Dyspepsia
An evidence based approach

Dr. John Igoe
Gastroenterology
NBIMU
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OBJECTIVES

- **Recognize different presentations of dyspepsia and when urgent care is needed**
- **Understand underlying pathophysiology related to functional dyspepsia**
- **Know different treatment options available to treat functional dyspepsia**

Conflict of Interest and Disclosures

Financial Interest or Affiliation	Commercial Enterprise(s)
Financial Disclosure	
Advisory Board or similar committee	AbbVie, Janssen, Lupin, Gilead, Ferring, Shire
Clinical trials or studies	
Honoraria or other fees (e.g., travel support)	AbbVie, Allergan, Shire, Janseen, Ferring
Research grants	
Other (specify)	3D bolus (Investment)

Cases

- 60M referred for refractory GERD
- Patient takes PPI twice daily, zantac, pepto bismol and gaviscon yet still having heartburn
- Has missed works and multiple social engagements- frustrated
- W/U to date negative with normal bloodwork, H.pylori stool antigen, U/S abdo, CT chest and abdo
- Patient referred for refractory GERD

CASE 2

- 33 Y/O female referred urgently for significant bloating and early satiety for endoscopy to R/O gastric cancer
- Patient reports symptoms have been getting significantly worse over past 6 months and having difficultly eating anything
- Will get nauseous when eating yet rarely vomits and has actually gained weight over past 6 months
- CBC, liver profile, CRP, H.pylori, pelvic US all normal
- Abdo U/S- Choleslithiasis and currently waiting to see surgeon
- Patient very concerned as great aunt had gastric cancer and wants endo

Dyspepsia

- Derived from Greek (dys) and (pepse) meaning “difficult digestion”
- Has been known and written about for centuries
- PEPSI originally produced in 1893 as treatment for dyspepsia
- Current studies suggest roughly 20% of western populations have dyspeptic symptoms

Moayyedi. P. ACG and CAG clinical guideline: Management of Dyspepsia. 2017

Epidemiology

- Of patients with dyspepsia roughly 40% seek medical attention
- More common in women, obesity, smokers and those taking NSAIDS
- Patients have normal life expectancy
- Significant cost to health care system
  - Estimated 18 billion dollars a year in US with societal costs double
  - 2-5% of people on disability/off work

Functional Dyspepsia. N Engl J Med 2015;373:1853-63.
March 2016. Journal of Gastro and Hepatol

Definition

- Dyspepsia currently defined as the presence of symptoms considered by the physician to be originating from the gastroduodenal region.
- 4 symptoms
  - Post Prandial fullness
  - Early Satiation
  - Epigastric Pain
  - Epigastric Burning
- However many patients also experience nausea, bloating, belching and heartburn

Functional Dyspepsia. N Engl J Med 2015;373:1853-63.

Organic Causes

- Most common organic causes are PUD and GERD
- PUD found in 5-10% of patients with dyspepsia
  - Risk factors- age, NSAIDS and Hp
- Erosive Esophagitis found in 10-15% of patients
- Gastric Cancer less than 1%
- Esophageal Cancer rarely presents as dyspepsia
- Infections, systemic diseases
- Medications

Red Flags

Table 2. Alarm Symptoms of an Underlying Upper Gastrointestinal Cancer.
Age >55 yr with new-onset dyspepsia*
Evidence of overt gastrointestinal bleeding including melena or hematemesis
Dysphagia, especially if progressive, or odynophagia
Persistent vomiting
Unintentional weight loss
Family history of gastric or esophageal cancer
Palpable abdominal or epigastric mass or abnormal adenopathy
Evidence of iron-deficiency anemia after blood testing

Functional Dyspepsia. N Engl J Med 2015;373:1853-63.

