

FUNCTIONAL GASTRO- INTESTINAL DISORDERS - UPDATE ON CURRENT TREATMENT MODIALITIES

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ROME III

- ▣ 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

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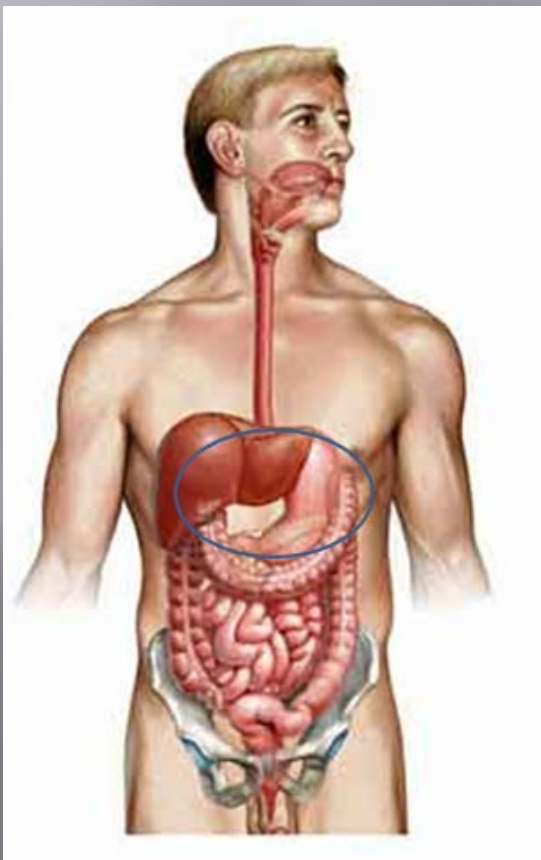
- ▣ Definitions FD & IBS
- ▣ Conditions to consider & Investigations
- ▣ FD & IBS: Scale of the problem
- ▣ Pathophysiology
- ▣ Current treatments
- ▣ Treatment Algorithm
- ▣ Treatment Failures
- ▣ Future of FD & IBS

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



Clinical Definition

▣ Dyspepsia

- ▣ Derived from the Greek duspepsi : dus-, dys- = *hard, with difficulty* + pepsis, = *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*

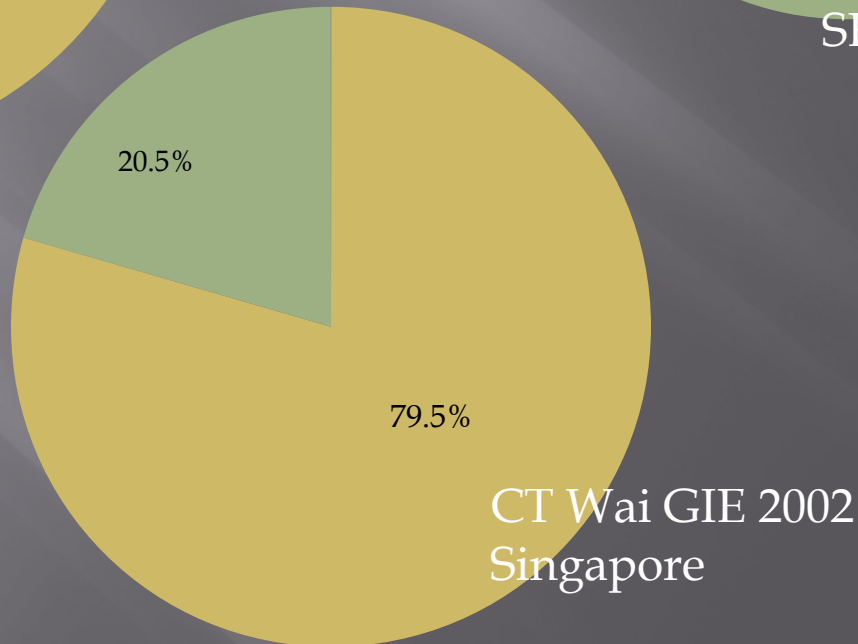
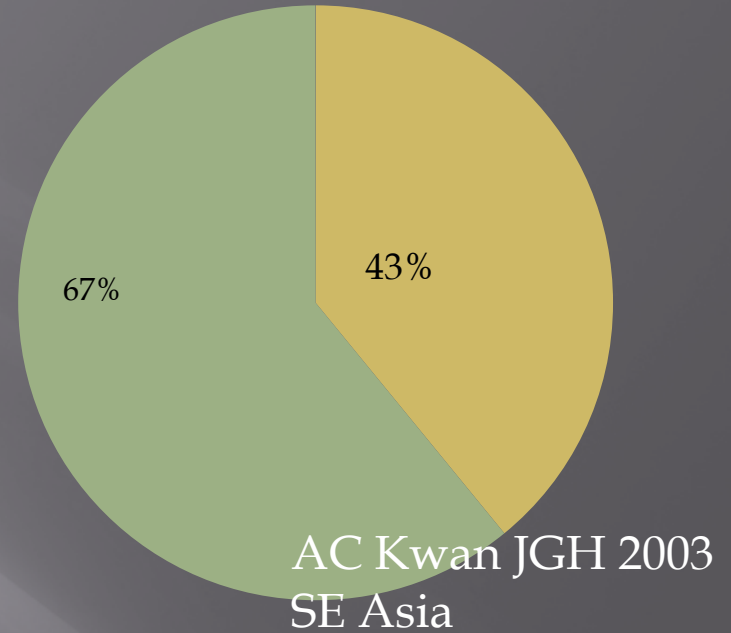
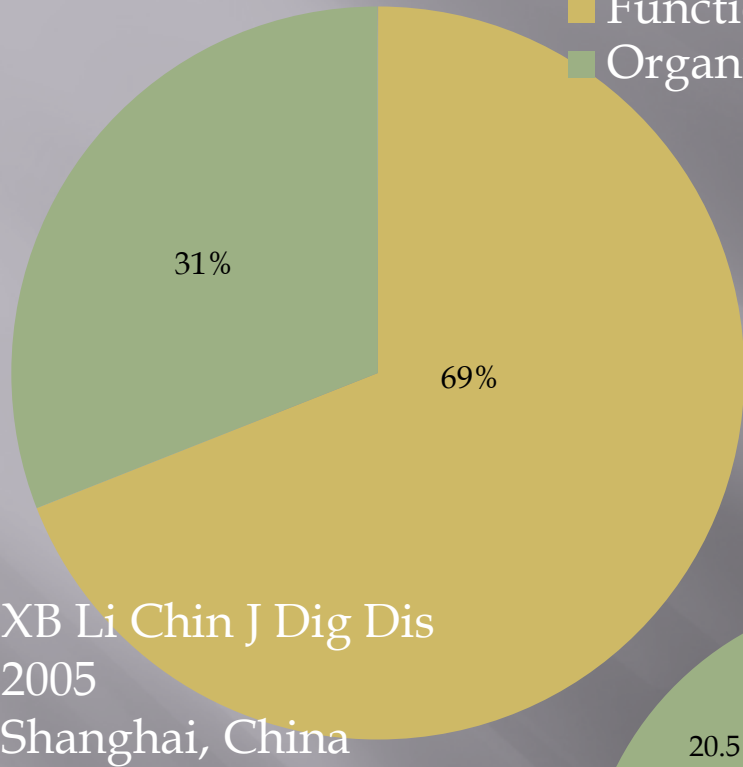
▣ Functional Dyspepsia

