Overview

- Irritable bowel syndrome: definitions and assessment
- Pathophysiology: no shortage of mechanisms
- Bacterial hypothesis of IBS
- Small Intestinal Bacterial Overgrowth (SIBO)
- Post-infectious IBS
- Dietary modification to treat IBS

Irritable Bowel Syndrome

- Irritable bowel syndrome (IBS) is the most common chronic medical condition worldwide.
- 15-20% of all populations suffer from IBS
- The cause has remained unknown: "diagnosis of exclusion"
- Accounts for 30% of all health related costs (direct and indirect) in gastroenterology; >$50B estimated costs.
Definition of IBS?
IBS: Rome III Criteria

- Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in form of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Still a diagnosis of exclusion

Longstreth GF et al. Gastroenterology. 2006;130:1480-1491.

Hot off the press: Rome IV IBS criteria

- Recurrent abdominal pain, ave ≥ 1 day per week in the last 3 months, associated with 2 or more of the following:
  - Related to defecation
  - Associated with change in frequency of stool
  - Associated with a change in form or appearance of stool

- Criteria fulfilled for the last 3 months with symptom onset 6 months before diagnosis

Lacy '16 Gastroenterol 150: 1393

Potential Differential Diagnoses for IBS

GI Conditions
- Functional abdominal pain
- Functional constipation or diarrhea
- Functional dyspepsia
- Celiac disease
- IBD
- Microscopic colitis
- Infectious colitis
- Ischemic colitis
- Colon cancer
- Food intolerances
- Bile malabsorption

Non-GI Conditions
- Food intolerances
- Endocrinologic conditions
  - Thyroid disease
  - Diabetes
- Gynecologic conditions
  - Endometriosis
  - Ovarian cancer
- Neurologic conditions
  - Parkinson's
- Medications
Alarm Features for Organic Disorders

- Age ≥50 years old
- Blood in stools
- Nocturnal symptoms
- Weight loss (unintentional)
- Change in symptoms
- Recent antibiotics
- Family history of organic GI disease

If alarm features are present, investigate and treat appropriately

Proposed Pathophysiology of IBS-FBD

Genetics
Visceral hyperalgesia
IBS-FBD
Inflammation
Abnormal brain-gut interactions

Pathophysiology of IBS

- Enteric Neuropathy
- Gastrointestinal (GI) Motor Disturbances
- Visceral hypersensitivity
- Abnormal central processing of sensations
- Psychological disturbances

Adapted from Rome Foundation Functional GI Disorders Specialty Modules.
Sensory Thresholds are Altered in Patients With IBS

Brain-gut-enteric microbiota axis

Pharmacologic Management of IBS
**STRATEGY**: Treat the CAUSE

- **BRAIN-GUT AXIS**
- **SEROTONIN**
  - Agonist/Antagonist
- **DYSMOTILITY**

**IBS**

**ACUTE GASTROENTERITIS**
- Salmonella, E. coli, Campylobacter, ...

**IBS**

**SIBO**

**Model**: Integrating gut microbiota into IBS-FBD pathophysiology

- Altered behavior → Psychiatric co-morbidity
- Chronic gut dysfunction → Symptom generation
- Low grade inflammation → Infection, antibiotics, or other factors (e.g., stress)
- Perturbation of the microbiota

**Bacterial Hypotheses in IBS**

**ACUTE GASTROENTERITIS**

**IBS**

**SIBO**
SIBO - What is it?

Colon: 10^10 cfu/mL
Small Bowel: ~ 0 cfu/mL
Duodenum: 10^3 cfu/mL
Jejunum: 10^1 cfu/mL
Ileum: 10^2 cfu/mL
Cecum: 10^1 cfu/mL

