2007: increase CV events

1Brandt LJ, et.al. Am J Gastroenterol 2009
Lubiprostone
• Activates gut lamina chloride channels
• Increases chloride and fluid release into the intestines
• Improves number of bowel movements, stool consistency, and global constipation symptoms
• Major side effect: nausea (>30%) at 24 mcg BID dose, though only 10% at 8 mcg BID
  – Limits widespread use

Linaclotide
• Increases intestinal fluid secretion and transit via guanylate cyclase mediated activation of CF transmembrane conductance regulator
• Minimally absorbed (no additional side effects above placebo)
• Increases spontaneous BM frequency, abdominal pain, and QOL in IBS/C
• Further study needed but promising

Alternative/herbal therapies
• Western medicine often falls short for IBS
• 11-43% of IBS patients try complementary alternative medicine/therapy at some point
• Systematic review:
  – Chinese herbal medication found effective but significant heterogeneity
  – Peppermint oil 4 RCTs for IBS: RR 0.43
    • NNT 2.5 for 1 improvement

What is celiac disease?
• Immune-mediated response to gluten
• Primarily involves digestive tract
  – Multiple other systems involved secondarily
• Marked by chronic inflammation of small intestinal mucosa
  – Villous atrophy
  – Intraepithelial lymphocytes
  – Crypt hyperplasia
Prevalence of celiac disease

- United States, adults 1% (symptomatic and asymptomatic combined)
- Osteoporosis 1-3%
- "Diarrhea-predominant IBS" 5%
- Type 1 diabetes mellitus 3-8%
- Iron-deficiency anemia 3-12%
- Down syndrome 5-12%

Who should be tested?

- Typical symptoms: chronic diarrhea, malabsorption, weight loss, abdominal distension
- Unexplained iron deficiency anemia, infertility, recurrent fetal loss, short stature, elevated LFTs
- Extraintestinal manifestations (eg dermatitis herpetiformis)
- First-degree relatives of confirmed celiac patients (15% concordance)

Who with IBS should I evaluate?

- Over age 50 for colon cancer screening
- Alarm symptoms
  - rectal bleeding
  - weight loss >10 pounds
  - family history of colon cancer
  - recurring fevers
  - Anemia
- chronic severe diarrhea
- IBS-D: Screen for celiac disease (?)
Serologic Testing

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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</thead>
<tbody>
<tr>
<td>AGA IgA</td>
<td>75-90%</td>
<td>80-90%</td>
<td>80s%</td>
<td>80s%</td>
</tr>
<tr>
<td>EMA IgA</td>
<td>90%</td>
<td>99%</td>
<td>90%</td>
<td>99%</td>
</tr>
<tr>
<td>TTG IgA</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
</tr>
</tbody>
</table>

AGA = Anti-gliadin Ab  EMA = Anti-endomysial Ab  TTG = Tissue transglutaminase

Pitfalls of serologic testing

- Patient must be actively ingesting gluten for IgA tests to be elevated
  - Tests normalize on gluten-free diet
- Sensitivity and specificity numbers derived from people with symptoms
  - Utility of any serological test for screening for celiac disease in asymptomatic people less clear
- If IgA deficient, can have false negative TTG IgA
  - Either test total IgA OR get TTG IgG

Genetic testing

- Celiac disease strongly associated with haplotypes HLA DQ2 and DQ8
- Negative predictive value of having neither haplotype is over 95%
- Can be useful in equivocal cases (where serology and biopsies are not concordant)
Treatment for celiac disease

• Gluten-free diet

What if celiac and no symptoms?

46,000 Swedish patients serology positive for celiac disease with biopsy specimens available were studied for all-cause mortality

<table>
<thead>
<tr>
<th>Findings of duodenal biopsy</th>
<th>HR for death in follow-up period</th>
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</thead>
<tbody>
<tr>
<td>Overt celiac: villous atrophy</td>
<td>1.39 (95% CI 1.33-1.49)</td>
</tr>
<tr>
<td>Intraepithelial inflammation only NO villous atrophy</td>
<td>1.72 (95% CI 1.64-1.79)</td>
</tr>
<tr>
<td>Latent celiac: normal duodenal biopsy</td>
<td>1.35 (95% CI 1.14-1.58)</td>
</tr>
</tbody>
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Ludvigsson JF, et al. JAMA, 2009

Small intestinal bacterial overgrowth (SIBO)

• Normal small bowel mostly sterile
• 10-80% of patients with irritable bowel have “excess” bacterial titers in small bowel
• Results in early fermentation of starch
  – EXCESS GAS FORMATION in form of methane and hydrogen sulfide
• May result in fat and nutrient malabsorption in advanced cases

Testing for SIBO

• Lactulose hydrogen breath testing
  – Measures exhaled labeled hydrogen which is released from ingested lactulose by small intestinal bacteria (should not normally break this down until colon)
  – Questionable reliability/consistency of test
• Up to 84% of IBS patients have abnormal lactulose H2 breath tests (control 20%)

**Rifaximin**

- Non-absorbable antibiotic
- Improved global IBS symptoms (41%) over placebo (32%) in large recent trial\(^1\)
  - Effective for IBS patients who do not have constipation
  - Rx 550 TID 2 wks; sx measured at 12 wks
  - NNT 10 for 1 response over placebo
  - Symptom relief most pronounced: bloating
  - Possibly truly treating bacterial overgrowth, not IBS.

\(^1\)Pimentel, et.al. NEJM 2011

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**Community-acquired Cdifficle**

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<tr>
<th></th>
<th>Community-acquired</th>
<th>Hospital-acquired</th>
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<tbody>
<tr>
<td>Average age</td>
<td>50</td>
<td>72</td>
</tr>
<tr>
<td>Women</td>
<td>76</td>
<td>60</td>
</tr>
<tr>
<td>Severe disease</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Antibiotic exposure</td>
<td>78</td>
<td>94</td>
</tr>
</tbody>
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Khanna S et al. Am J Gastroenterol 2012

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**Summary**

- IBS is probably a series of “organic” diseases we just haven’t worked out yet
- Don’t need to do testing to establish diagnosis in classic cases
- Treatment
  - symptom-based
  - multifaceted approach (nonpharm and pharm)
  - minimal evidence-basis
  - modest effectiveness in best cases