- ▣ Dyspepsia in the absence of detectable organic disease

▣ Defined first in 1988

Uninvestigated Dyspepsia

■ Functional Dyspepsia
■ Organic Causes

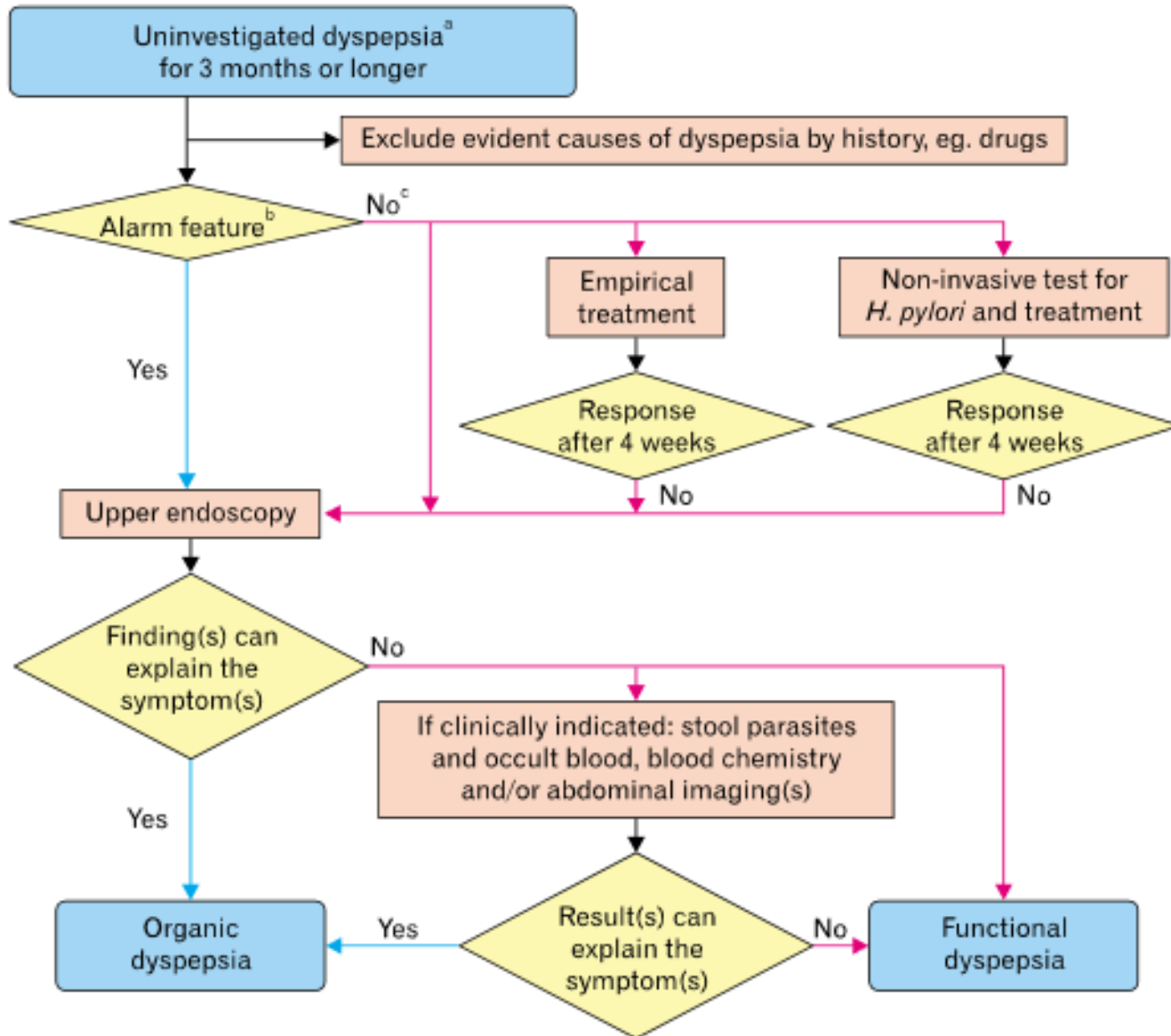


Dyspepsia

- ▣ 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



Research Definition

▣ Functional Dyspepsia

▣ Definition

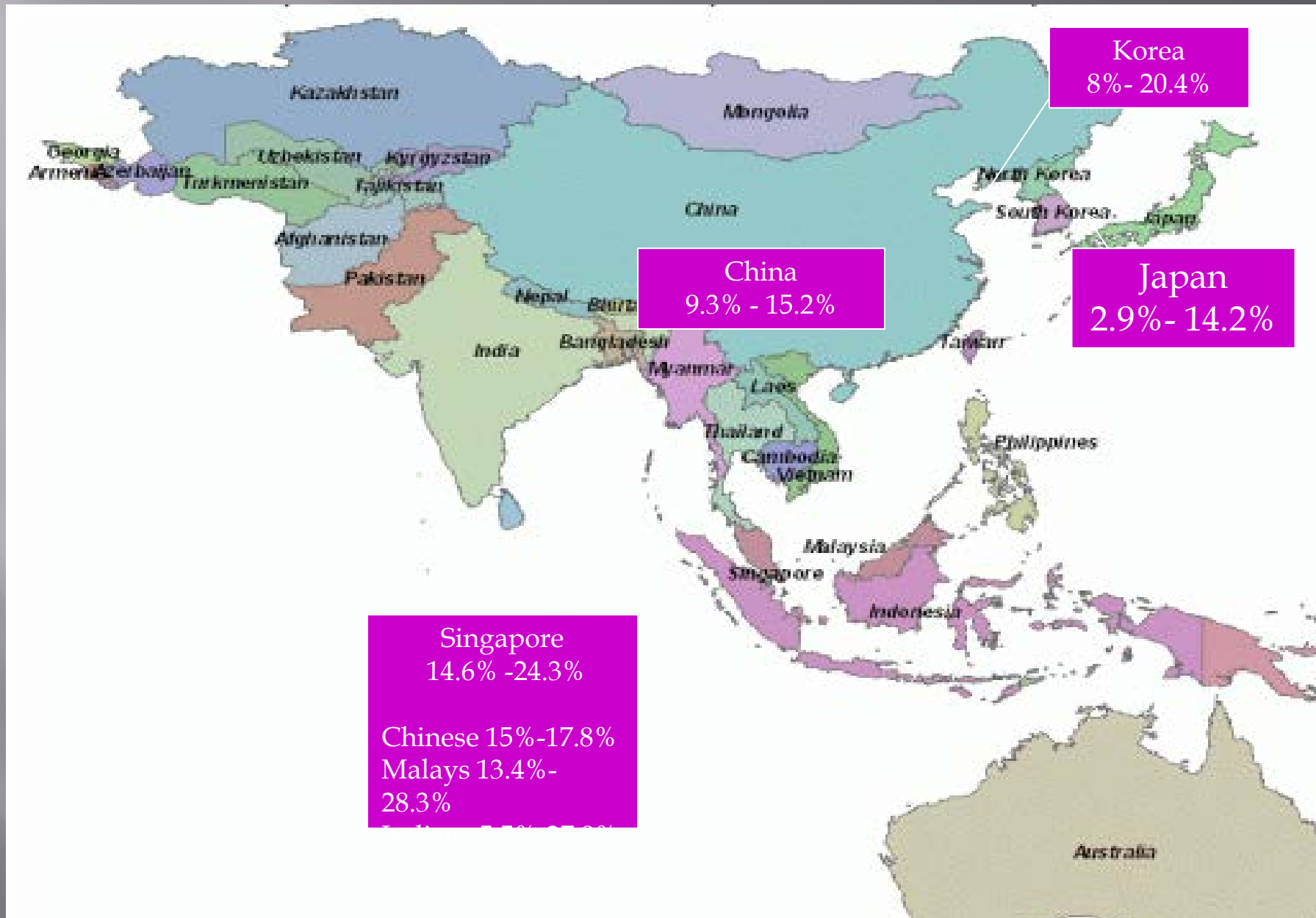
- ▣ Rome III criteria ¹
- ▣ Diagnosis of exclusion
- ▣ Presence of one or more chronic dyspepsia symptoms including post prandial fullness, early satiety, epigastric fullness or burning in the absence of any organic disease likely to explain the symptoms
- ▣ Duration criteria