Diagnosing SIBO

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Specific Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breath testing</td>
<td>Lactulose Breath Test</td>
</tr>
<tr>
<td></td>
<td>13C Xylose Breath Test</td>
</tr>
<tr>
<td></td>
<td>Glucose Breath Test</td>
</tr>
<tr>
<td></td>
<td>Sucrose Breath Test</td>
</tr>
<tr>
<td></td>
<td>Sorbitol Breath Test</td>
</tr>
<tr>
<td>Culture</td>
<td>Small bowel aspirate and culture</td>
</tr>
<tr>
<td>Empiric Approach</td>
<td>Test, treat and re-evaluate</td>
</tr>
</tbody>
</table>

Carbohydrate Breath Testing for SIBO

Saad RJ, Chey WD. Gastroenterology. 2007;133:1763-1766.
Lactulose Hydrogen Breath Test

Breath Testing in IBS

Forest plot of all age-sex matched studies

Small Bowel Culture in IBS vs. controls


Posserud, et al, Gut, 2007;56:802

P<0.05

P<0.001

N=165 IBS, 26 controls

Passerud, et al, Gut, 2007;56:802-8
Expectation: Antibiotics should improve SIBO-IBS

Rifaximin improves symptoms in non-selected IBS

TARGET 1 and 2: Primary and Key Secondary End Points for Entire 3-Month Study Period

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Odds Ratio (95% CI)</th>
<th>P for Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: Weekly global IBS symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGET 1</td>
<td>1.35 (1.10-1.66)</td>
<td>.005</td>
</tr>
<tr>
<td>TARGET 2</td>
<td>1.52 (1.32-1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Combined</td>
<td>1.44 (1.19-1.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Key secondary end point: Weekly IBS-related bloating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGET 1</td>
<td>1.28 (1.05-1.57)</td>
<td>.10</td>
</tr>
<tr>
<td>TARGET 2</td>
<td>1.56 (1.15-2.10)</td>
<td>.003</td>
</tr>
<tr>
<td>Combined</td>
<td>1.42 (1.15-1.75)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Target 1 and 2: Daily Adequate Relief of Global IBS Symptoms for Non-C IBS Patients

- 1260 patients from 179 sites
- NNT ~11

Meta-Analysis: Rifaximin Achieves Global IBS Symptom and Bloating Improvement

- NNT 11.0 – 11.4
- Pooled safety analysis (vs placebo)
  - No serious TEAE
  - No GI TEAE
  - No infectious TEAE
  - No C. difficile colitis
- High concentration to GI tract (<0.4% systemic absorption)
- In vitro activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria

Meta-Analysis of Rifaximin Efficacy on Global IBS Symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghaneie et al</td>
<td>3.70 (0.62, 14.06)</td>
</tr>
<tr>
<td>Prinental et al</td>
<td>4.32 (1.44, 10.39)</td>
</tr>
<tr>
<td>Lambert et al</td>
<td>1.36 (0.50, 3.67)</td>
</tr>
<tr>
<td>Target 2</td>
<td>1.52 (1.00, 2.31)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.47 (1.02, 2.14)</td>
</tr>
</tbody>
</table>

Methane Produced by Gut Methanogen Methanobrevibacter smithii Is Associated with Constipation and Slows Gut Motility

- 28% reducing on CH₄
- 64% normalizing on CH₄
- 100% normalizing on CH₄

Methane produced by gut methanogen Methanobrevibacter smithii is associated with constipation and slows gut motility.
• 32 C-IBS patients with positive methane breath test
• Randomized to either neomycin 500 mg BID ± rifaximin 550 mg TID x 7 d
• Rifax + neo subjects who eradicated methane (<3 ppm) had lower constipation severity score 4 weeks after treatment, compared to those who did not (p = 0.02)

Symptom Severity 7-Days after Antibiotic Treatment


Bacterial Hypotheses in IBS

ACUTE GASTROENTERITIS

IBS

S I B O

IBS after waterborne outbreak of AGE

• Livestock fecal contamination of water supply in Walkerton, Ontario in 2000
• AGE affecting >2000 locals
• Campylobacter jejuni and E. coli 0157:H7 most common
• Questionnaires administered 2 years later

