Irritable Bowel Syndrome

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Project ECHO
March 12, 2015
Definition of Irritable Bowel Syndrome (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:
  1. Improvement with defecation
  2. Onset associated with a change in frequency of stool
  3. Onset associated with a change in form of stool
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separate hard lumps, like nuts</td>
</tr>
<tr>
<td>Type 2</td>
<td>Sausage-like but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
<td>Like a sausage but with cracks in the surface</td>
</tr>
<tr>
<td>Type 4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges</td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces</td>
</tr>
</tbody>
</table>

World prevalence of IBS

- Canada: 12%
- New Zealand: 17%
- UK: 22%
- Nigeria: 30%
- Japan: 25%
- Australia: 12%
- China: 23%
- US: 10–20%
- Sweden: 13%
- Belgium: 8%
- Denmark: 7%
- Netherlands: 9%
- Germany: 12%
- France: 20%
- Spain: 13%
- Belgium: 8%
- Sweden: 13%
- Nigeria: 30%
- Australia: 12%
- New Zealand: 17%
Overall prevalence of IBS is greater in females

Drossman et al, Dig Dis Sci 1993; 38: 1569
Prevalence by IBS subgroups

Survey respondents (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-constipation</td>
<td>6.7</td>
<td>3.5</td>
</tr>
<tr>
<td>IBS-diarrhea</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>IBS-alternating</td>
<td>5.6</td>
<td>4.7</td>
</tr>
</tbody>
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Overall
Impact of IBS

- In a survey conducted by the International Foundation for Functional Gastrointestinal Disorders:
  - 42% of respondents reported having symptoms for 10 years or more
  - 43% reported symptoms as 'severe', 40% described them as 'moderate'
  - two-thirds of IBS sufferers describe their symptoms as extremely or very bothersome
## IBS patients suffer from multiple symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% IBS patients that suffer once a week or more</th>
<th>General US population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas / gas pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Straining with BM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain / discomfort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard / lumpy stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete evacuation after BM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloating / distension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to have BM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn / acid reflux</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden urges to have BM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentage of IBS patients and the general US population suffering from various symptoms once a week or more.
IBS consultation pattern in US

- Specialists: ~1%
- Primary care: ~25%
- Non-healthcare seekers: ~75%
- Healthcare seekers: ~25%
Who treats IBS?

IBS is a common diagnosis in primary care and gastroenterology practices.

- Primary care: 12% IBS, 88% other diagnoses
- Gastroenterology: 28% IBS, 72% other diagnoses
Economic burden of IBS in the US

IBS

Hypertensive disease

Stroke

Arthritis

Diabetes

Billions of dollars

Healthcare costs
Productivity costs
Costs associated with IBS

• **DIRECT costs to healthcare system:** diagnostic tests, physician visits, ER visits, hospitalizations and medications

• **INDIRECT costs:** reduced productivity due to absenteeism (missed days from work) and presenteeism (decreased productivity while at work), travel to consultations, co-payments or over-the-counter preparations

• **INTANGIBLE costs:** decreased quality-of-life
Total cost of IBS

• Total annual cost of IBS is:
  up to $30 billion

• indirect costs ~ $20 billion per annum

• direct costs ~ $1.7–10.5 billion per annum
Pathophysiology of IBS

Enhanced perception

Vagal nuclei

5-HT

Sympathetic

Altered motility

Visceral hypersensitivity
Visceral sensitivity in IBS patients

- IBS patients report
  - More intense pain than control subjects in response to rectosigmoid balloon distension
  - Pain at a lower volume/pressure of rectosigmoid distension than control subjects

- Visceral hypersensitivity
  - Is more pronounced in IBS patients
Effect of rectosigmoid balloon distention on pain in IBS patients vs control

Patients reporting pain (%)

- IBS patients (n = 25)
- Healthy controls (n = 20)

Rectosigmoid balloon volume (mL)

p<0.05
Etiology of Hypersensitivity

- Post infectious
- Bacterial overgrowth (SIBO)
- Hereditary component
- Bile acid malabsorption
- Food allergy and food intolerance
- Centrally mediated sensitization
- Possible inflammatory component
Associated Syndromes

- Fibromyalgia
- CFS
- Chronic pelvic pain
- Interstitial cystitis
- Non-cardiac chest pain
- Headache
- Anxiety/Depression
- Eating disorders
- TMJ disorder
Characteristics of Functional Syndromes