- ▣ Also called non ulcer dyspepsia or idiopathic dyspepsia

1. Tack et al Gastroenterol 2006

Research Definition

- ▣ 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



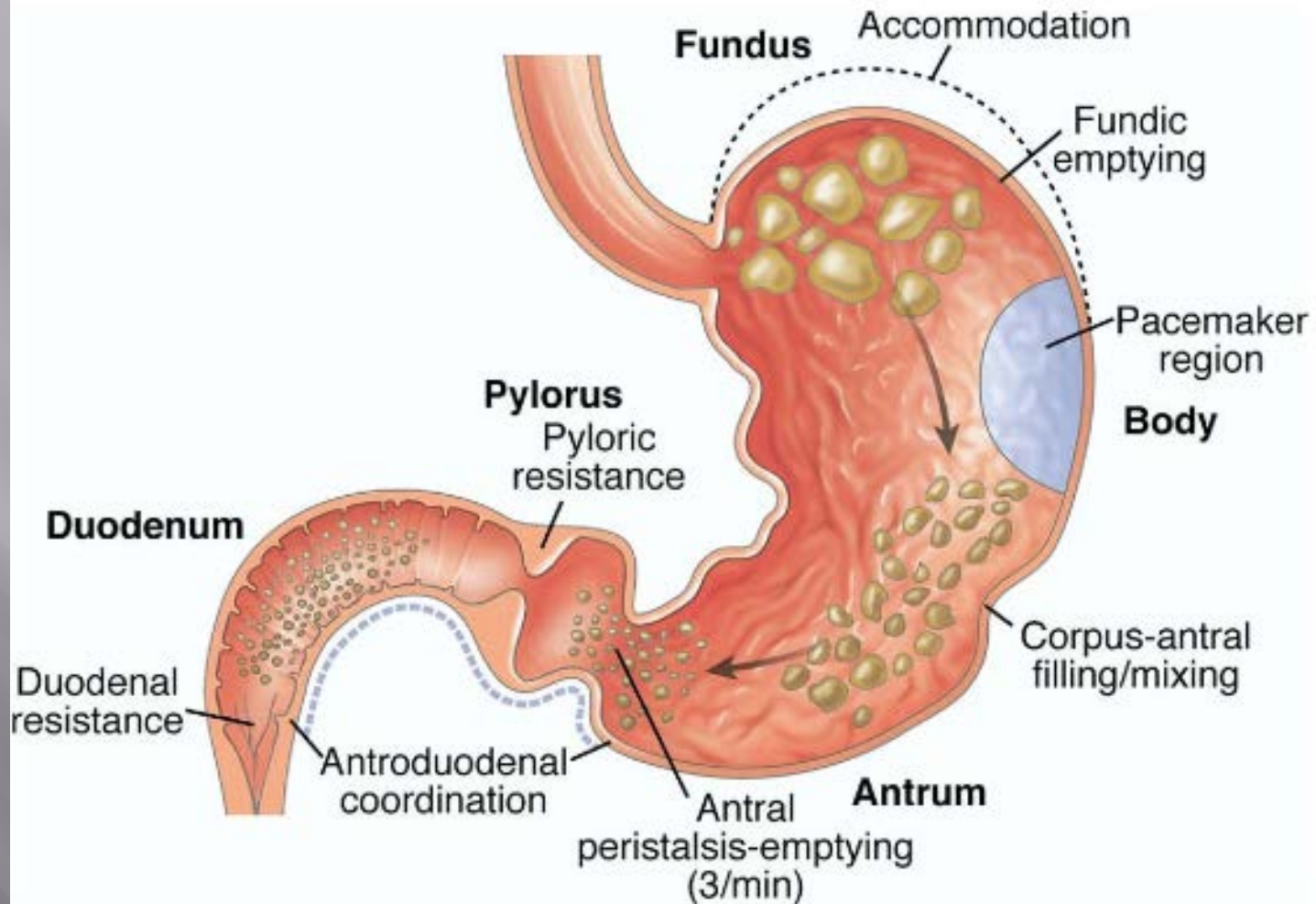
PREVALENCE OF FUNCTIONAL DYSPEPSIA in ASIA-PACIFIC

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 → IBS
 - 31.5% IBS → FD, 23.7% IBS → FD
 - 26.5% PDS vs 18.3% EPS, P=0.039 → IBS²
 - FD dysmotility like subtype

1. AK Tutega AMJ 2008, X Jiang Gut 2008, N Manabe SJGast 2010
2. A Wang BMC Gast 2008, MH Chen JGH 1997

Pathophysiology



Pathophysiology

- 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

1. Pilichiewicz et al Clin Gast Hep 2009.
2. Pilichiewicz et al Am J Gast 2008 .
3. Laine et al Ann Int Med 2001 .
4. Wong et al GUT 2002 .
5. Wang et al Clin Gast Hep 2007 .
6. Tan et al WJG 2012 .

