GI Health Foundation
DDW 2016
Functional Dyspepsia: A New Disease Model
Nicholas J. Talley MD, PhD
Disclosure

Grant / Research Support: Abbott Pharmaceuticals, Janssen, Prometheus, Pfizer, Rome Foundation and Salix

Consultancies: Adelphi Values, Allergens PLC, GI Therapies and Yuhan
Birth of “functional” or “non-ulcer dyspepsia”

1897: Bismuth used to outline the stomach (Roux & Balthazard)
1906: X-ray appearance of GU (Hemmeter)
1910: Drummond BMJ: causes of functional dyspepsia – cites Moynihan
1912: Typical DU symptoms (Moynihan)

Alvarez' syndrome: hysterical or neurotic abdominal bloating

Walter Alvarez: gastroenterologist, writer, Mayo physician

- Functional dyspepsia (Alvarez 1917)
- X-ray negative dyspepsia (Andersen 1935)
- Pseudo-ulcer syndrome (Hansen 1932)
Remarks on the causes and treatment of functional dyspepsia

Drummond

BMJ, 1910
Rome IV Functional Dyspepsia (FD)

Epigastric pain syndrome (EPS):

Postprandial distress syndrome (PDS): meal-related FD

Epigastric pain
Epigastric burning
Early Satiation
Postprandial heaviness or fullness

Chronic unexplained dyspepsia
Postprandial Distress Syndrome (B1a)

Inadequacy of prior approaches such as the predominant symptom
Results of factor analysis in tertiary care and general population

Epigastric Pain Syndrome (B1b)
Worldwide Prevalence of FGIDs

- FD - 1/5 individuals report dyspepsia
- IBS - 7-21%, globally, 11% of the population

Figure 1. Prevalence of IBS according to country.

Epidemiology of FD (Rome III)

Of 1000 Swedish subjects:
- 202 (20%) uninvestigated dyspepsia
- 157 (16%) FD
- 52 epigastric pain syndrome (EPS): 33% of FD
- 122 postprandial distress syndrome (PDS): 78%
- 17 EPS and PDS overlap: 11%

Of 1033 Italian subjects:
- 156 (15%) uninvestigated dyspepsia
- 114 (11%) FD
- 55 epigastric pain syndrome (EPS): 48% of FD
- 77 postprandial distress syndrome (PDS): 68%
- 18 EPS and PDS overlap: 16%

First SNP Linked to FD G-Protein (GNß3) Polymorphisms

FD %: 7.1 32.1 60.7
Controls %: 3.6 55.5 41.1

Amplified signal transduction responses

CT

CC:
OR = 2.2
(95% CI 1.1-4.3)

Independently confirmed

H. Pylori and Gastritis: A Nobel Story
Infections and Functional Dyspepsia

• Infections are linked to FD
**H. pylori** and Functional Dyspepsia

Eradication therapy beats placebo but is this a non-specific antibiotic effect (no trials in Hp negative cases)?

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum 98</td>
<td>0.92 (0.81,1.03)</td>
<td>13.4</td>
</tr>
<tr>
<td>McColl 98</td>
<td>0.85 (0.77,0.93)</td>
<td>23.0</td>
</tr>
<tr>
<td>Koelz 03</td>
<td>0.95 (0.81,1.11)</td>
<td>8.0</td>
</tr>
<tr>
<td>Talley(Orchid) 99</td>
<td>0.97 (0.85,1.11)</td>
<td>12.0</td>
</tr>
<tr>
<td>Talley(USA) 99</td>
<td>1.07 (0.86,1.34)</td>
<td>4.2</td>
</tr>
<tr>
<td>Miwa 00</td>
<td>0.91 (0.70,1.18)</td>
<td>2.9</td>
</tr>
<tr>
<td>Malfertheiner 03</td>
<td>0.95 (0.85,1.06)</td>
<td>17.6</td>
</tr>
<tr>
<td>Varannes 01</td>
<td>0.83 (0.68,1.00)</td>
<td>5.6</td>
</tr>
<tr>
<td>Froehlich 01</td>
<td>0.86 (0.60,1.24)</td>
<td>1.5</td>
</tr>
<tr>
<td>Koskenpato 01</td>
<td>0.91 (0.78,1.07)</td>
<td>8.1</td>
</tr>
<tr>
<td>Gisbert 04</td>
<td>0.76 (0.40,1.46)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hsu 01</td>
<td>0.93 (0.66,1.33)</td>
<td>1.6</td>
</tr>
<tr>
<td>van Zanten 03</td>
<td>0.94 (0.65,1.35)</td>
<td>1.5</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.91 (0.87,0.96)</td>
<td></td>
</tr>
</tbody>
</table>