Do not cause dyspepsia

- Choleslithiasis is not associated with dyspepsia

- Persons with dyspepsia should not be routinely investigated for choleslithiasis and cholecystectomy in persons with choleslithiasis is not indicated for dyspepsia alone.
- Biliary pain/colic is easily distinguishable from dyspepsia

Functional Dyspepsia. N Engl J Med 2015;373:1853-63.

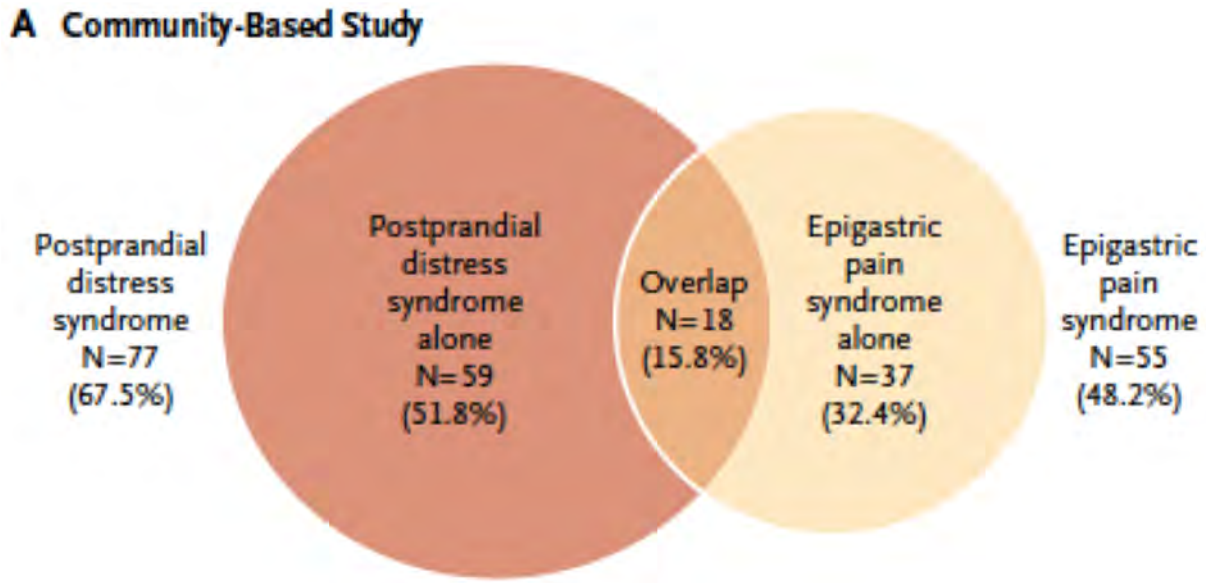
Functional Dyspepsia

- Roughly 70-80% of patients presenting with these symptoms will have a negative W/U
- These patients are diagnosed with functional dyspepsia or non ulcerative dyspepsia
- Typically presents in two fashions
  - Epigastric pain predominant
  - Post prandial distress syndrome

