IBS:
New drugs for an old Problem

NINA MEREL, MD
Approximately 12% prevalence in North America

IBS symptoms are 1.5 to 2 times more prevalent in women

Women report more abdominal pain and constipation, men report more diarrhea. Patients may change between IBS-C, IBS-D and IBS-M over time

Prevalence decreases with age
Patient #1

- Alternator
Patient #2

- Constipation
Patient #3

- Diarrhea
# Rome III Criteria

**TABLE 1.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abdominal pain or discomfort accompanied by at least two of the following symptoms 25% of the time:*</td>
<td>A. Improvement with defecation.</td>
</tr>
<tr>
<td></td>
<td>B. Onset associated with change in frequency of stools.</td>
</tr>
<tr>
<td></td>
<td>C. Onset associated with a change in form (appearance) of stools.</td>
</tr>
<tr>
<td>2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms</td>
<td></td>
</tr>
</tbody>
</table>
Rome III criteria for IBS

- Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following features:
  - Change in stool frequency
  - Change in stool form (appearance)
  - Improvement with defecation
- Symptoms present for 6 months or longer

Rome IV criteria released 2016
- Functional bowel disorders are a continuum of symptoms
IBS subtypes & Bristol Stool Form Scale

- **IBS-C** (BSFS 1 or 2 at least 25% of time)
- **IBS-M** (BSFS 1 or 2 25% of time and 6 or 7 25% of time)
- **IBS-D** (BSFS 6 or 7 at least 25% of time)

Rome IV criteria released 2016. Functional bowel disorders are a continuum of symptoms rather than a separate disease state. Subtypes may change over time.
Clinical Features

- Symptoms often present since childhood
- Symptoms triggered by food
- Symptoms and IBS subtypes may change over time (pain location, stool pattern)
Concerning features

- Symptoms onset after age 50
- Nocturnal symptoms of pain or diarrhea
- Weight loss
- Rectal bleeding
- FH of CRC, IBD, celiac disease
- Anemia
Medications that can contribute to IBS Symptoms

- **Over-the-Counter**
  - Anti-histamines
  - Calcium
  - Iron
  - Magnesium
  - NSAIDS
  - Supplements

- **Prescription**
  - Antibiotics
  - Antidepressants
  - Antipsychotics
  - Calcium-channel blockers
  - Metformin
  - Opioids
  - Antiparkinsonian drugs
### Diagnostic Tests in Patients With No Alarm Features

**ALL: CBC and appropriate CRC screening**

<table>
<thead>
<tr>
<th>IBS-D</th>
<th>IBS-M</th>
<th>IBS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein, total IgA, IgA TtG</td>
<td>TSH, C-reactive protein, total IgA, IgA TtG</td>
<td>TSH, Calcium (CMP)</td>
</tr>
<tr>
<td>Fecal calprotectin</td>
<td>Fecal calprotectin</td>
<td>Consider:</td>
</tr>
<tr>
<td>Consider colonoscopy with random biopsies for microscopic colitis</td>
<td>Consider abdominal X-ray to determine fecal loading</td>
<td>- Total IgA, IgA TtG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anorectal testing (manometry and/or fecal defecography)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If medically refractory, colonic marker study</td>
</tr>
</tbody>
</table>
Additional IBS-D tests

- Cytolethal distending toxin B and Anti-vinculin antibodies
  - Develop after gastroenteritis
  - Inhibit development of enteric neural cells
    - Impairment of GI motility
    - Dysbiosis
  - Fecal bile acids
IBS Pathophysiology is Multifactorial

HOST

ENVIRONMENTAL

LUMINAL
Host Factors

- Increased Visceral hypersensitivity
- Altered brain-gut axis (increased afferent pain signals)
- Altered GI motility
- Increased intestinal mucosal immune activation
- Increased luminal permeability
Luminal factors

- Intestinal microflora and dysbiosis
- Intestinal neuroendocrine mediators
- Bile acids
Environmental factors

- Early life stressors (psychosocial, abuse)
- Diet (FODMAPS, gluten, fiber) intolerance
- Antibiotic use
- Enteric infection
  - Half of post infectious IBS patients symptoms resolve
Post-Infectious IBS

- Increase risk with:
  - Severity of illness
  - Female gender
  - Psychological factors

- Altered microbiome and immune activation
  - Impairs serotonin enterocromaffin cells in the gut
    - Affects motility and secretion
    - Visceral hypersensitivity
  - Affects gas production

- Half of post infectious IBS patients symptoms resolve within 6 yrs
Bile Acids and IBS-D

- Approximately 25% of IBS-D patients have increased fecal bile acids
- Dysbiosis
- Increased fluid secretion
- Increased mucosal permeability
- Increased motility and transit
- Increased visceral sensitivity
"I'm afraid that your irritable bowel syndrome has progressed. You now have furious and vindictive bowel syndrome."
Diet affects IBS