**Favors eradication**  |  **Favors placebo**

NNT = 17
(95% CI 11 - 33)

**H. pylori** Eradication Efficacious, or is it the Antibiotics?

**HEROES trial**  N= 404 patients

New Onset of Dyspepsia Post Salmonella Gastroenteritis

AGE = acute gastroenteritis
Bacterial Dysentery and FD

- Cohort study Walkerton, Ontario, Canada 2002-2003 – follow-up 2008
- Of 2597 subjects eligible, 1088 (42%) provided data for analysis: 706 (65%) acute gastroenteritis
- Risk for dyspepsia at 8 years in exposed by Rome II 2.30 (95% CI 1.63-3.26)

- Prevalence of dyspepsia higher in females; smokers; premorbid IBS; anxiety or depression; >7 days diarrhea or cramps during illness

**Birth & Early Environment in FD**

Survey of 670 people from a random population sample from Sydney, Australia who responded to a valid survey in 1997 and 2009.

<table>
<thead>
<tr>
<th>Variables</th>
<th>FD % (n)</th>
<th>Non-FD % (n)</th>
<th>OR (95%CI), P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean Delivery</td>
<td>6.3 (5)</td>
<td>3.3 (19)</td>
<td>0.50 (0.18,1.38), P=0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.76 (0.24,2.38), P=0.64*</td>
</tr>
<tr>
<td>Prematurity (Yes)</td>
<td>7.0 (5)</td>
<td>7.8 (43)</td>
<td>0.90 (0.34,2.35), P=0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.96 (0.36,2.54), P=0.93*</td>
</tr>
<tr>
<td>Breastfed (Yes)</td>
<td>85.1 (57)</td>
<td>86.5 (463)</td>
<td>0.89 (0.43,1.81), P=0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.09 (0.50,2.35), P=0.83*</td>
</tr>
<tr>
<td>Duration of Breastfeeding</td>
<td>5.50 (3.20)</td>
<td>7.86 (4.87)</td>
<td>0.87 (0.76,1.0), P=0.05</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pet Exposure (Yes)</td>
<td>67.8 (61)</td>
<td>58.7 (393)</td>
<td>1.48 (0.93,2.37), P=0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.39 (0.85,2.28), P=0.19*</td>
</tr>
<tr>
<td>Herbivore Pet (Yes)</td>
<td>34.4 (31)</td>
<td>22.7 (152)</td>
<td>1.79 (1.19,2.87), P=0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.83 (1.17,2.99), P=0.02*</td>
</tr>
<tr>
<td>Carnivore Pet (Yes)</td>
<td>65.6 (90)</td>
<td>54.6 (366)</td>
<td>1.58 (1.0,2.51), P=0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.49 (0.92,2.42), P=0.11*</td>
</tr>
<tr>
<td>Omnivore Pet (Yes)</td>
<td>4.4 (4)</td>
<td>4.8 (32)</td>
<td>0.93 (0.32,2.69), P=0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.93 (0.31,2.75), P=0.90*</td>
</tr>
<tr>
<td>Sharing a bedroom (Yes)</td>
<td>79.3 (69)</td>
<td>72.3 (441)</td>
<td>1.47 (0.85,2.54), P=0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.45 (0.82,2.57), P=0.20*</td>
</tr>
<tr>
<td>Hygiene Factors (Yes)</td>
<td>92.2 (83)</td>
<td>84.0 (563)</td>
<td>2.25 (1.0,5.0), P=0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.90 (0.85,4.26), P=0.12*</td>
</tr>
</tbody>
</table>

*controlling for age and gender
Development of IBS was associated with:

- A shorter duration of breastfeeding
- Sharing a bedroom
- Exposure to a herbivore pet
- Hygiene factors (sharing bedroom, pet exposure)

Development of FD was associated with:

- Exposure to a herbivore pet

These findings provide intriguing potential support for the ‘disappearing microbiome’ theory in the pathogenesis of IBS and FD
Traditional Pathophysiology FD
Gastric Pathophysiology King?