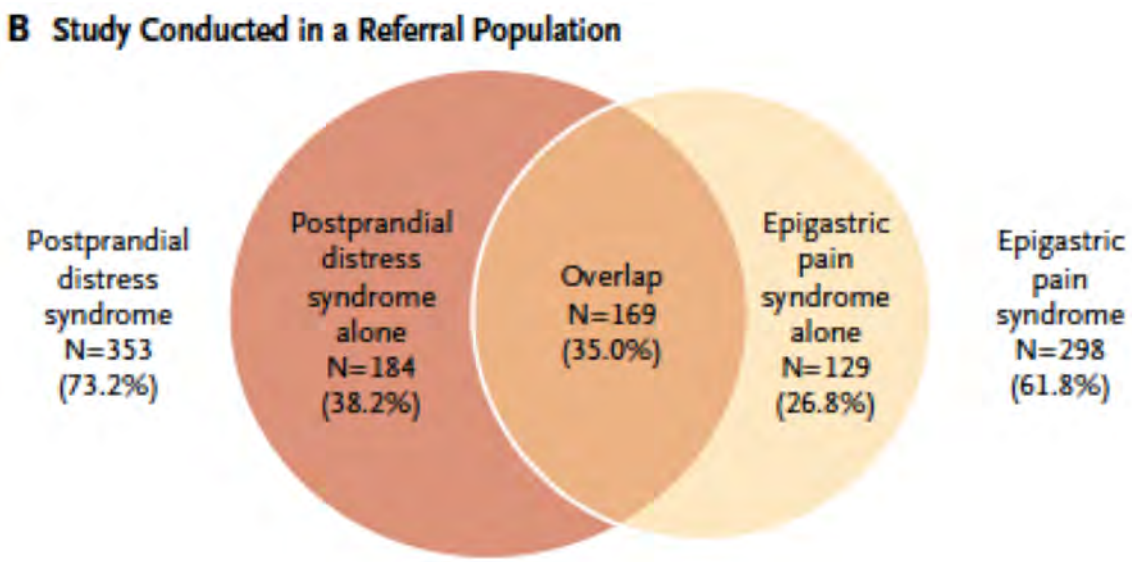
Functional Dyspepsia. N Engl J Med 2015;373:1853-63.

Functional Dyspepsia

Community Based



Referral Population



Functional Dyspepsia. N Engl J Med 2015;373:1853-63.

Pathophysiology

- Several proposed mechanisms or causes of functional dyspepsia
- Familial aggregation and genes
- Psychological distress
- Gastroduodenal motor and sensory dysfunction
- Duodenal eosinophilia
- Post Infectious

Functional Dyspepsia. N Engl J Med 2015;373:1853-63.

Genetics

- Familial aggregation of abdominal Pain has been reports in FD implying genes or early life factors are important
- Frequency of dyspepsia in 1st degree relatives of affected patients is increased compared with the frequency in their spouse
- Polymorphisms of the G-protein beta polypeptide 3 (GNB3) has been associated with the risk of functional dyspepsia.

Talley.N. Functional Dyspepsia: Advances in Diagnosis and Therapy. Gut and Liver 2017.

Psychological distress

- Review of literature reveals a clear association between psychological factors and FD
- Most commonly anxiety followed by depression, somatoform disorders and history of physical/sexual abuse
- Study where 700 community patients completed a questionnaire and endoscopy at entry
  - 10 years later the risk of FD developing was 8 fold increased in those with higher anxiety levels
- Anxiety tends to be associated with PDS as opposed to EPS

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Gastroduodenal Motor/sensory dysfunction

- Gastric emptying slow in 25% of FD
- Impaired gastric accommodation occurs in subset of patients
  - Recent studies linking anxiety to impaired accommodation

- Visceral hypersensitivity is considered a major mechanism of all functional disorders
  - Multiple studies have shown that patients with FD are hypersensitive to isobaric gastric distention

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Infections

- H.pylori often associated and treated in setting of dyspepsia and is a cause of organic dyspepsia
- There is only limited evidence to support a casual relationship between Hp and functional dyspepsia
- Most common chronic infection in humans
- Evidence humans infected as far back as 58,000 years ago
- Conservative estimates that 50% of all humans infected
- Transmission typically early in life among family members

