FUNCTIONAL GASTRO-INTESTINAL DISORDERS – UPDATE ON CURRENT TREATMENT MODALITIES

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Department of Medicine
Functional Esophageal Disorders
Functional Gastro-Duodenal Disorders
  Functional Dyspepsia
Functional Bowel Disorders
  Irritable Bowel Syndrome
  Functional Bloating Syndromes
Functional Abdominal Pain Syndromes
Functional Gallbladder & Sphincter of Oddi Disorders
Functional Ano-rectal Disorders
Childhood Functional GI Disorders
Functional Esophageal Disorders
Functional Gastro-Duodenal Disorders
  - Functional Dyspepsia
Functional Bowel Disorders
  - Irritable Bowel Syndrome
  - Functional Bloating Syndromes
Functional Abdominal Pain Syndromes
Functional Gallbladder & Sphincter of Oddi Disorders
Functional Ano-rectal Disorders
Childhood Functional GI Disorders
Definitions FD & IBS
Conditions to consider & Investigations
FD & IBS: Scale of the problem
Pathophysiology
Current treatments
Treatment Algorithm
Treatment Failures
Future of FD & IBS
Functional Dyspepsia
Clinical Definition

- **Dyspepsia**
  - Derived from the Greek duspepsi: dus-, dys- = hard, with difficulty + pepsi, = digestion
  - Pertains to “chronic or recurrent pain or discomfort centered in the upper abdomen”
  - Gastro-duodenal in origin

ACG Dyspepsia Practice Guidelines 2005
AP Consensus FD JNGM 2012
Dyspepsia

Derived from the Greek duspepsi : dus-, dys- = hard, with difficulty + pepsi, = digestion

Pertains to “chronic or recurrent pain or discomfort centered in the upper abdomen” Discomfort is defined as a subjective negative feeling that is non-painful, and can incorporate a variety of symptoms including early satiety or upper abdominal fullness. Patients presenting with predominant or frequent (more than once a week) heartburn or acid regurgitation should be considered to have gastroesophageal reflux disease (GERD) until proven otherwise.

Functional Dyspepsia

Dyspepsia in the absence of detectable organic disease

Defined first in 1988

ACG Dyspepsia Practice Guidelines 2005
Uninvestigated Dyspepsia

- Functional Dyspepsia
- Organic Causes

XB Li Chin J Dig Dis 2005
Shanghai, China

31% 69%

AC Kwan JGH 2003
SE Asia

43% 57%

CT Wai GIE 2002
Singapore

79.5% 20.5%
Dyspepsia

- Beware Alarm Symptoms
  - unintended weight loss
  - progressive dysphagia
  - recurrent or persistent vomiting
  - history of GI bleeding or anemia
  - family history of gastric cancer
  - new onset in > 40 vs 45-50 year olds
Dyspepsia: Investigational Algorithm

- Consider in a Dyspeptic Subject
  - medications
  - gastro-oesophageal reflux disease
  - peptic ulcer disease
  - hyper and hypothyroidism
  - electrolyte imbalances
  - chronic renal failure
  - parasitic infestations
  - Cancers/disorders of the GI and hepatobiliary tract
  - chronic pancreatitis
Uninvestigated dyspepsia for 3 months or longer

Exclude evident causes of dyspepsia by history, eg. drugs

Alarm feature

No

Empirical treatment

Response after 4 weeks

Non-invasive test for H. pylori and treatment

Response after 4 weeks

Upper endoscopy

Finding(s) can explain the symptom(s)

Yes

Organic dyspepsia

No

If clinically indicated: stool parasites and occult blood, blood chemistry and/or abdominal imaging(s)

Result(s) can explain the symptom(s)

Yes

Functional dyspepsia

No
Functional Dyspepsia

Definition

- Rome III criteria
- Diagnosis of exclusion
- Presence of one or more chronic dyspepsia symptoms including post prandial fullness, early satiety, epigastric fullness or burning in the absence of any organic disease likely to explain the symptoms
- Duration criteria