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Prokinetic Agents
Buspirone

PPI
Antidepressants

Antibiotics
FODMAPs

1. Talley et al JGH 2009

2. Hu et al Gastroenterol 2002

Psychological Factors

- Multiple studies demonstrating an association between Anxiety/Depression and FD¹
- Experimentally induced anxiety in healthy subjects fed a test meal is associated with²
 - 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 retention³
- Neuroimaging demonstrates the effect of anticipatory pain/anxiety on activation of the visceral pain pathways in the brain⁴
- mood disorders influence gastric function through decreased vagal activity⁵

1. WH HU ,Wong WM APT 2002
2. B Geeraerts GastroE 2005
3. L Van Oudenhove Psychosom Med 2007, TT Haug Psychosom Med 1994
4. L Yaguez, GastroE 2005
5. SL Lorena JCG 2004

Antidepressants in FD

- Early studies examined TCA
 - Benefit over placebo
- Venlafaxine SNRI
 - RCT demonstrated no benefit, large drop outs in Rx group 44%
 - ITT and PP no benefit

Antidepressants in FD

Hong Kong Data

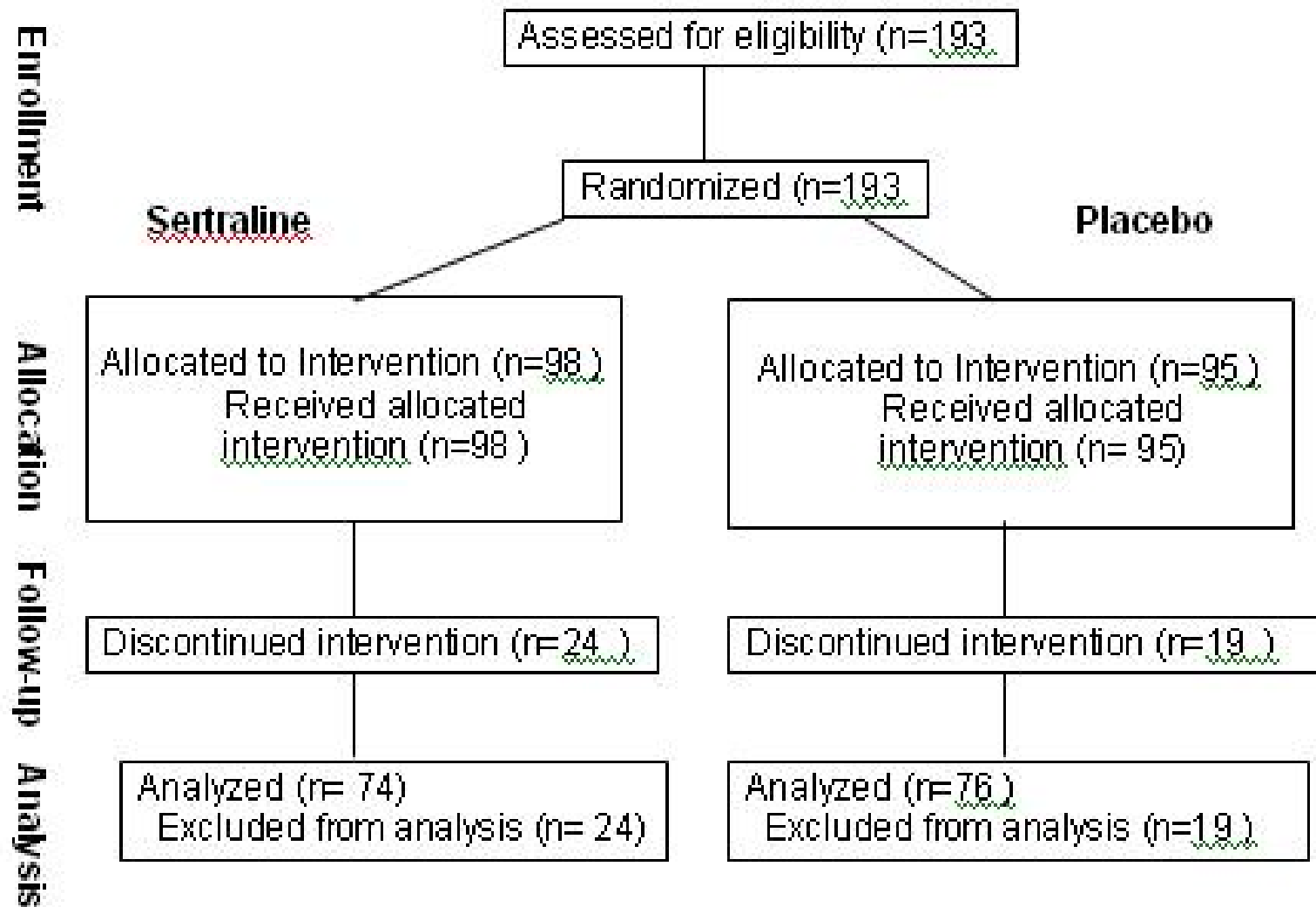


Figure 1: Study Patient Flow Chart

Table 1 Demographics of Study Patients (ITT)

	Sertraline	Placebo	p-value
Number of patients	98	95	
Age	43.0	41.6	0.515
Sex (Male)	27	27	1.000
Current smokers (%)	3.2	7.3	0.122
Alcohol (%)	6.2	8.3	0.295
H. pylori positive (%)	8.4	7.3	0.843
NSAID use (%)	3.1	2.6	1.000
Predominant symptom (%)			
Ulcer like	44.7	55.3	
Dysmotility like	49.2	51.8	
Reflux like	57.1	42.9	
Non-specific	68.4	31.6	

Table 2

Dyspepsia Index, SF-36 Score and Hospital Anxiety Scale Results (PP)

	Week 0	p-value	Week 4	p-value	Week 8	p-value
Mean dyspepsia score						
Setraline	25.83	0.124	22.59	0.740	20.53	0.02
Placebo	27.19		22.94		23.34	

Table 4
Default Patient Profile

			Reason for Default W8		
	Default W4 (n)	Default W8 (n)	No Reason Given (%)*	Adverse Effect of Drug (%)*	Other (%)*
<u>Sertraline</u>	23	24	7 (16.3 %)	14 (32.6 %)	3 (7 %)
Placebo	11	19	11 (25.6 %)	8 (18.6 %)	0 (0 %)

*Represents percentage of all default patients

SSRI in FD

- ▣ 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

1. Pilichiewicz et al Clin Gast Hep 2009.
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3. Laine et al Ann Int Med 2001 .
4. Wong et al GUT 2002 .
5. Wang et al Clin Gast Hep 2007 .

Dietary Modification

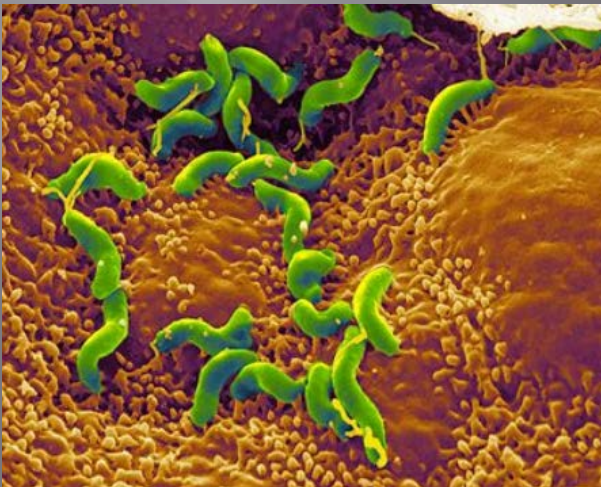
- ▣ No evidence to support any specific dietary intervention for FD
- ▣ Dietary Advice given by 80% of clinicians Rx FD¹
- ▣ Lactose restriction in lactose intolerance²
- ▣ IBS-FD overlap
 - FODMAP diet³
 - Fermentable Oligo, Di-, Monosaccharides & Polyols



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 14¹ however may be lower based on studies published in Chinese Journals