1/3 Impaired fundic accommodation

Functional dyspepsia with early satiety

1/3 Delayed gastric emptying

Correlates very poorly with symptoms

1/3 Hypersensitivity to gastric distention

Functional dyspepsia with pain

Gastric Emptying is Abnormal in Population-Based (Non-Health Care Seeking) Dyspeptic Subjects – A Disease Marker

- Gastric emptying time ($t_{1/2}$ in minutes) of healthy blood donors with versus those without GI symptoms, and of patients (*$p<0.025$, ***$p<0.001$ v asymptomatic controls).

Slow Gastric Emptying in FD NOT Linked to Any Specific Symptom Profile

<table>
<thead>
<tr>
<th>Symptom severity</th>
<th>Functional Dyspepsia</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>Upper</td>
<td>Lower</td>
<td>P-value</td>
</tr>
<tr>
<td>Fullness</td>
<td>0.997</td>
<td>0.989</td>
<td>1.005</td>
<td>0.5</td>
</tr>
<tr>
<td>Bloating</td>
<td>0.999</td>
<td>0.992</td>
<td>1.006</td>
<td>0.8</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td>1.002</td>
<td>0.996</td>
<td>1.009</td>
<td>0.5</td>
</tr>
<tr>
<td>Early satiety</td>
<td>1.001</td>
<td>0.996</td>
<td>1.006</td>
<td>0.7</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>1.000</td>
<td>0.995</td>
<td>1.005</td>
<td>0.99</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.001</td>
<td>0.996</td>
<td>1.006</td>
<td>0.8</td>
</tr>
<tr>
<td>Belching</td>
<td>0.998</td>
<td>0.992</td>
<td>1.003</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.000</td>
<td>0.994</td>
<td>1.006</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Abnormal Fundic Relaxation in Response to Meal in 40% with FD

Impaired Gastric Accommodation in FD

Impaired Gastric Accommodation in FD Greater if Anxiety

Possible pathways for which experimental data exist

Impaired gastric accommodation in FD more likely to occur with acute (?post-infectious) onset

Visceral Hypersensitivity (Barostat): All in the Stomach in FD and Why?

Prevalence (% of Patients)

- Control
- Organic dyspepsia
- Functional dyspepsia

- Normal sensitivity
- Hypersensitivity

Duodenal Perception Thresholds in FD (NUD) and Irritable Bowel Syndrome (IBS)

Impaired Sensory Thresholds and Small Intestinal Reflexes to Balloon Distension in FD

Duodenal distension inhibited motility in 5/12 patients with dyspepsia compared with 11/12 controls (P<0.05)

After acid infusion in the fasting period, a greater increase in acidity in the duodenal bulb (P = 0.007) and fewer duodenal pressure waves (P = 0.002) in dyspepsia, and significantly increased nausea score

Rare Disease Research at Mayo Clinic: Eosinophilic Gastroenteritis (EG)

- Small bowel: both eosinophil infiltration and extracellular MBP deposition scores significantly greater in EG.
- Gastric: extracellular MBP deposition scores significantly increased in EG; eosinophil infiltration scores did not differ.

Coeliac Disease, Dyspepsia and Eosinophils?

- Activated eosinophils in coeliac mucosa
- Release cytotoxic proteins – major basic protein (MBP)
- Contribute to mucosal damage
- Positive coeliac serology higher in dyspepsia (7.9%) vs. controls (3.9%: OR 1.89; 95% CI 0.90-3.99)

EG vs. Functional Dyspepsia?