Also called non ulcer dyspepsia or idiopathic dyspepsia

1. Tack et al Gastroenterol 2006
Two main sub types of FD

- Postprandial Distress Syndrome
  - Postprandial fullness and/or early satiation several times a week

- Epigastric Pain Syndrome
  - Intermittent pain/burning in the epigastrium, at least once per week
    - Not relieved by defaecation or passage of flatus
PREVALENCE OF FUNCTIONAL DYSPEPSIA in ASIA-PACIFIC

Singapore: 14.6% - 24.3%
- Chinese: 15% - 17.8%
- Malays: 13.4% - 28.3%
- Indians: 5.5% - 27.9%

Korea: 8% - 20.4%

China: 9.3% - 15.2%

Japan: 2.9% - 14.2%
FD in Asia Pacific Region

- FD encompasses epigastric/upper abdominal bloating
  - 69.9%-81.3% vs 42%\(^1\)
- Significant overlap with Irritable Bowel Syndrome
  - 24.8% FD $\rightarrow$ IBS
  - 31.5% IBS $\rightarrow$ FD, 23.7% IBS $\rightarrow$ FD
  - 26.5% PDS vs 18.3% EPS, P=0.039 $\rightarrow$ IBS\(^2\)
  - FD dysmotility like subtype

Heterogenous group of pathophysiological mechanisms have been implicated in the etiology \( ^{1,2} \)

- Delayed gastric emptying
- Antral hypo-motility
- Altered intestinal motility
- Decreased gastric accommodation
- H. Pylori infection/GE
- Excessive Gastric Acid Secretion
- Visceral hypersensitivity
- Psychological factors \(^2\)
- Genetics
- Role of Gut Microbiota
- Diet

1. Talley et al JGH 2009
2. Hu et al Gastroenterol 2002
Management

- Reassurance
- Dietary modification $^{1,2}$
- H. Pylori eradication $^3$
- PPI $^{4,5}$
- Prokinetic agent
- Antidepressants $^6$
- Other Therapies

Heterogenous group of pathophysiological mechanisms have been implicated in the etiology\(^1,2\):

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- Psychological factors\(^2\)
- Genetics
- Role of Gut Microbiota
- Diet

Prokinetic Agents
- Buspirone

PPI
- Antidepressants
- Antibiotics
- FODMAPs

References:
1. Talley et al. JGH 2009
2. Hu et al. Gastroenterol 2002
Multiple studies demonstrating an association between Anxiety/Depression and FD

Experimentally induced anxiety in healthy subjects fed a test meal is associated with:
- increased epigastric symptom scores
- decreased gastric compliance
- Accommodation

Anxiety in subjects with FD associated with discomfort/pain threshold & gastric compliance and prolonged antral retention meal retention

Neuroimaging demonstrates the effect of anticipatory pain/anxiety on activation of the visceral pain pathways in the brain

Mood disorders influence gastric function through decreased vagal activity

1. WH HU, Wong WM APT 2002
2. B Geeraerts GastroE 2005
4. L Yaguez, GastroE 2005
5. SL Lorena JCG 2004
Early studies examined TCA
- Benefit over placebo

Venlafaxine SNRI
- RCT demonstrated no benefit, large drop puts in Rx group 44%
- ITT and PP no benefit
Antidepressants in FD
Hong Kong Data