- Female predominance
- Absence of specific objective diagnostic tests
- Fluctuating clinical course
- Modulating effect of stress on symptoms
- Associated psychological co-morbidity
- Increased health care utilization
- Impaired quality of life
- Non-restorative sleep
- Physicians find patients “difficult”
There Is Significant Overlap Among GI Motility Disorders

- 29% of GERD patients have Chronic Constipation
- Diagnoses can shift from one disorder to another over time
- Possible common pathophysiological mechanisms

Serotonin (5-HT) and motor activity

Adapted from Grider et al, Gastroenterology 1998; 115: 370

Enterochromaffin cells release 5-HT

5-HT

5-HT\textsubscript{4} Receptors

Interneurons in the myenteric plexus

Orad motor neurons (contraction)
Ach

CGRP

Sensory neuron

Caudad Motor neurons (relaxation)
VIP / NO

Movement of gut content

Proximal

Distal

Enterochromaffin cells release 5-HT
**Summary of hypotheses on the pathophysiology of IBS**

- IBS is characterized by changes in motility in response to environmental or enteric stimuli.
- Visceral hypersensitivity is well documented in IBS patients.
- Serotonin, which has both motility and sensory modulating properties, could represent a common factor linking the symptoms of IBS.
Approach to the diagnosis of IBS

Identify Current Primary Symptoms

- Abdominal discomfort
- Constipation
- Diarrhea

Look for 'Red Flags' Based on:
- History
- Physical exam
- Laboratory tests

Perform Selected Physical and Diagnostic Tests to Rule Out Organic Disease

Make a Positive Diagnosis

Initiate a Treatment Plan Based on Symptoms

Follow Up
# Prevalence of Organic Disease in Patients Meeting Symptom-Based Criteria for IBS

<table>
<thead>
<tr>
<th>Organic GI Disease</th>
<th>IBS Patients</th>
<th>General Pop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis/IBD</td>
<td>0.51-.098%</td>
<td>0.3-1.2%</td>
</tr>
<tr>
<td>Colorectal CA</td>
<td>0-0.51%</td>
<td>0-6%</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>4.67%</td>
<td>0.25-0.5%</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>0.1.5%</td>
<td>5-9%</td>
</tr>
<tr>
<td>Lactose malabsorption</td>
<td>22-26%</td>
<td>25%</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>78%</td>
<td>?</td>
</tr>
</tbody>
</table>
Identify Red Flags

**History**
- Unintentional weight loss
- Onset in older patient (>50 years)
- Family history of cancer or IBD
- Pain that regularly awakens from sleep at night

**Physical**
- Abnormal exams
- Rectal bleeding
- Positive FOBT

**Labs**
- ↓ HGB
- ↑ WBC
- ↑ ESR/CRP
- Abnormal chemistry
- ↑ or ↓ TSH
- Positive stool studies
- Positive celiac serology
IBS: An enduring diagnosis

Most have no change in diagnosis after initial evaluation

112 consecutive Olmstead County residents first diagnosed with IBS during 1961–63.

No change in diagnosis: 97%
Treatment Goals IBS

- Overall Relief (impact on patient’s overall well-being)
- Symptom specific relief
  - Abdominal pain
  - Bloating
  - Constipation
  - Diarrhea
Approach to Therapy

- Elicit patient’s expectations of therapy
- Clarify realistic goals of therapy
- Develop a therapeutic partnership
- Provide continuity of care
Dietary advice

- Patients often relate their functional symptoms to certain foods
- Dietary restrictions are common
- Food allergens: milk, eggs, fish, nuts, shellfish
- Food intolerance: lactose, caffeine, wheat, FODMAPs, gas-forming vegetables
Non pharmacologic therapy

- Cognitive behavioral therapy is more effective than placebo at relieving individual IBS symptoms
- Relaxation therapy: down regulates ANS
- Hypnotherapy: may affect motility
- Psychotherapy: insight about life events role in symptoms
- Yoga
- Meditation
- Diet
- Exercise
- Reassurance!!!
Therapies for individual symptoms of IBS

Abdominal pain / discomfort
- Antispasmodics
- Tricyclics
- Analgesics
- SSRIs

Bloating and distention
- Dietary modifications
- Antispasmodics
- Anti-gas agents
- Digestive enzymes
- Antibiotics
- Tegaserod
- Probiotics