- 60% IBS patients believe food triggers symptoms
- Patients restrict their diet to prevent or improve their symptoms
- Minimal evidence to support diet therapies
- Diet therapy can be expensive
- Insufficient evidence to suggest true food allergies cause IBS
- Lactose and fructose intolerance more prevalent
Diet affects IBS
FODMAPs
Fermentable oligo-, di-, monosaccharides and polyols

FODMAPs
“prebiotics”
Poorly absorbed carbohydrate

Increased bacterial fermentation
SCFA more osmotic effects
Increased gas production
Luminal distention
Acceleration GI transit

Osmotic effects

IBS symptoms
Bloating
Abdominal pain
Change in bowel consistency
FODMAPs

- Australian controlled, crossover study of 30 IBS patients, 8 non-IBS patients followed for 21 days
  - Non-blinded, 83% pts identified the FODMAP diet
  - Low FODMAP diet patients had low overall symptom scores

- FODMAPs are a significant trigger of meal-related symptoms
- Not meant to be a long term diet
- Responders should gradually reintroduce FODMAPs to identify trigger foods with direction of a dietician
### Common Foods Containing FODMAPs

<table>
<thead>
<tr>
<th>EXCESS FRUCTOSE</th>
<th>LACTOSE</th>
<th>FRUCTANS</th>
<th>GALACTANS</th>
<th>POLYOLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Fruits</td>
<td>&gt; Milk</td>
<td>&gt; Vegetables</td>
<td>&gt; Legumes</td>
<td>&gt; Fruits</td>
</tr>
<tr>
<td>apples, pears,</td>
<td>casein,</td>
<td>artichokes,</td>
<td>chickpeas,</td>
<td>apples,</td>
</tr>
<tr>
<td>nashi, mangoes,</td>
<td>whey,</td>
<td>asparagus,</td>
<td>lentils,</td>
<td>apricots,</td>
</tr>
<tr>
<td>prunes, and</td>
<td>lactose</td>
<td>Brussel's</td>
<td>kidney,</td>
<td>cherries,</td>
</tr>
<tr>
<td>pear juice,</td>
<td>in milk</td>
<td>sprouts,</td>
<td>beans,</td>
<td>lollies,</td>
</tr>
<tr>
<td>watermelon</td>
<td>in yogurt</td>
<td>cabbage,</td>
<td>baked</td>
<td>carrot,</td>
</tr>
<tr>
<td>&gt; Sweeteners</td>
<td>&gt; Cheeses</td>
<td>onion,</td>
<td>beans.</td>
<td>pineapple,</td>
</tr>
<tr>
<td>fructose, high</td>
<td>soft and</td>
<td>spring</td>
<td>&gt; Cereals</td>
<td>&gt; Vegetables</td>
</tr>
<tr>
<td>fructose, corn</td>
<td>creamy</td>
<td>onions (white, green,</td>
<td>wheat and</td>
<td>artichokes,</td>
</tr>
<tr>
<td>syrup</td>
<td>cheese)</td>
<td>shallots)</td>
<td>and rice)</td>
<td>mushrooms,</td>
</tr>
<tr>
<td>&gt; Large total</td>
<td>&gt; Cereals</td>
<td>&gt; Fruits</td>
<td>when eaten</td>
<td>&gt; Sweeteners</td>
</tr>
<tr>
<td>fructose dose</td>
<td>wheat and</td>
<td>watermelon,</td>
<td>in large</td>
<td>sorbitol (E420),</td>
</tr>
<tr>
<td>concentrated fruit</td>
<td>rye when eaten in</td>
<td>castor sugar,</td>
<td>servings (e.g.:</td>
<td>maltitol (E421),</td>
</tr>
<tr>
<td>sources, large</td>
<td>small to medium</td>
<td>dates, figs,</td>
<td>bread, pasta,</td>
<td>xylitol (E400),</td>
</tr>
<tr>
<td>serves of fruit</td>
<td>servings</td>
<td>prunes</td>
<td>carrots,</td>
<td>maltitol (E555),</td>
</tr>
<tr>
<td>diet, fruit</td>
<td>(e.g.:</td>
<td></td>
<td>broccoli,</td>
<td>isomalt (E953)</td>
</tr>
<tr>
<td>juice</td>
<td>dates,</td>
<td>carrots)</td>
<td>garlic,</td>
<td></td>
</tr>
<tr>
<td>&gt; Honey</td>
<td>scottish</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cottage</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Suitable on a Low-FODMAP Diet