Figure 1: Study Patient Flow Chart
## Table 1: Demographics of Study Patients (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Sertraline</th>
<th>Placebo</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>98</td>
<td>95</td>
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<tr>
<td>Age</td>
<td>43.0</td>
<td>41.6</td>
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<td>Sex (Male)</td>
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<td>27</td>
<td>1.000</td>
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<tr>
<td>Current smokers (%)</td>
<td>3.2</td>
<td>7.3</td>
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<td>Alcohol (%)</td>
<td>6.2</td>
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<td>H. pylori positive (%)</td>
<td>8.4</td>
<td>7.3</td>
<td>0.843</td>
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<tr>
<td>NSAID use (%)</td>
<td>3.1</td>
<td>2.6</td>
<td>1.000</td>
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<td>Predominant symptom (%)</td>
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<tr>
<td>Ulcer like</td>
<td>44.7</td>
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<tr>
<td>Dysmotility like</td>
<td>49.2</td>
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<tr>
<td>Reflux like</td>
<td>57.1</td>
<td>42.9</td>
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<tr>
<td>Non-specific</td>
<td>68.4</td>
<td>31.6</td>
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<tr>
<td>Mean dyspepsia score</td>
<td>Week 0</td>
<td>p-value</td>
<td>Week 4</td>
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<tr>
<td>----------------------</td>
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<tr>
<td>Setraline</td>
<td>25.83</td>
<td>0.124</td>
<td>22.59</td>
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<tr>
<td>Placebo</td>
<td>27.19</td>
<td></td>
<td>22.94</td>
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<tr>
<td></td>
<td>Default W4 (n)</td>
<td>Default W8 (n)</td>
<td>Reason for Default W8 (%)</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>Sertraline</strong></td>
<td>23</td>
<td>24</td>
<td>7 (16.3%)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>11</td>
<td>19</td>
<td>11 (25.6%)</td>
</tr>
</tbody>
</table>

*Represents percentage of all default patients*
One of the limitations of the study is the drop out rate, 17.6% at week 4 and 22.3% at week 8.

Factors including sertraline’s side effects, cultural bias in the Chinese population against a diagnosis of psychiatric or functional disorders.

Outcome is important given the limited therapeutic options available to the frontline clinicians treating functional dyspepsia.
Management

- Reassurance
- Dietary modification $^{1,2}$
- H.Pylori eradication $^3$
- PPI $^{4,5}$
- Prokinetic agent
- Antidepressants
- Other Therapies

No evidence to support any specific dietary intervention for FD

Dietary Advice given by 80% of clinicians Rx FD

Lactose restriction in lactose intolerance

IBS-FD overlap
  - FODMAP diet
    - Fermentable Oligo, Di-, Monosaccharides & Polyols

1. S Miura JGH 2011
2. VP Tan unpublished date
3. D Ong P Gibson JGH 2010
H Pylori Eradication

- Important
  - HPylori causes histological gastritis
  - Asia Pacific region
  - Post Infectious FD
- NNT 14\(^1\) however may be lower based on studies published in Chinese Journals

P Moyaeddi Cochrane Database SR 2006
X Jin Helicobacter 2007
Multiple studies support use in FD
- All Western data
- NNT 15

Single Asian RCT data suggests no benefit in FD as per Rome II criteria

RCT Uninvestigated Dyspepsia also suggest no benefit over placebo

Overlap with GERD
Prokinetic Agents

- Biologically plausible
- Small studies
- Cochrane analysis
  - Superior to placebo 57% vs. 47%
- Multiple agents

P Moyaeddi Cochrane Database SR 2006
Anti-Depressants

- Definitely if symptoms of clinical anxiety and/or depression
- Definitely if IBS overlap
- Consider in event of failure of other therapies
  - Must discuss short term side effects
  - Slow onset of effect
  - NK Talley with multicentre study TCA vs SSRI due 2013/2014
Gastric Emptying Studies

- Gastroparesis vs. Functional Dyspepsia
- 20-50% demonstrate delayed gastric emptying
- Meta-analyses demonstrated ~40% delayed gastric emptying in FD
- MRI vs Nuclear Medicine studies
- Prokinetics
Treatment Failures

- Manometry/pH/Impedance Studies
- Breath Testing
- FODMAPs diet
- Enrolment in studies
  - Dietary Therapies in FD
  - Novel Therapeutics in FD
Irritable Bowel Syndrome
ROME III

- Recurrent abdominal pain or discomfort associated with
- two or more of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in form (appearance) of stool
- Clinical divisions – IBS-C, IBS-D, IBS-M
Irritable Bowel Syndrome

- Beware Alarm Symptoms
  - unintended weight loss
  - altered bowel habit
  - change in stool form
  - history of GI bleeding or anemia
  - nocturnal symptoms
  - Fever, abnormal physical examination
  - family history of colon cancer
  - new onset in > 40 vs 45-50 year olds
Investigational Algorithm

