IBS: New Approaches

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Evidence-based medicine

• David Sackett\(^1\): “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available clinical evidence from systematic research.”
• “good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough.”

Evidence-based medicine

How good is the evidence?
Systematic reviews are not perfect

- Errors in the conduct of 8 meta-analyses of pharmacological interventions for IBS:\(^1\):
  - 13—29% of included trials were ineligible by reviewers criteria
  - 6 of 8 meta-analyses missed published trials
  - All had errors in data extraction → errors in 15 of 16 reported pooled treatment effects (≥10% in 5 of 8 studies and change in estimate of statistical significance in some)


American College of Gastroenterology
IBS Task Force

An evidence-based systematic review on the management of IBS
Task Force Report Sections

- Burden of illness
- Utility of alarm features
- Role of alarm features
- Role of diagnostic testing
- Diet and IBS
- Dietary fiber, bulking agents and laxatives
- Antispasmodics and peppermint oil
- Antidiarrheals

Task Force Report Sections

- Antibiotics
- Probiotics
- 5-HT_{3}-receptor antagonists
- 5-HT_{4}-receptor agonists
- Selective C-2 chloride channel agonists
- Antidepressant agents
- Psychological therapies
- Herbal therapies/acupuncture
Diet for IBS: ACG Recommendations

• Patients often believe certain foods exacerbate their IBS symptoms

• There is, however, insufficient evidence that food allergy testing or exclusion diets are efficacious in IBS and their routine use outside of a clinical trial is not recommended (Grade 2C)


Very Low Carbohydrate Diet for IBS-D: Results from a Pilot Study

• 15 females, mean age 46 years, BMI 32

• 2 weeks standard diet followed by 4 weeks very low carbohydrate diet
  – 51% fat, 45% protein, 4% carbohydrate

• Adequate relief responder rate: 13/13 (100%)
  – 10/13 (77%) improved 4/4 weeks
  – Improvements in stool frequency ($P<.001$), consistency ($P<.001$), pain ($P<.001$), QoL ($P=.02$)
  – Mean weight loss of 3.1 kg

What are FODMAPs?

• Fermentable oligo-, di-, monosaccharides and polyols
• Fruits with fructose exceeding glucose
  – Apples, pears, watermelon
• Fructan-containing vegetables
  – Onions, leeks, asparagus, artichokes
• Wheat-based products
  – Bread, pasta, cereal, cake, biscuits
• Sorbitol- and lactose-containing foods
• Raffinose-containing foods
  – Legumes, lentils, cabbage, brussels sprouts


Impact of FODMAP Diet on Breath Hydrogen Production and Symptoms

• Design
  – Single-blind crossover study in 15 healthy and 15 IBS patients
  – 2-day consumption of high-FODMAP diet (50 g/d) or low-FODMAP diet (9 g/d)
• Results
  – Higher levels of breath hydrogen produced with high FODMAP diet
  – Gastrointestinal symptoms and lethargy induced by high FODMAP diet in IBS but not control patients

HFD=high-FODMAP diet; LFD=low-FODMAP diet
Fructose and Fructans as Dietary Triggers for IBS Symptoms

25 IBS patients with fructose malabsorption who improved with a FODMAP diet

Glucose  Fructose  Fructans  F&F


Fiber for IBS: ACG Recommendations

- Psyllium hydrophilic mucilloid (ispaghula husk) is moderately effective and can be given a conditional recommendation (Grade 2C)
- A single study reported improvement with calcium polycarbophil
- Wheat bran or corn bran is no more effective than placebo in the relief of global symptoms of IBS and cannot be recommended for routine use (Grade 2C)

Traditional Medications for IBS

Antispasmodics: ACG Recommendations

• Certain antispasmodics (hyoscine, cimetropium, pinaverium, and peppermint oil) may provide short-term relief of abdominal pain / discomfort in IBS (Grade 2C)
• Evidence for long-term efficacy is not available
• Evidence for safety and tolerability is limited (Grade 2C)

Antibiotic Therapy: Percentage of Patients With Adequate Relief

**Combined Analysis**

- **14-d double-blind treatment phase**
- **10-week follow-up (no study medication)**