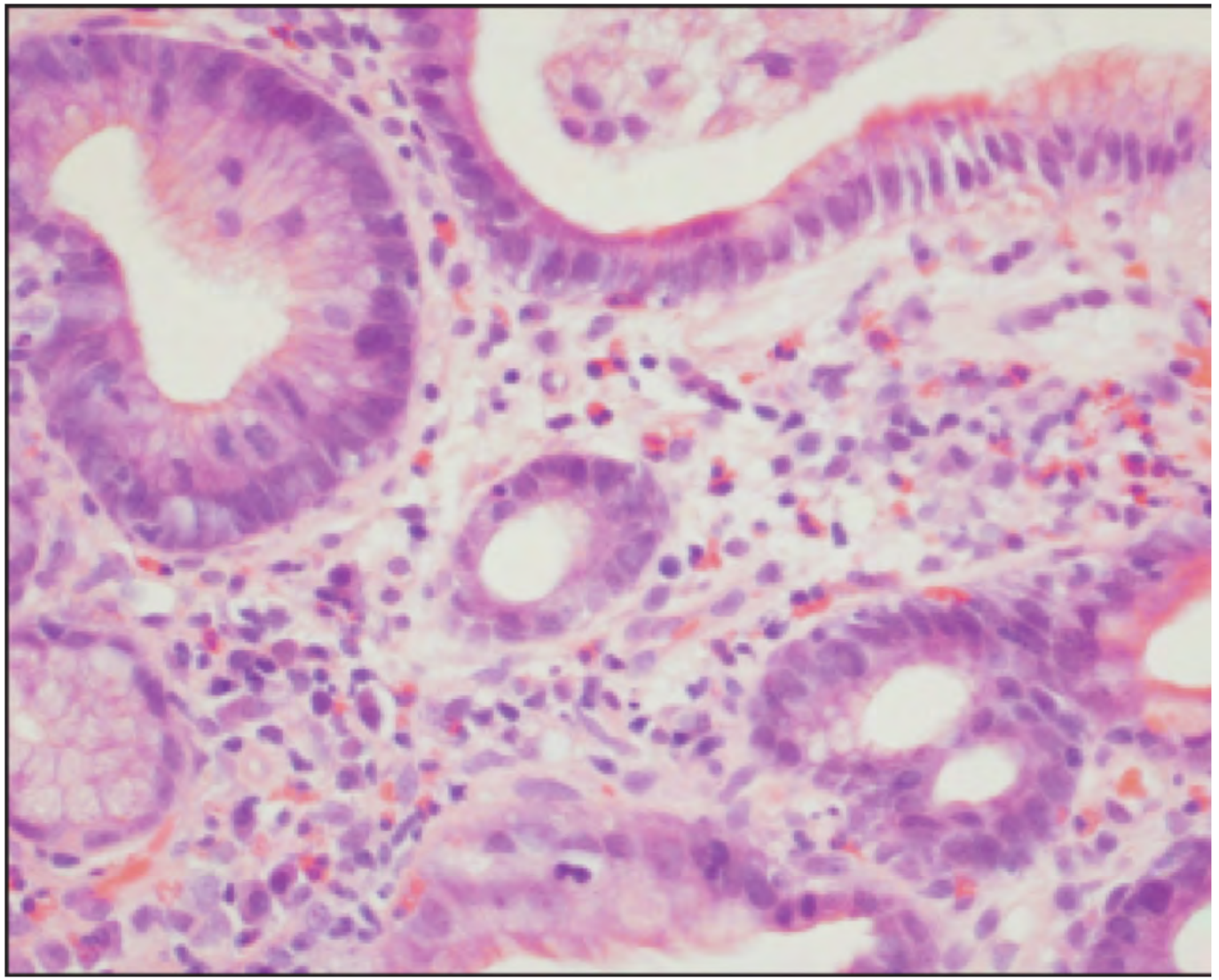
Bacteriology and epidemiology of H.pylori infection. Nature 2007

Infections

- Post infectious functional dyspepsia now recognized as cause
    - Usually early satiation, wt loss, nausea/vomiting
- Functional dyspepsia increased 5-fold in patients after salmonella
- Typically will have increase in duodenal eosinophilia

Duodenal eosinophilia

- Consistent finding of duodenal eosinophilia in FD and mostly PDS
- Typically 22 eosinophils in 5 high power fields is considered abnormal
- Submucosal neuronal structural and functional changes have been identified in the duodenum in FD patients
- Smoking is risk factors for duodenal eosinophilia
- Other possible triggers
    - Diet, environment, infections, antibiotics, microbiome



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What to do?

