Lady with abdominal pain

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History

- F/ 30
- Chinese
- Accountant
- Non smoker
- Non drinker
- Unremarkable past medical history
- No history of GI surgery
- No family hx of GI cancer/ inflammatory bowel disease
- No known history of psychiatric illness
History

- Presented to private practitioner for
  - Colicky central abd discomfort for 6 months
    - 1-2 times per week
    - occur at day time
    - Relieved by defecation
    - Bloating
  - Constipation
    - BO 2-3 times per week with hard stool
    - No blood in stool but occ mucus passage
- No weight loss
Investigation

- WCC 4
- Hb 12
- Plt 300
- ESR 10
- CRP < 5
- TSH N

- Cr 80
- Na 140
- K 3.5
- ALT 30
- Alb 40
- FBS 6
ROME III CRITERIA

- Recurrent abdominal pain or discomfort
  - with onset at least 6 months prior to diagnosis
  - at least 3 day/months
  - in the last 3 months
  - associated with 2 or more of the following

1. Relieved with Defecation
2. Onset Associated with a Change in Frequency of Stool
3. Onset Associated with a Change in Form (Appearance) of Stool
ROME III CRITERIA

Symptoms that cumulative support the diagnosis:
- Abnormal stool frequency
  - > 3 bowel movement per day or < 3 bowel movement per week
- Abnormal stool form
  - Lump/hard or loose watery stool
- Abnormal stool passage
  - Straining, urgency or feeling of incomplete emptying
- Passage of mucus
- Bloating or feeling of abdominal distension
Subtype of IBS

- **IBS with constipation**
  - hard or lumpy stools >25% & loose or watery stools <25% of bowel movement

- **IBS with diarrhoea**
  - loose or watery stools >25% of bowel movement & hard or lumpy stools <25%

- **Mixed IBS**
  - loose or watery stools >25% of bowel movement & hard or lumpy stools >25%
“Red flags”

- Anemia
- Fever
- Persistent diarrhea
- Rectal bleeding
- Weight loss

- New onset of symptoms in patients 50+ years of age
- Nocturnal symptoms of pain and abnormal bowel function
- Family history of GI cancer, inflammatory bowel disease, or celiac disease

Progress

- OGD: normal
- Colonoscopy: haemorrhoid
- CT abd: normal
- Refer to HA hospital because of persistent symptoms
- What can we offer to her?
Current management components of IBS

- Education
- Reassurance
- Lifestyle modification
- Fiber
- Pharmacological treatment
- Alternative treatment

Current management of IBS

- Establish a positive diagnosis
- Build up therapeutic physician-patient relationship
- Reassure patient that there is no serious organic disease or alarming symptoms

Kaptchuk. BMJ. 2008;336:999.
Therapeutic relationship

- Compare placebo effect and patient-health care provider interaction

- 262 patients
- Group 1: waitlist
- Group 2: shame acupuncture with little interaction with HCP
- Group 3: shame acupuncture with much more interaction with HCP

Global improvement

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: P<0.001; 95% CI 0.18 to 0.90 for limited v waiting list; 0.32 to 1.11 for augmented v limited

Adequate relief

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: P<0.001; 95% CI 2.7 to 30.7 for limited v waiting list; 3.2 to 32.3 for augmented v limited

Symptom severity

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: P<0.001; 95% CI -7.9 to 31.2 for limited v waiting list; 16.2 to 63.2 for augmented v limited

Quality of life

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: P<0.001; 95% CI -2.1 to 3.2 for limited v waiting list; 1.7 to 8.8 for augmented v limited
Physical exercise

- 20-60 minutes of moderate to vigorous activity 3-5 days per week for 12 weeks

- Clinical improvement in severity of IBS symptoms and less likely of worsening of IBS symptoms