<table>
<thead>
<tr>
<th>FRUIT</th>
<th>VEGETABLES</th>
<th>MILK PRODUCTS</th>
<th>GRAIN FOODS</th>
<th>OTHERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Fruit</td>
<td>bamboo shoots, grapefruit, blueberries, grapes, honeydew melons, kiwi, lemons, limes, mandarins, oranges, pawpaw, passionfruit, tangerines, raspberries, rock melons, strawberries, tangelos</td>
<td>&gt; vegetables</td>
<td>&gt; cereals</td>
<td>&gt; Sweeteners</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; milk</td>
<td></td>
<td>sorbitol (E420), maltitol (E555), isomalt (E953)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; cheese</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; yogurt</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; ice cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; milk substitutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; ice cream substitutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; butter substitutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; milk-free spread</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; sugar-free bread</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; glucose-free bread</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Components of FODMAPs

- Excess Fructose
  - Honey, apples, pears, peaches, mangos, fruit juice, dried fruit
- Fructans
  - Wheat (large amounts), rye (large amounts), onions, garlic, leeks, zucchini
- Lactose
  - Milk (cow, goat, sheep), custard, ice cream, yogurt, soft unripened cheese (cottage, ricotta)
- Sorbitol
  - Apricots, peaches, artificial sweetener additive, sugar-free gum and candy
- Raffinose
  - Lentils, chickpeas, legumes, green beans, cabbage, Brussel sprouts, asparagus
Gluten

- Protein in wheat, barley, rye
- 34 IBS patients with a history of gluten sensitivity studied with a placebo-controlled “re-challenge” trial x 6 weeks
  - Gluten worsened:
    - Pain
    - Bloating
    - Stool consistency
    - “tiredness”
- 45 patients with IBS-D GCD vs GFD
  - Gluten increased frequency of bowel movements per day
Psychosocial therapies are more effective than usual medical treatment for global IBS symptoms

- Psychotherapy
- Cognitive-behavioral therapy
- Hypnotherapy

- Limited availability of resources (time, cost and therapists)
Tricyclic Antidepressant Therapy

- Tricyclic antidepressants (TCA)
  - Reduce global IBS symptoms and abdominal pain
  - Less effective in relieving bowel symptoms
- Side effect profile may be beneficial in treating bowel symptoms
- Anticholinergic effects, constipation and drowsiness
  - Patients with IBS-D
  - Patients with insomnia
Selective Serotonin Reuptake Inhibitor Therapy

- Selective serotonin reuptake inhibitors (SSRI)
  - Limited data, improves global IBS symptoms and abdominal pain
  - Less effective in relieving bowel symptoms
- Serotonin norepinephrine reuptake inhibitors not yet studied in large trials
- Side effect profile may be beneficial in treating bowel symptoms
  - Serotonin prokinetic effects in treating IBS-C
  - Patients with significant anxiety and IBS
Probiotics

- Improve global IBS sx, bloating and abdominal pain
- Most probiotics on the market have not been studied
- Strains and species vary
- No specific probiotic is recommended for IBS
Antispasmodics

- OTC
  - Peppermint oil
- Prescription
  - Hyoscyamine
  - Dicyclomine
Peppermint Oil

- Active ingredient L-menthol
- May relax smooth muscle and modulate pain
  - Thought to act on smooth muscle calcium channel antagonism
  - k-opioid agonism
  - anti-inflammatory effects
  - Serotonin 5HT3 receptor antagonism
Hyoscyamine and Dicylomine

- Assumed to reduce colonic smooth muscle spasm and contraction
- Low quality of evidence, not studied in RCTs
  - Improvement in global IBS symptoms
  - Improvement in abdominal pain
- Decreases exaggerated gastrocolonic reflex
  - Use with postprandial cramping and loose stools
- Use may be limited by anticholinergic effects
IBS-C

- **OTC**
  - PEG

- **Rx FDA approved therapies:**
  - Linaclotide
  - Lubiprostone

- **In trials:**
  - Plecanatide - Guanylate cyclase type-C receptor agonist
  - Elobixibat (CIC) - Ileal bile acid transporter inhibitor
  - Prucalopride (Restalor) (CIC) - 5-HT4 receptor agonist
Polyethylene Glycol (Miralax)

- Osmotic laxative
- 139 patients with IBS-C
  - 17g q D to TID vs placebo x 4 weeks
- Improves stool consistency and frequency
- No improvement in abdominal pain or bloating
Linaclotide (Linzess)

- Binds to guanylate cyclase-C receptor agonist
  - Increases secretion of chloride in the intestines
  - Possible suppression of visceral afferent pain fibers, reducing hypersensitivity
- 2 trials with 1,604 patients with IBS-C
  - 290 mcg drug vs placebo x 12 weeks
  - Trial 31: 33.6% vs 21.0%
  - Trial 302: 33.7 vs 13.9%
- Composite end point included 30% improvement in abdominal pain and increase in at least 1 SBM over baseline
- Also improvement in bloating, fullness, cramping
Lubiprostone (Amitiza)