Current Recommendations

- Currently CAG/ACG guidelines recommend any patient over age of 60 with new dyspepsia to undergo an upper endoscopy
  - Currently costs health care system $80,000 to diagnose one gastric cancer in patient with dyspepsia (US)
- Patients from Southeast Asia, South America, previous gastric surgeries, borderline age and Male

Moayyedi. P. ACG and CAG clinical guideline: Management of Dyspepsia. 2017

Recommendations

- Recommend against endoscopy in patient under age of 60 with alarm features to rule out malignancy
  - Recent systematic review of seven studies found alarm features have limited value
- Individualized alarm features such as weight loss, anemia and dysphagia had sens and spec of 66%
  - 2-3 fold increase in having an upper GI malignancy yet risk so low in persons under 60 it is still less than 1%
  - Unlikely endoscopy of all young patients with alarm features would be cost-effective
  - Pancreatic cancer under age of 60 with dyspepsia <0.01%

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Recommendations

- Patients under the age of 60 with dyspepsia should be screened for H.pylori non invasively and treated if positive
  - NNT to improve symptoms ranges from 7-15 depending on population and study
- Recommend empirical PPI therapy if H. Pylori negative or remain symptomatic post eradication
  - 6 RCT comparing PPI to placebo in dyspeptic patients with statistical improvement in PPI group with NNT of 6 (4-11)
  - Recommend once daily PPI as currently no evidence for BID PPI in dyspepsia
  - If no benefit after 8 weeks the PPI should be discontinued

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Recommendations

- In patients who do not respond to PPI and/or H.pylori eradication, a prokinetic/TCA can be offered
  - Maxeran no longer than 12 weeks and domperidone 30mg/day or less
  - NNT of 12.5

- Systematic review identified 3 trials using TCA in dyspepsia and all trials had significant effect in reducing symptoms
  - NNT of 6
  - No benefit with SSRI
- Buspirone improves gastric accommodation and option in patients with PDS

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Recommendations

- Patients not responding to any drug therapy be offered psychological therapies
  - 12 RCT's involving 1563 patients with FD
  - All trials had significant benefit
- Cognitive behavioral therapy or other forms of psychotherapy were used
- NNT of 3

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Recommendations

- Recommend against routine use of complementary and alternative medicines
- 50% of patients with functional dyspepsia seek alternative treatments
- Nearly half of patients in one study would take a medication with a 12.7% risk of sudden death if cure rate was 99%
- Iberogast is herbal medication that relaxes gastric fundus and has weak data

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Motility Testing?

- Recommend against routine motility testing in patients with functional dyspepsia
- Up to 30% of patients with functional dyspepsia will have altered motility
  - Recent study showed that 21% of patients fulfilling criteria for functional dyspepsia had delayed gastric emptying
- However multiple studies have shown gastric emptying does not correlate necessarily with symptoms
- Motility testing only in patients with severe nausea and vomiting who fail empiric therapy

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Level of evidence	Comment
Helicobacter pylori eradication (level 1)	First line therapy in infected
Acid suppression (level 1)	
Proton pump inhibitors	First line therapy especially for epigastric pain
H_2 receptor antagonists	
Prokinetic (level 1–2)	
Cisapride	Cisapride withdrawn
Acotiamide	Available in Japan
Itopride	Mixed data
Centrally acting drugs (level 1–2)	
Tricyclic low dose (level 1)	Epigastric pain improved
Mirtazapine (level 2)	Efficacy not established
Buspirone (level 2)	Postprandial distress syndrome improved
Miscellaneous therapy	
Iberogast (level 2)	Relaxes the gastric fundus
Montelukast	One small pediatric trial
Not efficacious	
Selective serotonin reuptake inhibitors	
Selective norepinephrine reuptake inhibitors	
Antacids	
Sucralfate	
Bismuth	
Mosapride	