IBS after Salmonella outbreak

- S. enteritidis outbreak in Catalonia village, 2002
- 1243 persons affected
- Self administered questionnaires every 3 months by affected and cohort from same county
- 1 year RR for having IBS symptoms: 7.8 (3.1-19.7)

Travelers with diarrhea

- Is traveler’s diarrhea (TD) associated with new onset IBS (PI-IBS)?
  - Travelers visiting Israeli clinic enrolled before trip abroad
  - Questionnaires before, during and after (6-7 months) trip
  - 405 subjects finished study
- Results:
  - 118 travelers with TD → 13.6% developed IBS
  - 287 travelers with no diarrhea → 2.4% developed IBS
  - Relative risk of developing PI-IBS = 5.7

Risk of PI-IBS in young, healthy population

- Reviewed records of Defense Dept Medical Surveillance System (all medical encounters of active duty US military personnel)
- Follow acute gastroenteritis patients who grew out Campylobacter, Salmonella, Shigella, or Yersinia
- Match each patient with 4 healthy controls
  - 1,753 pathogen-specific gastroenteritis cases followed for median of 3.8 years
  - Incidence (per 100,000 person-years) of PI-IBS was 3.0, compared to 1.0 for control group
Meta-analysis: Risk of PI-IBS increases 7-fold after AGE

Prevalence: 9.8% IBS in cases vs 1.2% IBS in controls

OR (95% CI)

<table>
<thead>
<tr>
<th>Study (year/bacteria)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ji (2005/Shigella)</td>
<td>2.6 (1.9-3.5)</td>
</tr>
<tr>
<td>Mearin (2005/Salmonella)</td>
<td>10.7 (5.5-23.4)</td>
</tr>
<tr>
<td>Okhuysen (2004/Unspecified)</td>
<td>16.1 (10.5-25.6)</td>
</tr>
<tr>
<td>Wang (2004/Unspecified)</td>
<td>6.5 (3.9-10.0)</td>
</tr>
<tr>
<td>Skrypej (2005/Unspecified)</td>
<td>3.7 (2.0-6.5)</td>
</tr>
<tr>
<td>Parry (2010/Bacterial NOS)</td>
<td>4.9 (2.3-10.8)</td>
</tr>
<tr>
<td>Rodriguez (2010/Bacterial NOS)</td>
<td>11.3 (4.3-30.4)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td>7.1 (4.8-10.0)</td>
</tr>
</tbody>
</table>

*Systematic review of 8 studies involving 589,011 subjects, follow-up ranged from 3 to 12 months.


Impact of foodborne illness

US foodborne pathogens per year cause:
- 48 million illnesses
- >100,000 hospitalizations
- 3000 deaths

• Unreported
• Underappreciated
• Further sequelae

Increasing globalization of our food supply
Treatment options for PI-IBS

Treatment trials specifically for PI-IBS are lacking. Gradual recovery seen in pooled studies, over several years. Consider:

• Test for SIBO: treat accordingly, e.g. Rifaximin
• 5-ASA: small RCT reported at DDW 2008
• Cholestyramine: BA malabsorption from pathogen damage to TI and R-column
• Probiotics: adjunctive therapy
• Standard IBS treatment:
  - General dietary laxative avoidance
  - Loperamide
  - Low dose TCA
  - Serotonin antagonists
• No improvement in IBS sx or enteroendocrine cell # after prednisolone 30mg/d x 3 weeks (Dunlop, et. al. ’03, APT 18:77)

Psychological factors in PI-IBS

- More “life events” and hypochondriasis independently predictive of PI-IBS
- Scores for somatisation, neuroticism and anxiety also significantly elevated
- Higher levels of perceived stress, somatisation, anxiety, and negative illness beliefs
- Higher likelihood of reporting acute gastroenteritis?
**Elevated intra-epithelial T-cells in rectal mucosa following C. jejuni infection and PI-IBS**