P Moyaeddi Cochrane Database SR 2006
X Jin Helicobacter 2007

PPI

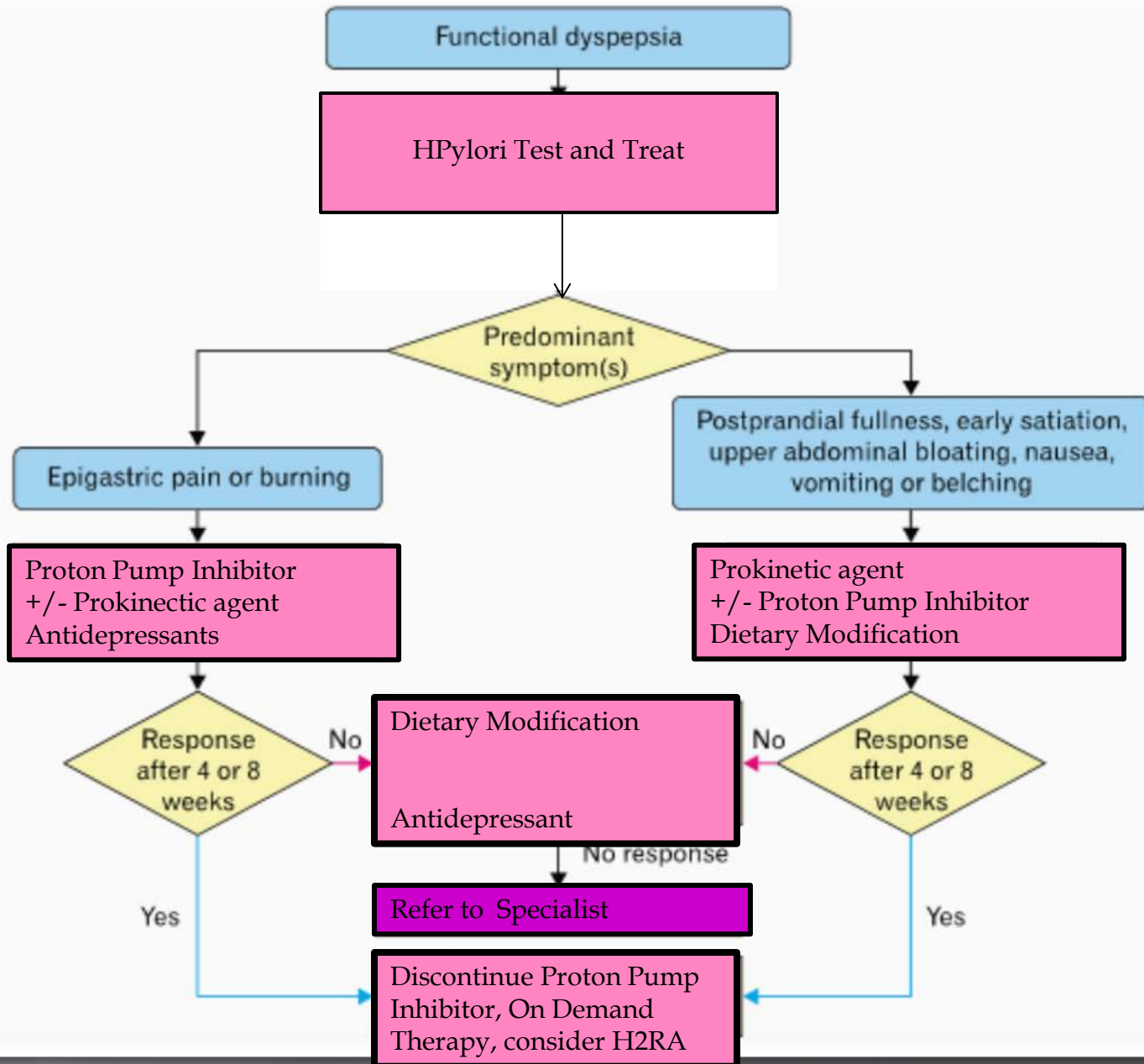
- ▣ Multiple studies support use in FD
 - All Western data
 - NNT 15
- ▣ Single Asian RCT data suggests no benefit in FD as per Rome II criteria¹
- ▣ RCT Uninvestigated Dyspepsia also suggest no benefit over placebo
- ▣ Overlap with GERD

Prokinetic Agents

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

Anti-Depressants

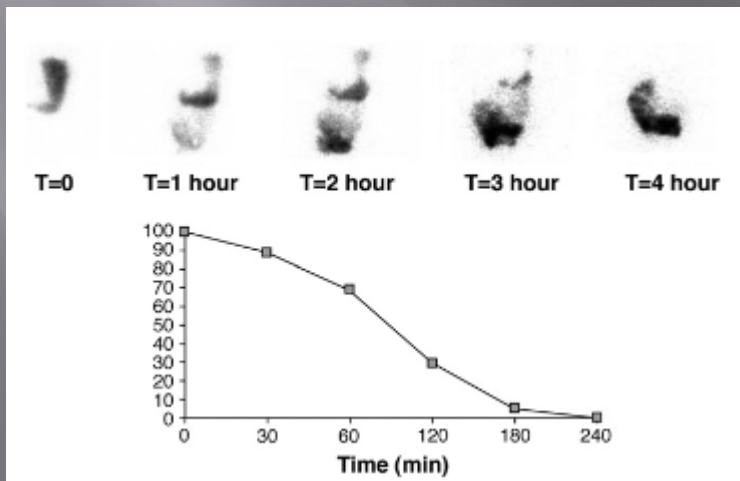
- ▣ Definitely if symptoms of clinical anxiety and/or depression
- ▣ Definitely if IBS overlap
- ▣ Consider in event of failure of other therapies
 - Must discuss short term side effects
 - Slow onset of effect
 - NK Talley with multicentre study TCA vs SSRI due 2013/2014



Treatment Failures

▣ 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



1. AO Quartero DigDSc 1998

Treatment Failures

- ▣ Manometry / pH / Impedance Studies
- ▣ Breath Testing
- ▣ FODMAPs diet
- ▣ Enrolment in studies
 - Dietary Therapies in FD
 - Novel Therapeutics in FD