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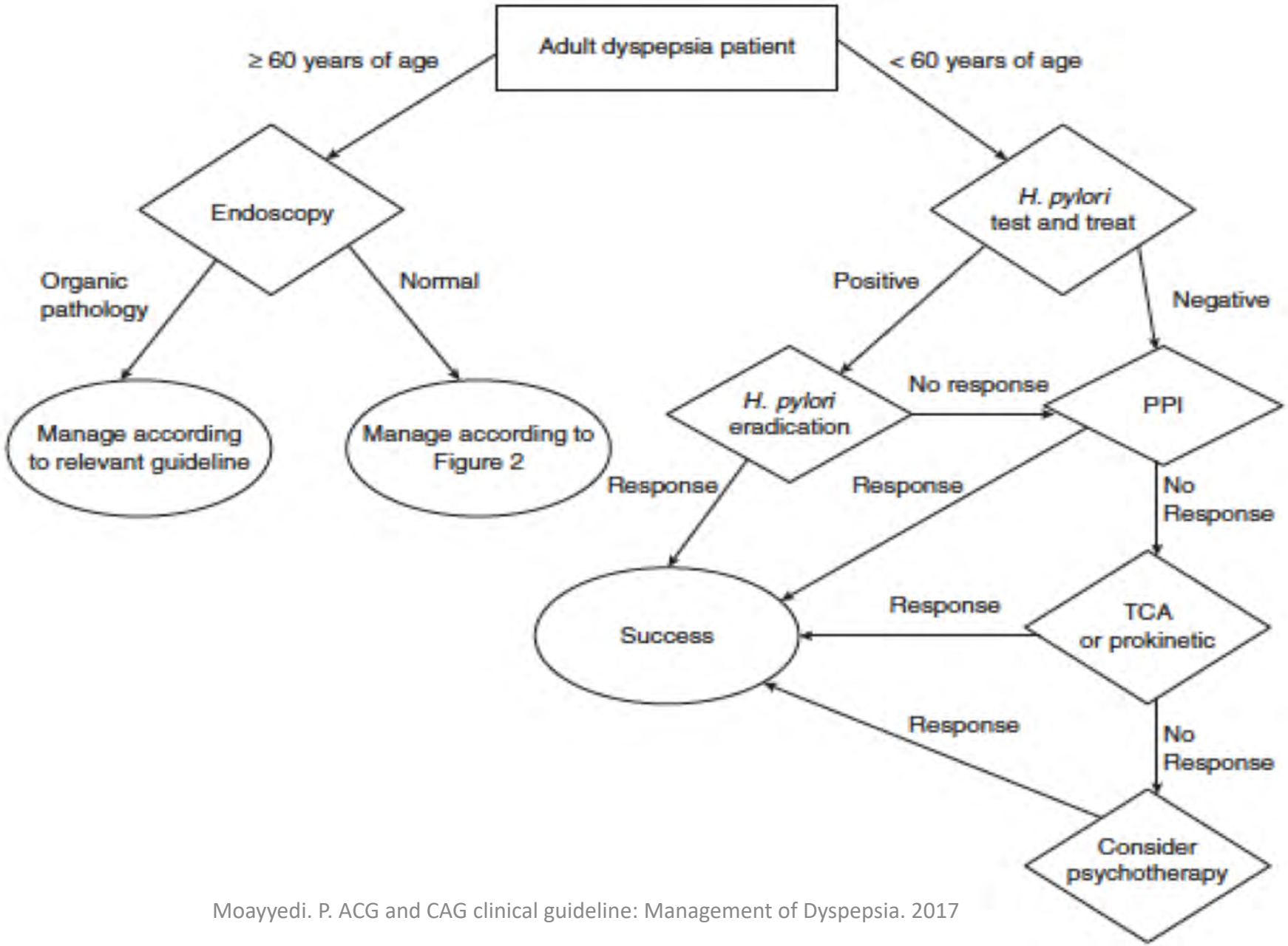