- Type-2 chloride channel activator
  - Increases the secretion of chloride, sodium, water in the lumen
- Prostaglandin derivative
  - Stimulate smooth muscle contraction and promote motility
- 1,171 patients with IBS-C
  - 8 mg drug vs placebo x 12 weeks
  - 17.9% vs 10.1%
ibs-d

- Anti-diarrheals
  - Loperamide
- 5-HT3 Antagonists
  - Alosetron and Ondansetron
- Affect microbiota:
  - Rifaximin
  - Probiotics
- Opioid receptor agonist/antagonist
  - Eluxadoline
- Bile acid sequestrants
- Anti-diarrheals
- Anti-spasmodics
Loperamide

- Opioid receptor agonist
  - Inhibits peristalsis and prolongs intestinal transit time
  - Limited penetration of blood brain barrier
- Effective in reducing frequency and increases consistency
- May be used prophylactically in IBS-D
- Low quality of evidence in IBS trials
  - No improvement in global IBS symptoms
Alosetron (Lotrenex)

- 5-HT3 antagonist
  - Improves bowel urgency and global IBS symptoms
- Voluntarily withdrawn from market due to reports of colonic ischemia and dose dependent severe constipation
- Re-introduced with a risk management program
  - 0.5 mg BID for female IBS-D patients who have not responded to conventional therapy
Ondansetron (Zofran)

- 5-HT3 antagonist, less potent in blocking 5-HT3 receptor than alosetron
- Widely used as anti-nausea medication without assoc ischemic colitis
- Inexpensive, safe generic drug

- Primary efficacy
  - Improved stool consistency and increased gut transit time
- Secondary efficacy
  - Improved urgency, frequency, bloating and global IBS symptoms
  - Did NOT improve pain
120 patients with IBS-D, placebo controlled crossover study

4 mg qD to TID (titration) vs placebo x 5 weeks, 2 weeks washout, then crossover x 5 weeks
Rifaximin (Xifaxan)

- Non-absorbable antibiotic
  - Reduce bacterial load and change the bacterial composition in the gut
- Trial TARGET 1 and 2:
  - 1,260 patients with non IBS-C
  - 550 mg drug TID vs placebo x 14 days, followed for 4 weeks
    - 40.7% vs 31.7% improvement in Global IBS symptoms
    - 40.2% vs 30.3% improvement in IBS-related bloating
Rifaximin (Xifaxan)

- TARGET 3
- 2,438 patients with IBS-D
- Open label, received 550 mg drug x 14 days
  - 44.1% responded after 4 weeks
  - 64.4% had recurrent sx over 18 weeks, median time 10 weeks
    - Retreated vs placebo, up to 2 retreatments
- Urgency and bloating improved with both retreatments
- Abdominal pain and stool consistency improved with first retreatment
Eluxadoline (Viberzi)

- Minimally absorbed mixed opioid receptor modulator
- 2,427 patients with IBS-D
  - 75 mg drug or 100 mg drug or placebo x 26 weeks
    - Week 12: 27.0% vs 16.7%, Week 26: 31.0% vs 19.5%
  - Endpoint of 30% improvement in IBS-related pain and Bristol
    Stool Form Score of <5 on 50% of days
  - Improvement is secondary endpoints of bowel frequency, urgency, IBS global symptoms, IBS QOL scores
  - Rare reaction of SOD spasm in patients without a gallbladder and pancreatitis assoc with heavy alcohol use
Conclusion

- IBS diagnosis is based upon careful history with minimal testing
- Clear, symptom-based diagnosis of IBS reduces patient anxiety
- Fear of GI symptoms leads to reduced quality of life
- Management should be individualized and targeted to address symptoms
- Open, effective communication
- Create a follow-up plan
- Recognize that IBS is a continuum of symptoms
- Therapies may change over time
Future

- Rome IV criteria released 2016
  - Functional bowel disorders are a continuum of symptoms rather than a separate disease state
  - Subtypes may change over time
“Looks like the doctor confirmed my diagnosis. It’s not just your bowel. Everything about you is irritable.”
<table>
<thead>
<tr>
<th>Table 1</th>
<th>PICO Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Intervention</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>Placebo</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>Lubiprostone</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>Micobell</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>Misty</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>Splia</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>Microcystis</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>PROs top</td>
</tr>
<tr>
<td>Adults with IBD</td>
<td>Lyophilise</td>
</tr>
</tbody>
</table>

Gastroenterology 2014;147:1149-1172
References

- Biesiekierski et al. Am J Gastroenterology 2011;106(3):508-514