Irritable Bowel Syndrome

Clinical Definition

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

Gwee JGH 2010

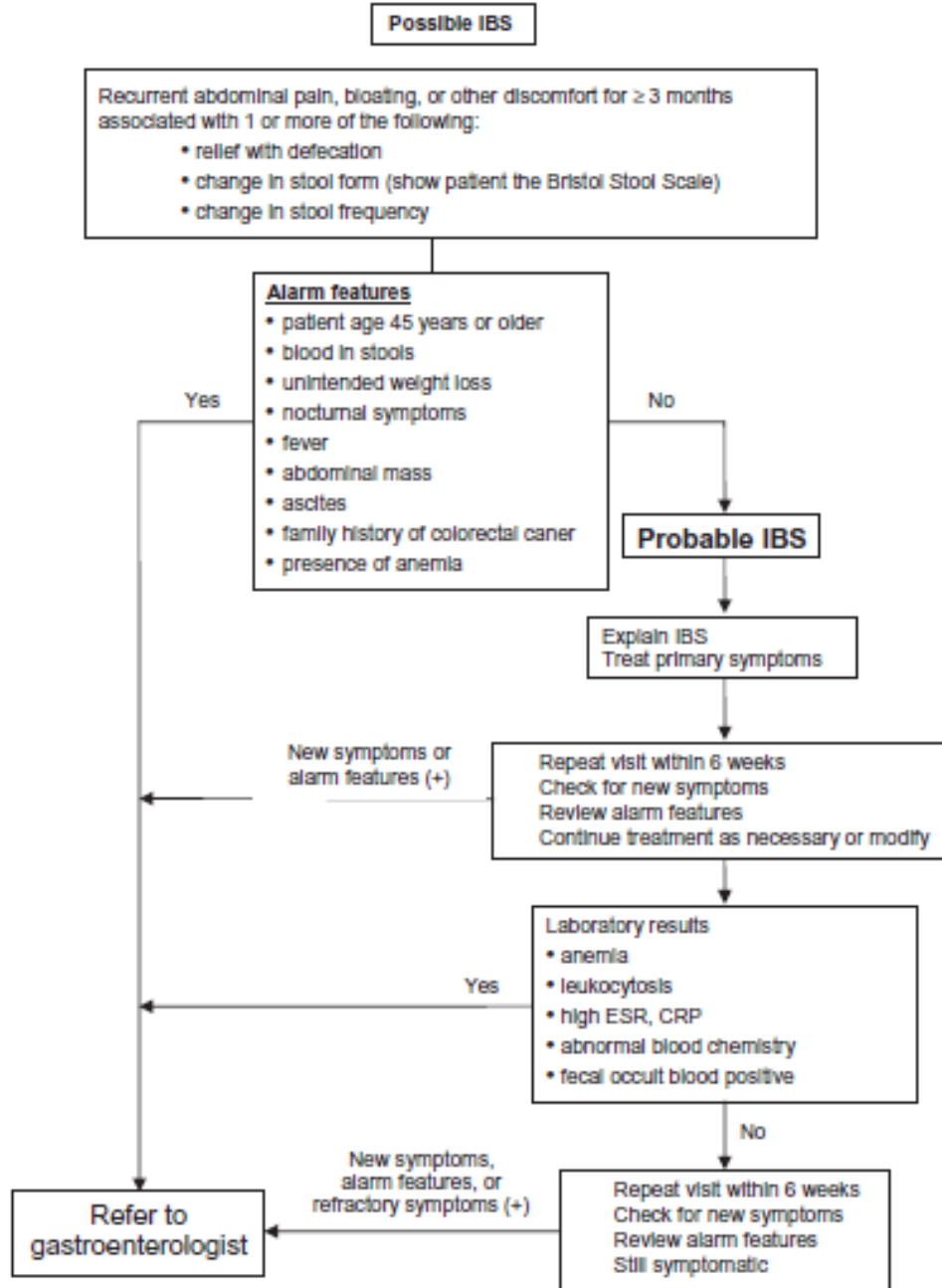
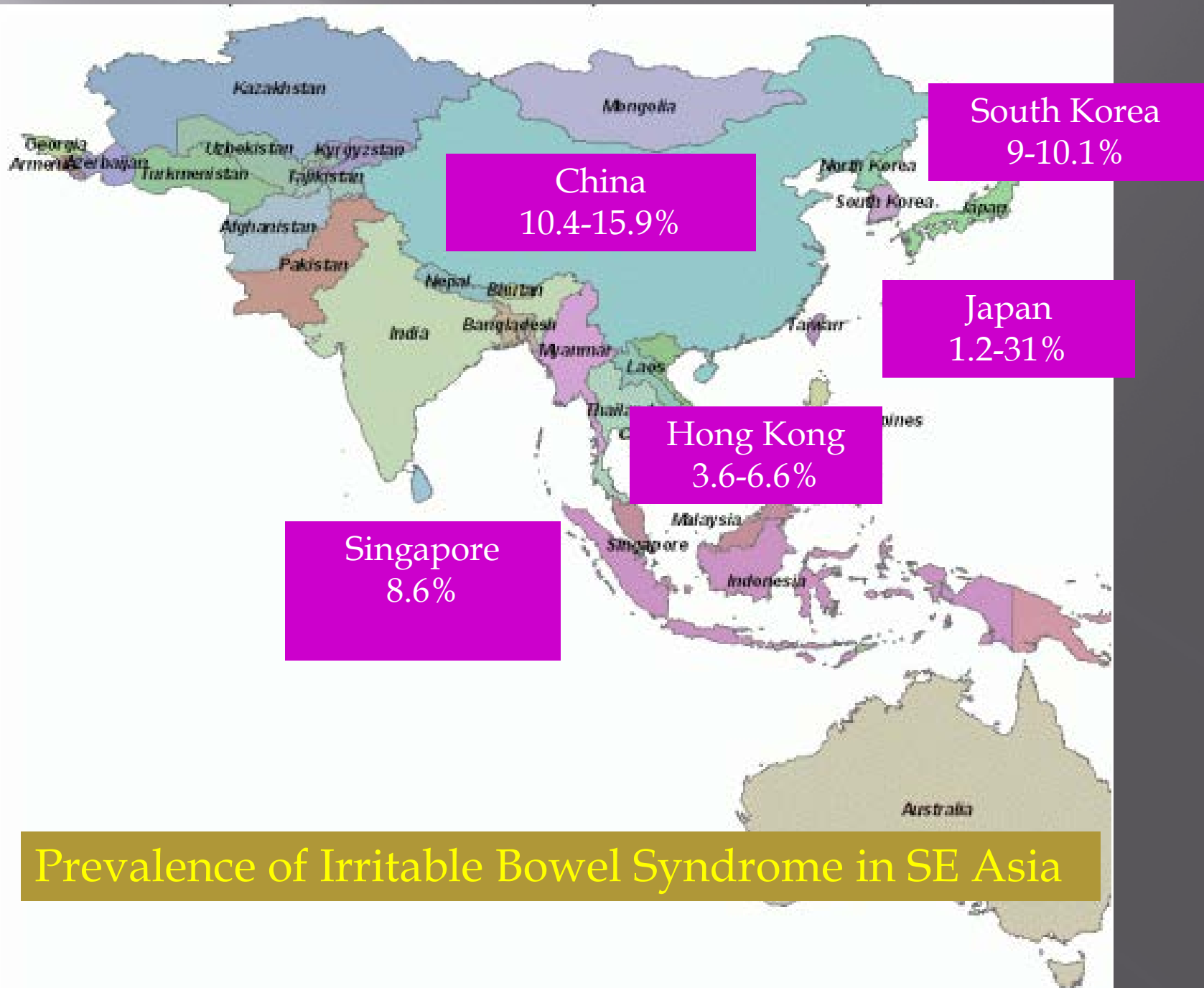
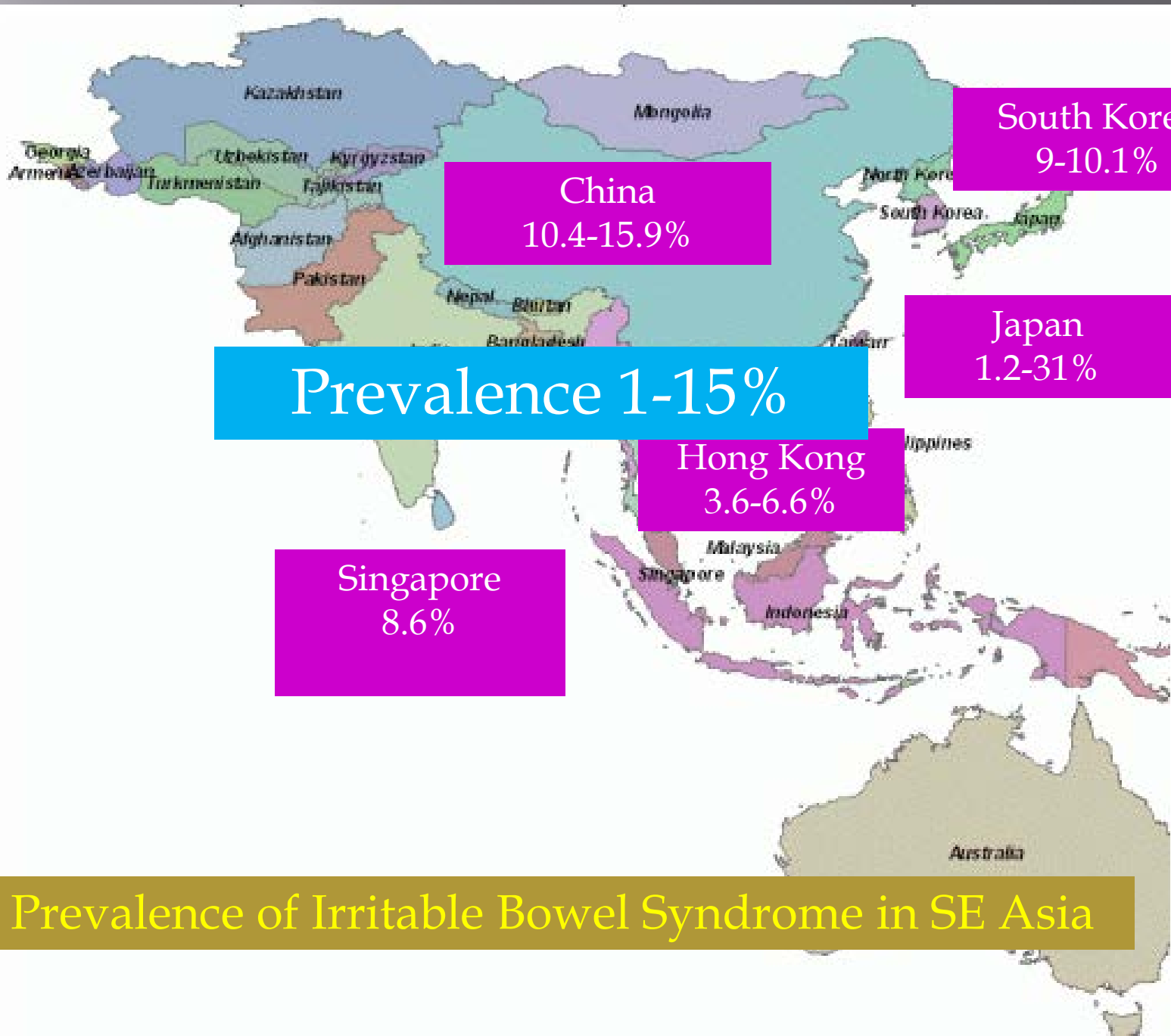