- Microscopic Colitis
- Inflammatory Bowel Disease
- Gastro-intestinal Infections
  - Parasites
  - Tropical sprue
  - SIBO
- Neoplastic Disorders
**IBS diagnostic algorithm**

**Possible IBS**

- Recurrent abdominal pain, bloating, or other discomfort for ≥ 3 months associated with 1 or more of the following:
  - relief with defecation
  - change in stool form (show patient the Bristol Stool Scale)
  - change in stool frequency

**Alarm features**

- patient age 45 years or older
- blood in stools
- unintended weight loss
- nocturnal symptoms
- fever
- abdominal mass
- ascites
- family history of colorectal cancer
- presence of anemia

**Yes**

- Probable IBS

  - Explain IBS
  - Treat primary symptoms

  - New symptoms or alarm features (+)

  - Repeat visit within 6 weeks
  - Check for new symptoms
  - Review alarm features
  - Continue treatment as necessary or modify

**Laboratory results**

- anemia
- leukocytosis
- high ESR, CRP
- abnormal blood chemistry
- fecal occult blood positive

**Yes**

- New symptoms, alarm features, or refractory symptoms (+)

**No**

- Refer to gastroenterologist

- Repeat visit within 6 weeks
  - Check for new symptoms
  - Review alarm features
  - Still symptomatic

---

*Figure 1* Diagnostic algorithm for irritable bowel syndrome (IBS). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Prevalence of Irritable Bowel Syndrome in SE Asia

- Singapore: 8.6%
- China: 10.4-15.9%
- South Korea: 9-10.1%
- Japan: 1.2-31%
- Hong Kong: 3.6-6.6%
Prevalence of Irritable Bowel Syndrome in SE Asia

- Singapore: 8.6%
- China: 10.4-15.9%
- South Korea: 9-10.1%
- Japan: 1.2-31%
- Hong Kong: 3.6-6.6%

Prevalence 1-15%
Figure 1. Mechanisms Underlying the Irritable Bowel Syndrome (IBS).
A variety of peripheral mechanisms initiate perturbation of gastrointestinal motor and sensory functions and lead to IBS symptoms. Identification of the peripheral irritants provides an opportunity to prevent or reverse symptoms. CNS denotes central nervous system.
Visceral Hypersensitivity

Abnormal colonic transit
- IBS-C – 25% will have slowed colonic transit
- IBS-D – 15-45% have accelerated colonic transit

Luminal and mucosal factors activate immune, motor, and sensory mechanisms in the small intestine or colon
- Diet
- Intra-colonic bile acids
- Gut Microbiota
Visceral Hypersensitivity
Landmark study demonstrated through rectal barostat that subjects with IBS experienced more symptoms than controls to identical volumes of rectal distension. 

Multiple subsequent studies have confirmed these findings.

As many as one third of subjects with IBS will not demonstrate visceral hypersensitivity.

PET & MRI studies
- Enhanced activation

Comorbid Psychiatric Diagnoses

Psychosocial Factors

1. Mertz GastroE 1995
Meta-analysis demonstrated that low dose TCA or SSRI effective in IBS \(^1\)
- 12 studies
- RR of IBS symptoms persisting with antidepressants versus placebo was 0.66 (95% CI, 0.57 to 0.78)
- NNT was 4
- TCA for IBS-D
- SSRI for IBS-C
- SSRI for IBS-M

1. Ford GUT 2009
DIET
Carbohydrates ➔ FODMAPs

- Limited absorptive capacity and/or ability to hydrolyze glycosidic linkages leading to mal-absorption
- Selective reduction and escalation of lactose, fructose, fructan and sorbitol intake and its effect on gastro-intestinal function
- Low vs. High FODMAP diet
  - Unabsorbed carbohydrates/carbohydrate chains are metabolized by the colonic bacteria to short fatty acids, CO2, methane and H2
Malabsorption of sugars, such as lactose, fructose, and sorbitol ≠ IBS

Malabsorption of sugars, such as lactose, fructose, and sorbitol may exacerbate the symptoms of IBS