Johannesson E, Am J Gastroenterol 2011;106:915
## Dietary modification

### FODMAPs

- **Fermentable oligosaccharides, disaccharides, monosaccharides and polyols**

### Table: FODMAPs

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess fructose</td>
<td>Apple, mango, nashi, pear, tinned fruit in natural juice, watermelon, sweeteners</td>
</tr>
<tr>
<td>Lactose</td>
<td>Milk, milk from cows, goats or sheep, custard, ice cream, yogurt</td>
</tr>
<tr>
<td>Fructans</td>
<td>Vegetables: asparagus, beetroot, broccoli, brussel sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion, shallots, spring onion, cereals</td>
</tr>
<tr>
<td>Galactans</td>
<td>Legumes: baked beans, chickpeas, kidney beans, lentils</td>
</tr>
<tr>
<td>Polyols</td>
<td>Fruit: apple, apricot, avocado, blackberry, cherry, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon, vegetables: cauliflower, bell pepper, mushroom, sweet corn, sweeteners: sorbitol, mannitol, isomalt, maltitol, xylitol</td>
</tr>
</tbody>
</table>
Dietary modification

- Study on IBS patients on high FODMAPs diet has ↑GIs such as abd pain, bloating, flatus ¹

- Trial of low FODMAPs diet can be conducted for 4-6 weeks, follow by rechallenge of any potentially more well absorbed carbohydrates e.g. fructose, lactose ²

- Exclusion diets however have not been definitely shown to be of benefit, their routine use outside of a clinical trial is not recommended³

1. Ong DK, J Gastroenterol Hepatol 2010;25:1366-73,
AJG 2009 Vol 104 Supp 1
Current management components of IBS

- Education
- Reassurance
- Lifestyle modification
- Fiber
- Pharmacological treatment
- Alternative treatment

Fiber

- Insoluble Fiber
  - Wheat Bran, Corn fiber

- Insoluble fiber undergo minimal change in GI tract
  → form faecal mass & reduce colonic transit time
  → improve constipation but may worsen abd pain

C.J.Bijkerk. *Aliment Pharmacol Ther* 2004;19;241-51
Fiber

- **Soluble Fiber**
  - Psyllium, Calcium polycarbophil

- Soluble fiber dissolves in water and form gels
  - fermented by colonic bacteria
  - short chain fatty acid
  - reduce colonic transit and intracolonic pressure
  - improved both constipation and possibly abd pain

C.J.Bijkerk. *Aliment Pharmacol Ther* 2004;19;241-51
Recent data favor use of Soluble fiber over insoluble fiber for IBS patients with improvement of global IBS symptoms and constipation.

Adverse event rare.

In clinical practice, sudden increase fiber intake may cause bloating, abdominal distension and flatulence.

Trial of fiber is reasonable in IBS-C patients with dosage titration to symptoms.

AJG 2009 Vol 104 Supp 1
Current management components of IBS

- Education
- Reassurance
- Lifestyle modification
- Fiber
- Pharmacological treatment
- Alternative treatment

Pharmacological therapy

- Pharmacological agents are only adjunctive
- Chronic use of drugs should be minimized
  - life long nature of disorder
  - lack of convincing therapeutic benefit
    - heterogeneous population
    - lack of disease markers
    - high placebo response rates

Antispasmodic agents

- Short term relieve abdominal pain, bloating, faecal urgency
- Intestinal smooth muscle relaxation e.g. mebeverine, pinaverine
- Anticholinergic or antimuscarinic properties e.g. hyoscine
- Evidence of long term efficacy not available
- S/E: dry mouth, dizziness, blurring of vision

AJG 2009 Vol 104 Supp 1
Antidepressant

- Tricyclic antidepressant, Serotonin reuptake inhibitor

- Analgesic properties independent of mood effects
  - Facilitation of endogenous endorphin release
  - Blockade of norepinephrine reuptake
  - Enhancement of descending inhibitory pathways
  - Blockade of pain neuromodulator

- TCA potential slow intestinal transit and may benefit in IBS-diarrhoea patient

- SSRI has potential prokinetic effect and may work better in IBS-Constipation patient
Antidepressant

- Systematic review showed both TCA and SSRI has improvement global symptoms control in IBS patient and appear to reduce abdominal pain

- No head to head comparison on TCA vs SSRI on symptom control, but SSRI seems better tolerated