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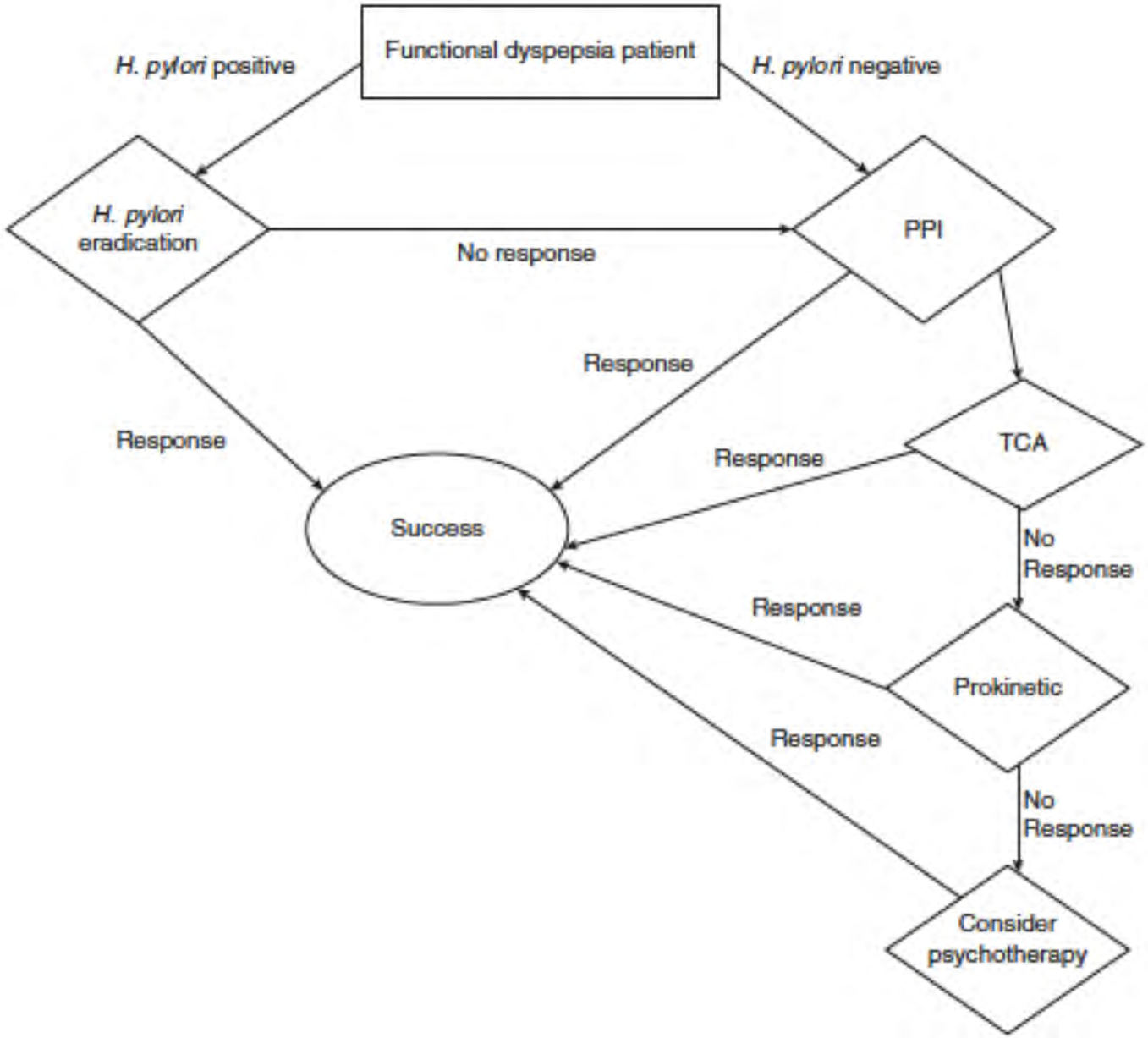