- 4 males and 2 females; mean age 31.5 years with dyspepsia
- Median duration of symptoms prior to diagnosis 5 weeks to 13 years
- Epigastric pain or discomfort (100%), nausea (67%), vomiting (33%)
- 50% history of allergy
- 67% peripheral eosinophilia
- EGD normal or erosions
- All responded to oral steroids within two months
- One third needed to continue on a small dose of maintenance steroids to remain in remission

Duodenal Disturbances in FD - 10 years Copenhagen UEGW: Talley & Walker 2005

- Duodenal hypersensitivity
- Duodenal acid sensitivity
- Duodenal acid “hold up”
- Duodeno-gastric reflex/vagal alterations
- Duodenum reported to be normal histologically: What is normal?
- Eosinophil hypothesis - subtle eosinophilia (link to coeliac/EG)?
Forskare viii studera cancerörekomster

Unik studie genomfors i ostra Norrbotten

KAUKE HARRANDA
2 500 Kallax- och Haparans invånare ska delta i en unik studie genomförd av Kallax och Haparans kommuner. Studien är utförd för att studera hur långt det är möjligt att förlänga livslängden på grund av en bättre och effektivare behandling av cancer.

Studien kommer att utgöras av en långsiktig studie som inkluderar ett antal olika variabler som kan påverka risken för cancer. Studien är utförd av Kallax och Haparans kommuner och kommer att täcka en tidslagring på 10 år.

Studien kommer att inkludera patienter med både sol- och kropshälsor, samt patienter med cancer av både huvud- och bröstkanslierna. Studien kommer att inkludera patienter med både sol- och kropshälsor, samt patienter med cancer av både huvud- och bröstkanslierna.

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Duodenum Normal in FD? NO!

- Count eosinophils H&E (x40 magnification)
- High power field (standardised microscope)
- Eosinophil counts in 5HPF
- Sum and mean calculated for the 5 counts (concordance good to excellent)

SWEDEN

- 55 subjects with FD
- Duodenal eosinophilia & early satiety
- Clusters
- Eosinophil degranulation
Duodenal Eosinophilia in 40% of FD – Early Satiety

- Clusters of eosinophils (circled) in the lamina propria adjacent to glands in a subject with non-ulcer dyspepsia

### Association Between Duodenal Eosinophil Counts (sums) and Functional Dyspepsia

<table>
<thead>
<tr>
<th></th>
<th>Univariate Results</th>
<th>Adjusting for Age, Gender &amp; <em>H. pylori</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eosinophils</strong></td>
<td>n/N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Duodenal bulb</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;22</td>
<td>12/42 (29)</td>
<td>7.7 (3.0,19.6)</td>
</tr>
<tr>
<td>≥22</td>
<td>37/49 (76)</td>
<td></td>
</tr>
<tr>
<td><strong>Duodenum 2nd portion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21</td>
<td>13/47 (28)</td>
<td>6.9 (2.8,16.8)</td>
</tr>
<tr>
<td>≥21</td>
<td>37/51 (73)</td>
<td></td>
</tr>
</tbody>
</table>

The values chosen to dichotomize the continuous values of eosinophils is ≥ median value

## Association of Troublesome Upper GI Symptoms with Eosinophilia in the Duodenum

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Duodenal bulb</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR†(95%CI)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Epigastric Pain</td>
<td>1.09 (0.92, 1.29)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Postprandial fullness</td>
<td>1.05 (0.92, 1.21)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td><strong>Early satiety</strong></td>
<td><strong>1.21 (1.04, 1.40)</strong></td>
<td><strong>0.01</strong>*</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1.18 (1.00, 1.39)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.10 (0.88, 1.36)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td><strong>Retching</strong></td>
<td><strong>1.21 (1.03, 1.42)</strong></td>
<td><strong>0.02</strong>*</td>
<td></td>
</tr>
<tr>
<td>Retrosternal pain</td>
<td>1.32 (1.08, 1.61)</td>
<td><strong>0.01</strong>*</td>
<td></td>
</tr>
<tr>
<td>Heartburn</td>
<td>0.98 (0.80, 1.21)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1.08 (0.79, 1.48)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>1.08 (0.94, 1.24)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Borborygmi</td>
<td>1.03 (0.88, 1.20)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.08 (0.88, 1.33)</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>