<table>
<thead>
<tr>
<th>Patients with Adequate Relief (%)</th>
<th>Placebo</th>
<th>Rifaximin</th>
<th>P = .001</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td></td>
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<td></td>
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<tr>
<td>10</td>
<td></td>
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<tr>
<td>12</td>
<td></td>
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</tr>
</tbody>
</table>


Retreatment with Rifaximin after Return of IBS Symptoms

- 84 IBS patients were treated with rifaximin
- **Response***
  - 69% of rifaximin patients
  - 37% of neomycin patients
- Rifaximin or neomycin used as retreatment in patients with symptom relapse
  - 100% of rifaximin patients responded to retreatment
  - 25% of neomycin patients responded to retreatment
- Rifaximin used a third time in 4 patients; all responded

*Response was defined as 50% or greater improvement in IBS symptoms
Antibiotics: ACG Recommendations

- A short-term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating (Grade IB)
- There are no data available to support the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms


Probiotics
**Single-organism Probiotics (Selected)**

- Isolated *Lactobacillus spp*
  - *L reuteri*
  - *L casei*
- Lacteol Fort
  - Combination of *L acidophilus* LB, lactose monohydrate, calcium carbonate, silicic acid, talc, magnesium stearate, anhydrous lactose
- *L plantarum*
- *L salivarius*
- *B infantis*
- *B animalis*


**Combination Probiotics (Selected)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSL no. 3</td>
<td>Bifidobacterium (3 spp), lactobacillus (4 spp), <em>Streptococcus salivarius</em></td>
</tr>
<tr>
<td>Prescript assist</td>
<td>29 microorganisms with a prebiotic component</td>
</tr>
<tr>
<td>SCM III</td>
<td><em>Lactobacillus acidophilus, Lactobacillus helveticus, Bifidobacterium spp.</em></td>
</tr>
</tbody>
</table>

Lactobacillus and Bifidobacterium in IBS: Relationship to Cytokine Profiles

- Symptom improvement associated with normalization of cytokine ratio, suggesting an anti-inflammatory effect of *B. infantis* in IBS
- Composite score = sum of scores for abdominal pain, bloating, and bowel movement difficulty


Probiotics: ACG Recommendations

- In single-organism studies, lactobacilli do not appear effective for patients with IBS
- Bifidobacteria and certain combinations of probiotics demonstrate some efficacy

Newer Medications for IBS

Efficacy of Alosetron in IBS: A Meta-Analysis of RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camilleri et al.</td>
<td>1.28 (0.98, 1.67)</td>
</tr>
<tr>
<td>Jones et al.</td>
<td>1.69 (1.42, 2.32)</td>
</tr>
<tr>
<td>Bardhan et al.</td>
<td>1.6 (0.93, 2.63)</td>
</tr>
<tr>
<td>Camilleri et al.</td>
<td>1.35 (0.98, 1.83)</td>
</tr>
<tr>
<td>Camilleri et al.</td>
<td>1.99 (1.45, 2.71)</td>
</tr>
<tr>
<td>Lembo et al.</td>
<td>2.76 (2.04, 3.72)</td>
</tr>
<tr>
<td>Pooled (excluding alosetron and mebeverine)</td>
<td>1.85 (1.57, 2.18)</td>
</tr>
<tr>
<td>Pooled (all studies)</td>
<td>1.81 (1.57, 2.10)</td>
</tr>
</tbody>
</table>

5-HT₃ Antagonists: ACG Recommendations

- The 5-HT₃ receptor antagonist alosetron is more effective than placebo at relieving global IBS symptoms in male (Grade 2B) and female (Grade 2A) IBS patients with diarrhea.
- Potentially serious side effects including constipation and colon ischemia occur more commonly in patients treated with alosetron compared with placebo (Grade 2A).
- Benefits and harms balance for alosetron is most favorable in women who have not responded to conventional therapies (Grade 1B).
- The quality of evidence for efficacy of 5-HT₃ antagonists in IBS is high.