- Data on long term safety and tolerability limited in IBS patients

- Lower dose required than in treatment for depression

- Delayed onset of action, titrate after 3-4 wks interval

1. Ford AC. Am J Gastroenterol 2008;103: supp1
2. AJG 2009 Vol 104 Supp 1
Antidiarrheals

Loperamide

- Only antidiarrhoeal drugs studied in RCT for IBS-D
- Improve stool frequency and consistency
- But no effect on overall IBS symptoms
- Long term safety and tolerability lacking

AJG 2009 Vol 104 Supp 1
Laxative

- Laxative has not been studied in RCT in IBS adults patient

- Small trial in IBS-C adolescent patient show PEG improve in stool frequency but not abdominal pain
# Summary of symptomatic treatment

<table>
<thead>
<tr>
<th></th>
<th>Lower abdominal pain</th>
<th>Bloating</th>
<th>Altered stool form</th>
<th>Altered stool passage</th>
<th>Urgency</th>
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</thead>
<tbody>
<tr>
<td>Antispasmodic&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Tricyclic antidepressants and SSRIs&lt;sup&gt;2&lt;/sup&gt;</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Laxative&lt;sup&gt;3&lt;/sup&gt;</td>
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<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Fiber&lt;sup&gt;4&lt;/sup&gt;</td>
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<td></td>
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<td>X</td>
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</tr>
<tr>
<td>Antidiarrheals&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Novel therapy
Physiological distribution of 5HT

CNS – 5%

GI tract – 95%
- enterochromaffin cells
- neuronal

Alosetron

- 5-HT₃ receptor antagonist
- Reduce colonic tone
- Blunt the gastrocolic reflex
- Decrease visceral sensation
- Improved global IBS symptoms in female and male IBS-D
- Approved by FDA in Feb 2000 for IBS-D female patients

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Alosetron

- **Adverse event:**
  - constipation *dose dependent*
  - ischaemic colitis *dose independent*

- Withdrawal from market in November 2000

- Approve in June 2002 for chronic severe IBS-D patients who failed to respond to conventional therapy

*AJG 2009 Vol 104 Supp 1*
Alosetron

- **Recommended dose**: 0.5mg bd

- **Can increase to 1mg bd after 4 week if**
  - drug well tolerated
  - symptoms not adequately controlled

- **Discontinue if**
  - s/s of severe constipation or ischaemic colitis
  - no clinical response after 1mg bd for 4 weeks
Tegaserod

- Partial 5-HT$_4$ receptor agonist
- Stimulate release of neurotransmitter
- Increase colonic motility
- Improved global IBS symptoms in female IBS-C/IBS-M

AJG 2009 Vol 104 Supp 1
Tegaserod

Enterocytes

ECs

5-HT

ACh, Substance P

VIP, PACAP, NO

activation

Tegaserod
**Tegaserod**

- **Adverse event:**
  - diarrhoea
  - cardiovascular events e.g. MI, unstable angina/ stroke

- **Withdrawal from market in March 2007**
Lubiprostone

- Selective C-2 chloride channel activators

- C-2 chloride channel
  - lower capacity chloride channel
  - physiological regulation of paracellular permeability and intracellular volume

- Poorly absorbed in the systemic circulation and work topically in the small intestine

- Approved by FDA for chronic idiopathic constipation at dose of 24 μg BD

Am J Physiol Cell Physiol 2004;284:c1173-83
Lubiprostone

- Phase 3 study for IBS-C with lubiprostone 8mcg bd vs placebo for 12 week

*Abdominal pain, bloating, constipation

Aliment Pharmacol Ther 2009;29:329-341
Lubiprostone

- Approved IBS-C female patient
- Side effects: nausea, diarrhoea
- No long term safety data
- Reserved for IBS with severe constipation with unsuccessful treatment

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Linaclotide

- Peptide agonist of Guanylate cyclase 2C

- Guanylate cyclase-2C
  - intestinal transmembrane receptor
  - responsible for chloride, bicarbonate and fluid secretion in intestinal lumen

Forte.LR. Regul Pept. 1999;85:25-39
Linaclotide

- Phase 3 study for IBS-C with linaclotide 290mcg daily vs placebo for 12 weeks

\[ \geq 30\% \text{ Worst abdominal pain reduction for } \geq 6/12 \text{ weeks (secondary)} \]