Prevalence across ethnic groups and races is unclear

- Chinese ~80% lactose malabsorbers, ~22% fructose malabsorbers

Distinction between mal-absorption and intolerance

Tan VP Submitted for Publication
<table>
<thead>
<tr>
<th>Excess Fructose</th>
<th>Lactose</th>
<th>Oligo-saccharides</th>
<th>Polyols</th>
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<tbody>
<tr>
<td><strong>Known</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Apples</td>
<td>• Milk</td>
<td>• Wheat products e.g. wheat bread, cakes, biscuits, wheat noodles</td>
<td>• Mushrooms</td>
</tr>
<tr>
<td>• Pears</td>
<td>• Butter</td>
<td>• Garlic/onions</td>
<td>• Watermelon</td>
</tr>
<tr>
<td>• Nashi pears</td>
<td>• Ice cream</td>
<td>• Beans e.g. red/green beans, soy beans</td>
<td>• Apples</td>
</tr>
<tr>
<td>• Honey</td>
<td>• Milk powder</td>
<td>• Cabbage</td>
<td>• Nashi pears</td>
</tr>
<tr>
<td>• Dried fruit e.g. grapes, dates</td>
<td>• Commercial sweet teas and coffees</td>
<td>• Watermelon</td>
<td></td>
</tr>
<tr>
<td><strong>Suspected</strong></td>
<td></td>
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</tr>
<tr>
<td>• Commercial sauces e.g. char sui sauce, oyster sauce</td>
<td></td>
<td>• Cabbage</td>
<td>• Fruit chews</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Watermelon</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Persimmon</td>
<td></td>
</tr>
</tbody>
</table>
Proteins

- Gluten implicated in the pathogenesis of non-celiac gluten sensitivity¹
- In IBS-D those receiving gluten had increased stool frequency and bowel permeability and reduced messenger RNA expression of tight-junction proteins in bowel mucosa ²
- In IBS with non-celiac gluten sensitivity, after controlling for FODMAPs no gluten effect was seen ³

1 Gibson AMJ 2011
2 Camilleri GastroE 2013
3 Gibson GastroE 2013
Other Macronutrients

- **FAT**
  - Small studies, conflicting results
  - Further studies required

- **Fiber**
  - Partial or total fermentation in the distal small bowel and colon leading to the production of short-chain fatty acids and gas
  - Soluble supplement such as ispaghula/psyllium
  - Exacerbates abdominal distension, flatulence, constipation, and diarrhea
Microbial interactions with intraluminal factors
Microbiota profile resulting in IBS is unknown
  - Suggests relative Firmicutes abundance and/or Bacteroidetes reduction seen in IBS
Probiotics
  - Meta-analysis\(^1\)
  - 19 RCT
  - 1650 IBS subjects
  - RR of IBS not improving=0.71; 95% CI 0.57 to 0.88)
  - NNT=4 (95% CI 3 to 12.5)
Limitations
  - Publication bias
  - Heterogenous studies
  - Effective species, strains, formulation uncertain

1. Moyaeddi Gut 2010
Rifaximin
- Minimally absorbed antibiotic
- Improvement in global IBS symptoms, bloating, stool consistency and abdominal pain

GE patients had increased risk of IBS-D
- 3.6 to 32% patients with acute GE develop PI-IBS during 3-12 month follow-up
- Danish study RR 4.85, 95% confidence interval (CI) 2.02-11.63. GE patients had increased risk of IBS up to 5 years post-exposure (RR 5.40, 95% CI 2.60-11.24)

1. Pimental NEJM 2011
2. Kowalcyk JE 2013
Establish Firm Diagnosis

Reassurance & Symptom Control

Laxatives ± fiber
Anti Spasmodic
Prokinetic
Lubipristone

Anti-diarrhoeal
Anti-spasmodic
Bile Acid Binders
Antibiotics

Anti-spasmodic
Prokinetic
Antibiotics

Hydrogen & Methane Breath Testing

Dietary Therapies

Anti Depressants

Clinical Trials
Future FD/ IBS

- Faecal Microbiota
  - Prebiotic
  - Probiotics
  - Synbiotics
  - Antibiotics
- Dietary Therapies
- Immuno-modulators
Thank you & Questions