Lubiprostone: IBS with Constipation

\[
P = 0.001
\]

\[
\begin{array}{c}
\text{Lubiprostone} \\
\text{8 µg bid} \\
n = 780
\end{array}
\]

\[
\begin{array}{c}
\text{Placebo} \\
n = 387
\end{array}
\]

\[
\begin{array}{c}
17.9 \\
10.1
\end{array}
\]

Selective C-2 Chloride Channel Activators: ACG Recommendations

- Lubiprostone in a dose of 8 µg twice daily is more effective than placebo in relieving global IBS symptoms in women with IBS-C (Grade 1B)


Antidepressants and Psychological Therapies
Available Antidepressants and Dosages for IBS

<table>
<thead>
<tr>
<th>Agents</th>
<th>TCAs</th>
<th>SSRIs</th>
<th>SNRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amitriptyline</td>
<td>Fluoxetine</td>
<td>Duloxetine</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>Sertraline</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>Paroxetine</td>
<td>Desvenlafaxine</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>Citalopram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose range</td>
<td>10-200 mg</td>
<td>10-100 mg</td>
<td>30-90 mg (duloxetine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75-224 mg (venlafaxine)</td>
</tr>
</tbody>
</table>

TCAs-tricyclic antidepressant; SSRIs-selective serotonin reuptake inhibitor; SNRIs-serotonin-norepinephrine reuptake inhibitor


Antidepressants: ACG Recommendations

- TCAs and SSRIs are more effective than placebo at relieving global IBS symptoms, and appear to reduce abdominal pain
- There are limited data on the safety and tolerability of these agents in patients with IBS

Psychological Therapy for IBS: Meta-analysis

- 20 studies (various psychological therapies), 1278 patients

<table>
<thead>
<tr>
<th>Improvement: Psychological therapy (%)</th>
<th>Improvement: “Usual management” or control therapy (%)</th>
<th>RR symptoms remain (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.1</td>
<td>27.5</td>
<td>0.67 (0.57-0.79)</td>
</tr>
</tbody>
</table>

- Significant heterogeneity and funnel plot asymmetry
- Lack of small studies showing no effect of psychological therapies on the symptoms of IBS


Psychological Therapies: ACG Recommendations

- Psychological therapies, including cognitive therapy, dynamic psychotherapy, and hypnotherapy, but not relaxation therapy, are more effective than usual care in relieving global symptoms of IBS (Grade 1B)

Emerging Agents for the Management of IBS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
</tr>
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<tbody>
<tr>
<td>Prucalopride</td>
<td>5-HT₄ agonist</td>
</tr>
<tr>
<td>Mosapride</td>
<td>5-HT₄ agonist</td>
</tr>
<tr>
<td>Itopride</td>
<td>Dopamine D₂ antagonist/Ach inhibitor</td>
</tr>
<tr>
<td>Cilansetron</td>
<td>5-HT₃ antagonist</td>
</tr>
<tr>
<td>Ramosetron</td>
<td>5-HT₃ antagonist</td>
</tr>
<tr>
<td>Pumosetrag</td>
<td>5-HT₃ agonist</td>
</tr>
<tr>
<td>Linaclootide</td>
<td>Guanylate cyclase-C receptor agonist</td>
</tr>
<tr>
<td>Plecanatide</td>
<td>Guanylate cyclase-C receptor agonist</td>
</tr>
<tr>
<td>Crofelemer</td>
<td>Chloride secretion inhibitor</td>
</tr>
<tr>
<td>A3309</td>
<td>Bile acid transporter inhibitor</td>
</tr>
<tr>
<td>Asimadoline</td>
<td>Opioid receptor agonist</td>
</tr>
<tr>
<td>Dextofisopam</td>
<td>Atypical benzodiazepine</td>
</tr>
<tr>
<td>AST-120</td>
<td>Oral carbon adsorbent</td>
</tr>
<tr>
<td>LX1031</td>
<td>Tryptophan hydroxase-1 inhibitor</td>
</tr>
</tbody>
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Future Approaches to IBS Diagnosis

- Current criteria-based diagnosis identifies a syndrome (i.e., a group of symptoms), not a unitary pathophysiology
- In time, I believe that IBS will be viewed as an intermediate diagnosis that will require further evaluation to establish a “final” diagnosis
- Personalized diagnosis will lead to more effective treatments