![Graph showing elevated intra-epithelial T-cells](image)

Similar trends in immune cells of the lamina propria

Spiller, et al. '00, Gut 47: 804

**Increased serotonin-positive enteroendocrine cells in PI-IBS rectal biopsies**

![Images showing increased serotonin-positive enteroendocrine cells](image)

- Serotonin (5-HT) predicted to increase frequency of loose stools, may promote hyperalgesia and homing of inflammatory cells
- Elevated serotonin release after a test meal in PI-IBS (Dunlop, et al. '05, CGH 3:349)

Spiller, et al. '00, Gut 47: 804

**Acute GI infection: the most important risk factor for IBS**

![Diagram showing various factors contributing to IBS with Acute GI Infection as the primary risk factor](image)
The new paradigm?

IBD
Microscopic colitis
IBS
Normal

Increasing inflammation

NORMAL

ACUTE GASTROENTERITIS

90%

10%

COMPLETE RECOVERY

-GENETIC SUSCEPTIBILITY
-ABNORMAL HOST RESPONSE
-TOXIN INTENSITY

FUNCTIONAL GI DISEASES?

IBS
Mechanism/Sequence/Main

Food Poisoning
Bacterial Toxin
Autoimmunity
 Gut Neural Damage
Bacterial Overgrowth
IBS
Could all IBS be post-infectious?

Take home points...so far

- IBS is currently a symptom-based disorder: Abdominal discomfort + bowel irregularity.
- IBS is probably not a single disease entity, but rather likely consists of several different disease states and pathophysiology. Established data suggests alterations in:
  - Gastrointestinal motility
  - Visceral sensitivity
  - Brain-gut regulation
- More recent evidence indicates that excess bacteria in the small bowel (SIBO) may underlie a significant fraction of IBS cases. Alterations in the normal balance of gut microbes may also underly IBS. Treatment with antibiotics often leads to symptom resolution in select patients.
- Post-infectious IBS occurs in susceptible individuals with a prevalence of ~10% after acute gastroenteritis.
- IBS may be associated with immune activation and an autoimmune mechanism secondary to gut infections.
- Alterations in the gut microbiome may play an increasingly recognized role in IBS.

Food and IBS: lots of confusion

- >60% of IBS patients report worsened sx after meals
- Common suspects: wheat, corn, dairy, coffee, tea, and citrus fruits
- Swedish study (Bohn'14, AJG)
  - Incompletely absorb carbs: dairy, beans, lentils, apple, flour, plum
  - Biogenic amines: beer/wine, salami, cheese
  - Histamine-releasing: beer/wine, milk, pork
  - Fried and fatty foods
- Norwegian study (Monsbakken '06, Eur J Clin Nutr)
  - 70% had sx related to food intake
  - 62% limited or excluded food from diet
  - 12% had inadequate diet
- Mayo survey of IBS or dyspepsia pts (Saito '05, AJG) vs HC
  - No differences in consumption of frequently implicated "culprit" foods
    - E.g. wheat, dairy, caffeine, fructose beverages
- ACG IBS guidelines 2009: "insufficient evidence that food allergy testing or exclusion diets are efficacious" (grade 2C)
What are FODMAPs?
Fermentable oligo-, di-, monosaccharides and polyols

- **Excess Fructose**: Honey, apples, pears, peaches, mangoes, fruit juice, dried fruit
- **Fructans**: Wheat (large amounts), rye (large amounts), onions, leeks, zucchini
- **Sorbitol**: Apricots, peaches, artificial sweeteners, artificially sweetened gums
- **Raffinose**: Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes

**Absorptive patterns of different FODMAPs**

<table>
<thead>
<tr>
<th>Absorptive pattern</th>
<th>FODMAP</th>
<th>Mechanism</th>
<th>Assessed in individual's capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly absorbed in the small intestine</td>
<td>Lactose (lactulose)</td>
<td>Scurvy of disaccharides</td>
<td>Breath hydrogen test, lactulose breath test</td>
</tr>
<tr>
<td>Slowly absorbed in the small intestine and poorly absorbed in the colon</td>
<td>Fructose, fructans, fructo-oligosaccharides, galacto-oligosaccharides</td>
<td>Glucose-6-phosphate dehydrogenase deficiency</td>
<td>Breath hydrogen test, breath carbon dioxide test, breath hydrogen breath test, glucose breath test, fructose breath test</td>
</tr>
<tr>
<td>Poorly absorbed in the colon</td>
<td>Fructose, galacto-oligosaccharides, lactulose</td>
<td>High capacity fructose malabsorption</td>
<td>Breath hydrogen test, breath carbon dioxide test, breath hydrogen breath test, glucose breath test, fructose breath test</td>
</tr>
</tbody>
</table>

**How FODMAPs Can Lead to GI Symptoms**

- Diarrhea
- Distention

Shepherd et al. 2013, AJG 108:707
Improved symptoms after 4 weeks of low FODMAP diet

- (Not shown) ITT analysis: more low FODMAP pts (13/19, 68%) reported adequate sx control compared to control diet (5/22, 23%), P = 0.005.
- Low FODMAP pts had better reduction in mean daily sx score (incidence + severity) for bloating, borborygmi, urgency and overall

Overall GI symptoms improve in IBS cohort on low FODMAP

- Randomized, controlled cross over study. 30 IBS, 8 HC subjects
- 21 days low FODMAP or "typical" Australian diet. 21 d washout period before crossing over to other diet.
- Almost all food provided during intervention diet period. (< 0.5 gm FODMAP per meal goal on LFD)
- Daily symptoms rated on 0-100mm VAS. Ave score last 14 d in red.
- 70% IBS subjects had sx improvement >10 mm.

Specific symptoms and satisfaction with stool consistency improved on low FODMAP

- Abdominal pain, bloating, and flatus had similar improvements as overall GI sx in IBS.
- Dissatisfaction with stool consistency improved in both IBS-D and IBS-C subjects (47.8 vs 25.9, typical vs LFD)
- Fecal characteristics including water content, did not change significantly with diet.
Implementing low FODMAP diet trial

- Empiric strategy to eliminate or significantly restrict the most likely offending foods
- Limits false positives from bias or placebo effect seen in single food sequential elimination strategies; limits false negatives if patient has multiple food reactions/intolerances.
- Full elimination of FODMAPs not the goal
- If available, trained dietician is important partner
- Rechallenge examples:
  - Mannitol: ½ cup mushrooms
  - Sorbitol: 4 dried apricot halves
  - Lactose: 250 cc milk or 200 gm yogurt
  - Fructose: 2 teaspoons honey
  - Fructans: 2 slices wheat bread or 1 clove garlic
  - GOS: ½ cup lentils or legumes
Additional recommendations for implementing dietary changes

• Food and symptom diary may help identify trigger foods.
• Food reactions usually occur within 3 days of eating the food, and should occur consistently on >3 separate occasions.
• Specificity important in multi-component foods (e.g. pizza)
• Assessment of diet change should take at least 2 weeks; if no clear benefit, it didn’t work or try repeating.
• Elimination/exclusion of identified foods need not be permanent. Attempt to re-introduce the food should be made after 3-6 months.

Parting thoughts to chew on…

• Dietary manipulation keeps pts engaged in improving their sx. Added placebo effect?
• Most IBS pts attribute sx to specific foods. Testing or blinded challenges often contradict pt perceptions.
• Likely multiple mechanisms: poorly absorbed molecules? Microbiota changes?
• Low FODMAP diet improves IBS sx in several recent studies.