Figure 1 Diagnostic algorithm for irritable bowel syndrome (IBS). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.



Prevalence of Irritable Bowel Syndrome in SE Asia



Prevalence 1-15%

South Korea
9-10.1%

China
10.4-15.9%

Japan
1.2-31%

Hong Kong
3.6-6.6%

Singapore
8.6%

Prevalence of Irritable Bowel Syndrome in SE Asia

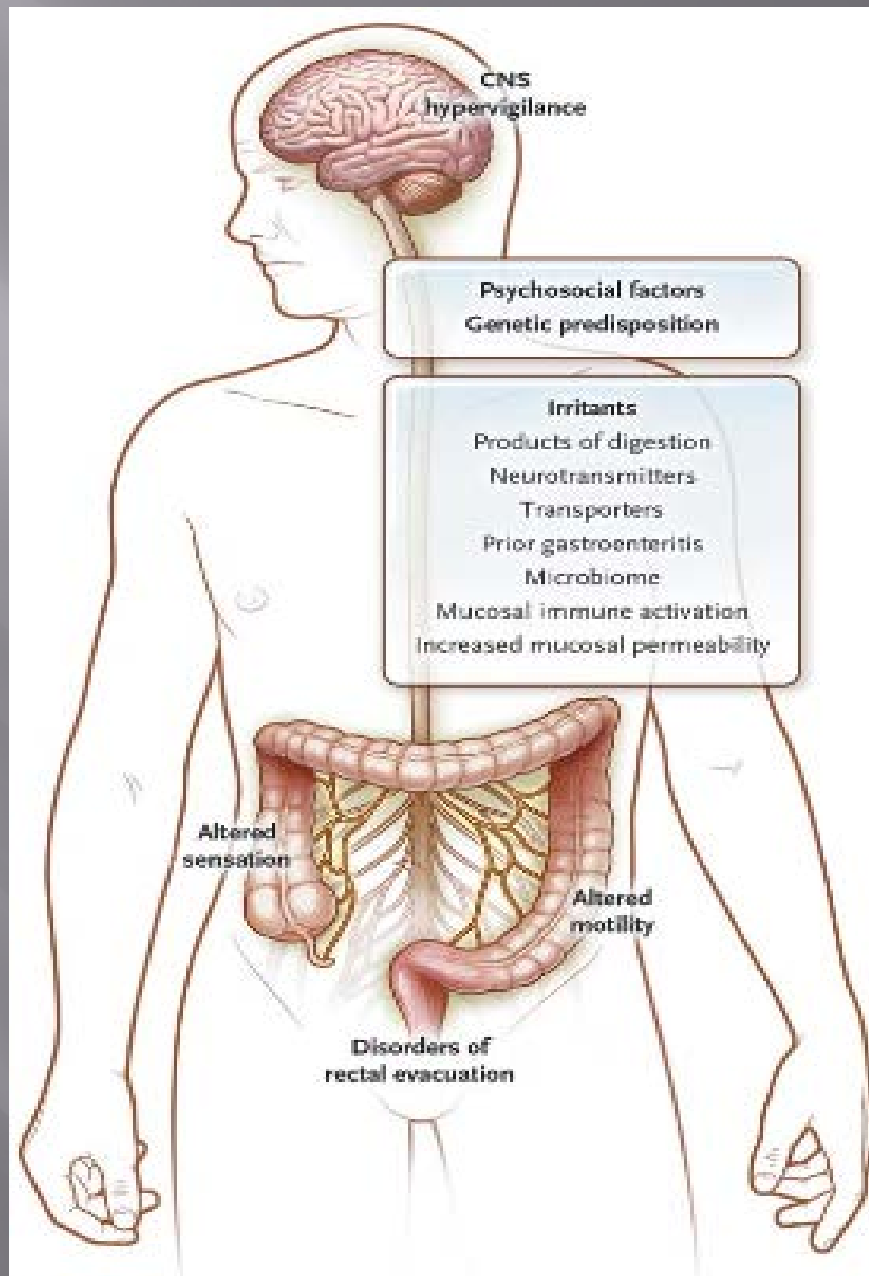


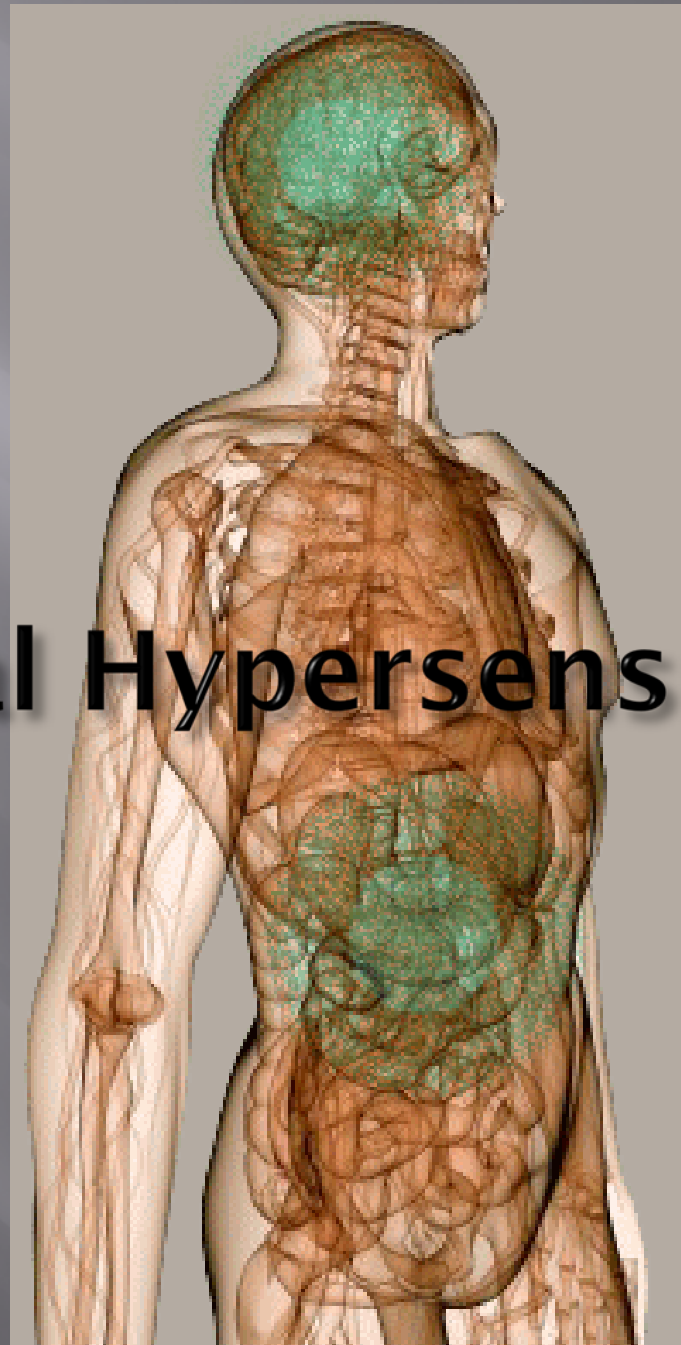
Figure 1. Mechanisms Underlying the Irritable Bowel Syndrome (IBS).

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.

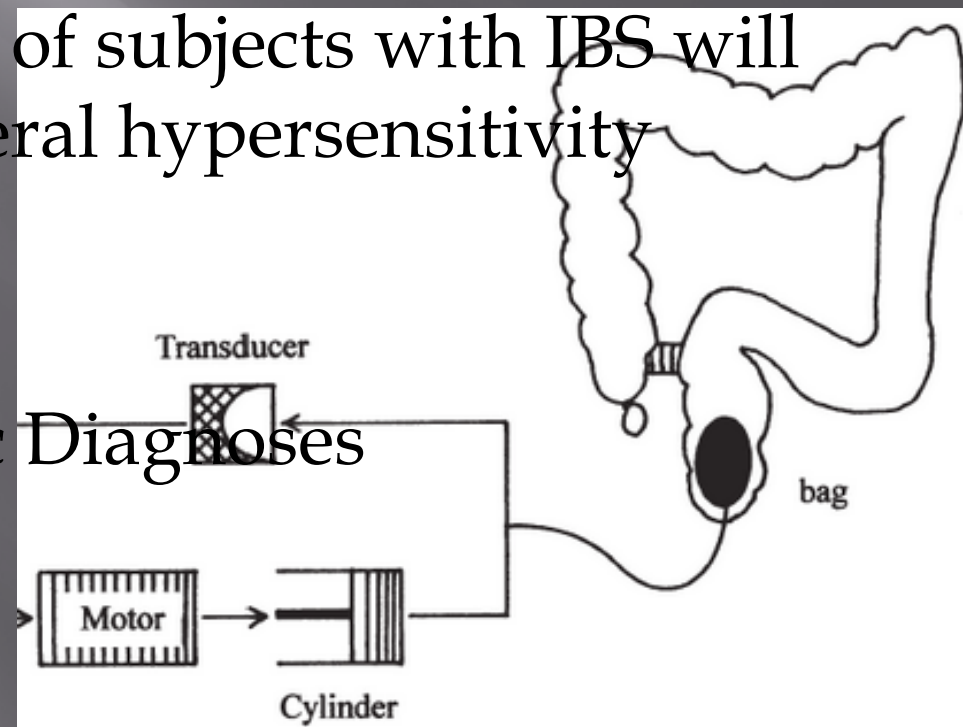
Pathophysiology

- ▣ **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 ¹
- ▣ 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



Anti Depressants

- ▣ 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



DIET

Carbohydrates

- ▣ 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

FODMAP malabsorption

- ▣ Malabsorption of sugars, such as lactose, fructose, and sorbitol \neq 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 malabsorbers¹
- ▣ Distinction between mal-absorption and intolerance

Table 5 Examples of common FODMAPs indentified in the Chinese Diet

	Excess Fructose	Lactose	Oligo-saccharides	Polyols
Known	<ul style="list-style-type: none"> • Apples • Pears • <u>Nashi</u> pears • Honey • Dried fruit e.g. grapes, dates 	<ul style="list-style-type: none"> • Milk • Butter • Ice cream • Milk powder • Commercial sweet teas and coffees 	<ul style="list-style-type: none"> • Wheat products e.g. wheat bread, cakes, biscuits, wheat noodles • Garlic/onions • Beans e.g. red/green beans, soy beans • Cabbage • Watermelon • Persimmon 	<ul style="list-style-type: none"> • Mushrooms • Watermelon • Apples • <u>Nashi</u> pears
Suspected	<ul style="list-style-type: none"> • Commercial sauces e.g. char sui sauce, oyster sauce 			<ul style="list-style-type: none"> • Fruit chews

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

Gut Microbiota

- ▣ 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-analysis¹
 - 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

Gut Microbiota

- ▣ Rifaximin ¹
 - Minimally absorbed antibiotic
 - Improvement in global IBS symptoms, bloating, stool consistency and abdominal pain¹
- ▣ 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) ²

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