- Placebo: 37.5%
- Lina 290 mcg: 50.1%***

\[ \text{NNT} = 7.9 \]

\[ \text{Increase } \geq 1 \text{ CSBM from baseline for } \geq 6/12 \text{ weeks (secondary)} \]

- Placebo: 29.6%
- Lina 290 mcg: 48.6%****

\[ \text{NNT} = 5.3 \]

\[ \text{FDA end point (primary)} \]

- Placebo: 21.0%
- Lina 290 mcg: 33.6%****

\[ \text{NNT} = 7.9 \]

[Am J Gastroenterol 2012;107:1714-24]
Linaclotide

- Approved by FDA for IBS with constipation
- Side effects: diarrhoea
- No long term safety data
- Reserved for IBS with severe constipation with unsuccessful treatment
Miscellaneous
Rifaximin

- Nonabsorbable antibiotic
- Approved by FDA for traveller’s diarrhoea at dose of 200mg bd x 3days
- Higher dose use in trial for IBS-D patient at does 400mg tid x 10-14 days
- With improvement in bloating, abd pain, diarrhoea
- May be due to suppression of gas producing bacteria

Forte.LR. Regul Pept. 1999;85:25-39
Rifaximin

- Short term course provide symptoms relieve for 10-12 weeks
- Symptoms may recur after 3-9 months
- No data to support the long term safety and efficacy

Forte.LR. Regul Pept. 1999;85:25-39
**Probiotic**

- Microorganism that have beneficial properties to the host
- *E.g* Lactobacillus, Bifidobacterium

**Potential benefit**
- Suppression of growth/ epithelial binding by pathogenic bacteria
- Ferment carbohydrate without gas production
- Modulation of pain perception through induce expression of opioid or cannabinoid receptor

- Improved IBS symptoms particular bloating & flatulence

*BMJ*. 2012;345
Probiotic

- Short term heterogenous study
- Modest magnitude of benefit
- Lactobilli alone not effective
- Trends toward bifidobacteria and certain combination of probiotics

BMJ. 2012;345
Peppermint oil

- Antispasmodic properties
- Smooth muscle relaxation via calcium channel blockade
- Provide short term relieved in abdominal pain
- Efficacy based on few small studies
- Few adverse event report
Herbal therapy

- Different herbal preparation has been shown to improve global IBS symptoms
  - STW 5 (Iberogast), fixed combination of hydroethanolic herbal extracts

- Cannot combine to evaluate in meta-analysis due variable component, preparation, purity

- Also concerns of potential hepatotoxicity

- Further work need before any recommendation made

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Psychological therapy

- Different psychological therapies have been shown to improve global IBS symptoms.
- Cognitive behavioral therapy, dynamic psychotherapy, hypnotherapy, except relaxation therapy.
- Unknown exact biological mechanism.
- Most of the study performed on patients refractory to standard treatment, so efficacy as first-line treatment uncertain.
- Best reserve for more refractory patients.

AJG 2009 Vol 104 Supp 1, GUT 2007;56:1770-98
MANAGEMENT OF IBS

Symptom Features

- Constipation
- Diarrhea
- Pain/Gas/Bloat

Mild
- Education, reassurance, lifestyle modification
- fiber

Moderate
- Laxative
- Loperamide
- Antispasmodic

Severe
- Lubiprostone
- Linaclootide
- Alosetron
- Rifaximin
- Antidepressant
- Psychological therapy
- Probiotics

Gut 2007;56:1770-98
IBS is a chronic medical condition characterized by abdominal pain, diarrhea or constipation, bloating, passage of mucus and feelings of incomplete evacuation.

Precise etiology of IBS is unknown and therefore treatment is focused on relieving symptoms rather than "curing disease."
Take Home Points

- Cornerstone of treatment is a successful patient-physician therapeutic relationship, education and reassurance
- Specific pharmacological therapies are determined by individual patient symptoms
- Life-style and dietary modifications may relieve symptoms
- Psychological therapy may consider for refractory patients
THANK YOU