Diarrhea
- Loperamide
- Diphenoxylate/Atropine
- Opium
- Fiber
- Cholestyramine
- Antibiotics
- Alosetron

Constipation
- MOM
- Fiber
- Laxatives
- PEG
- Lactulose
- Lubiprostone
- Linaclotide
Bulking Agents

- 13 RCTs
- Psyllium but not bran more effective than placebo at relieving global IBS symptoms
- Effective at improving stool bulk and frequency as well as easing passage of stool
- May worsen bloating and discomfort
- Useful in IBS with both constipation and diarrhea
Osmotic laxatives

- 2 RCTs in IBS
- Lactulose (Kristalose)
- PEG (Miralax, Nulytely, Golytely)
- Sorbitol
- Milk of magnesia
- No improvement of global symptoms of IBS
- Decreases stool transit time
- Can worsen bloating
- Effective in chronic idiopathic constipation (CIC)
Antispasmodic agents

- 3 RCTs of low quality with varying results
- Dicyclomine (Bentyl)
- Hyoscyamine (NuLev, Levsin, Levbid)
- Donnatal
- Scheduled vs prn
- High incidence of anticholinergic side effects including constipation
Peppermint Oil

- 5 RCTs
- May relax smooth muscle, attenuate visceral hypersensitivity and modulate pain sensation
- Superior to placebo in relieving global symptoms of IBS
- Administered as an enteric-coated preparation in dose range from 187-225mg tid
Anti-gas medications

- Ineffective
- Simethicone
- Activated charcoal
- Enzyme supplements (Beano, Lactaid)
Probiotics

- 8 RCTs: Improve global symptoms, pain, bloating and flatulence
- Species: Lactobacillus, Bifidobacterium, Streptococcus, Saccharomyces boulardii
- Forms: acidophilus, yogurt (Activia), tablet (Align, Flora-Q, VSL#3)
- Issues: formulation, standardization, cost, purity, safety
Antidepressants

- Tricyclics and SSRIs are more effective than placebo at relieving global IBS symptoms
- Amitriptyline, Nortriptyline, Desipramine, Doxepin, Fluoxetine, Paroxetine, Sertraline
- Some studies show improvement in abdominal pain
- Anticholinergic side effects common in tricyclics
- May be more efficacious in those with associated anxiety or depression
Anti-diarrheals

- Loperamide (Imodium)
- Diphenoxylate/atropine (Lomotil)
- Cholestyramine (Questran, Colestid)
- Tincture of opium
- 3 RCTs only on Loperamide
- Not more effective than placebo at relieving global IBS symptoms
- Effective in treating diarrhea
Serotonin antagonists

- Alosetron (Lotronex), 5HT3 antagonist
- Effective in relieving global IBS symptoms in females with diarrhea
- Previously withdrawn from market due to increased occurrence of ischemic colitis
- Restricted use in women with severe IBS/diarrhea who have failed standard treatment
Serotonin Agonists

- Tegaserod (Zelnorm), 5HT4 agonist
- More effective than placebo at relieving global IBS symptoms in female IBS patients with constipation
- Restricted use due to possibility of ischemic colitis
- Increases motility and reduces visceral hypersensitivity
- Side effects: diarrhea, headache
Chloride Channel Activators

- Lubiprostone (Amitiza)
- Prostaglandin E1bicyclic fatty acid
- Activates type 2 chloride channels, increasing intestinal fluid secretion
- Increases intestinal motility and softens stool
- Indicated for IBS-C and CIC
- Side effects: nausea, headache, diarrhea
- Dosage: 8mcg(ibs-c) or 24mcg(cic) bid
Guanylate Cyclase Agonists

- Linaclotide (Linzess)
- Guanylate cyclase-C agonist that acts locally within the intestinal epithelium
- Increases intestinal fluid secretion and decreases activity of pain sensing nerves
- Indicated for adults with IBS-C and chronic idiopathic constipation
- Side effects: diarrhea
- Dosage: 290mcg(IBS-C) or 145mcg(CIC) qd
- Contraindicated in children up to 6 years and should be avoided in ages 6-17
Summary of IBS Therapy

- Multiple medications for specific symptoms
- Limited evidence based therapy
- Antibiotics, probiotics, antidepressents, Alosetron, Lubiprostone and Tegasarod provide global relief of symptoms
- Doctor-patient relationship crucial component