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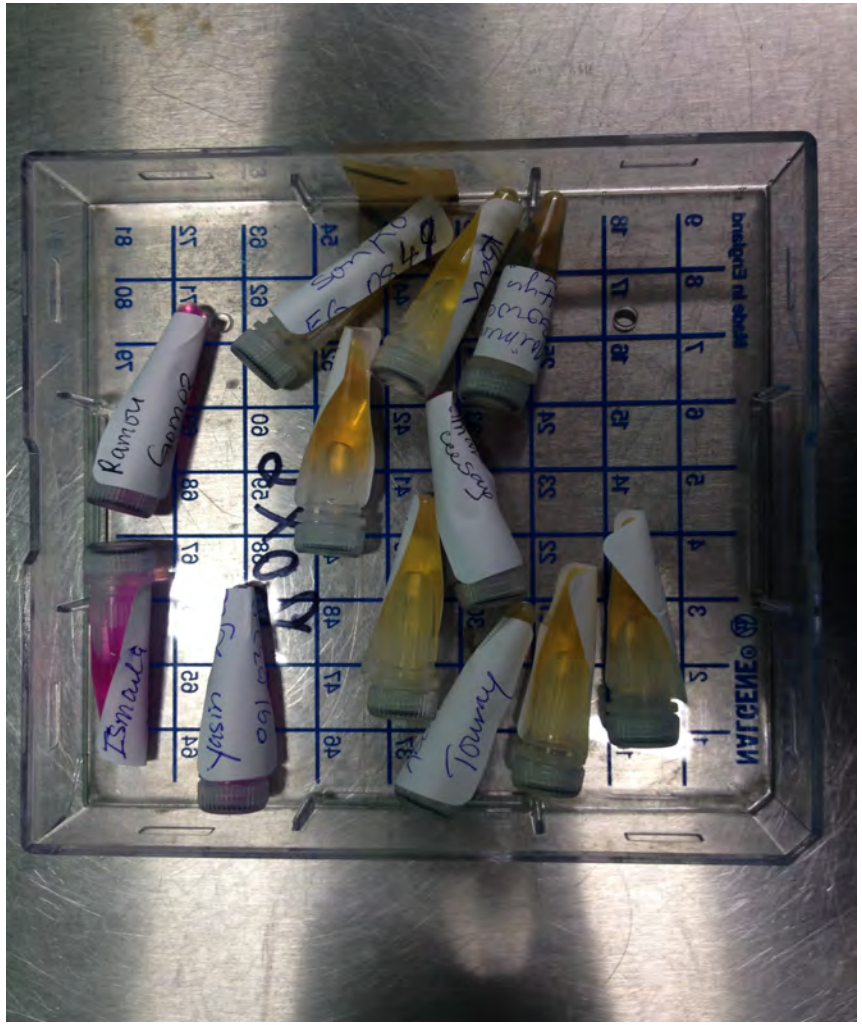
Functional Dyspepsia worldwide



Back to cases

Back to cases

- Given age and severity of symptoms underwent Endo to R/O pathology and Barrett's
- Patients asked to hold PPI and bismuth 2 weeks prior to scope
- CLO was positive for H.pylori
- Underwent eradication therapy and symptoms significantly improved

Case 2

- 33 y/o female revealed symptoms started after lost job
- ++++ Anxiety but doesn't believe it is related
- Crying in office when told high likelihood scope would be normal
- Undergoes endoscopy which was completely normal with normal histology
- Recommendation to primary care practitioner to treat with TCA

Take Home points

- Dyspepsia common in general population and commonly no organic cause found
- Patients under age of 60 do not require endoscopy even with alarm features (case by case)
- Patients over 60 should have endoscopy to detect early malignancy
- Pathophysiology not completely understood yet progress being made
- Several drug therapies yet unfortunately many not overly effective
- Psychotherapy can be very effective

Questions?