† Odds Ratio per 5 counts from logistic regression models including age, gender, and H. pylori infection as covariates
Mast cells in the upper small intestine a marker for IBS, not pure FD

Muscularis mucosa

Gastric Eosinophils: *H. pylori* Positive vs. *H. pylori* Negative


\[ \text{Including age and gender as covariates in the model} \]
155 patients (mean age 55 years, 59% females) with normal duodenal biopsies at random

Postprandial distress syndrome (PDS) mean eosinophil counts (20.2/5HPF, p<0.04) and prevalence of duodenal eosinophilia (47%, p<0.04) higher

Duodenal eosinophilia associated with allergy (OR 5.04, 95% CI 2.12-11.95, p<0.001) but not IBS or medications

Australian Study 2015: FD and Duodenal Eosinophilia

- Two observers counted eos in duodenal bulb (D1) and second part (D2).
- *H. pylori* assessed by gastric histology

Smoking Associated with Higher Eosinophil Counts in FD

Mast Cells & Eosinophils in the Duodenum of Smokers (Kalixanda)

- There was a tendency for eosinophilia in D1 of smokers
- Mast cells significantly reduced in the first part of the duodenum of smokers, compared to non-smokers (median: 167 vs 238, p=<0.01)

Eosinophils as a Biomarker in Subsets of FD – Degranulation and Nerves

- Early satiety
- Abdominal pain
- Smoking
Carbol Chromotrope (Pink Cytoplasmic Granules) and CD 4 (Brown Cytoplasm) Double Staining in Duodenal Mucosa to Show Juxtaposition of TH2 T Cells and Eosinophils

Case

Control

Independent Verification Leuven
Duodenal Eosinophils in FD

- Duodenal biopsies n= 15 FD Rome III and 15 controls
- Transepithelial electrical resistance (TEER) and paracellular permeability measured in Ussing chambers
- Expression of cell-to-cell adhesion proteins
- Mast cells, eosinophils immunohistochemistry
- FD lower TEER and increased paracellular passage
- Abnormal expression of cell-to-cell adhesion proteins
- Increased infiltration mucosal mast cells and eosinophils
- Association between extent of increased permeability and the severity of low-grade inflammation
Immune cell infiltration. Duodenal biopsy specimens from healthy volunteers (black dots) and patients with FD (white dots) were stained for eosinophils using eosinophilic MBP (A, B), for mast cells using tryptase (C, D) and for IELs using CD3 (E, F). Cells positive for MBP (n=14 for controls and n=12 for patients with FD) (A) and tryptase (n=15 for controls and n=12 for patients with FD) (C) were counted in at least seven non-overlapping HPFs per subject.
Integrity of Duodenal Mucosal Barrier in FD

Intestinal integrity of healthy controls (black dots) and patients with FD (white dots) was evaluated in Using chambers by measuring TEER (A) and passage of FITC-dx4 (B) of four duodenal biopsy specimens per subject. (A) TEER was recorded every 30 min over 2 h, and the average of all time points of the four specimens was taken. FD, functional dyspepsia; FITC-dx4, fluorescently labelled dextran; TEER, transepithelial electrical resistance

FD Characterized by Functional/Structural Abnormalities within Submucous Ganglion Plexus

- Submucous plexus isolated duodenal biopsies
- Neuronal functioning impaired in submucous plexus of FD - decreased calcium responses to depolarization
- Glial (S100) and neuronal (HuCD) markers show gliosis, altered ganglionic architecture, and neuronal abnormalities
- Increased eosinophils and mast cells infiltrated the submucous layer of FD vs. controls
- Significant correlation between number of eos/mast cells and calcium transient amplitudes in submucous ganglia

FD & Duodenal Eosinophilia
Global Perspective

Pre-morbid Anxiety Strongly Increases the Risk of Functional Dyspepsia

- Prospective Australian population data
- Controls (n=626) followed for 12 years (1997-2009)

Homing Small Bowel T Cells, Cytokines and FD Symptoms

- **Cytokine release** and CD4+α4β7+CCR9+ lymphocytes correlated with symptom intensity pain, cramps, nausea, vomiting

- **Delayed gastric emptying** correlated \((r=0.78, p=0.02)\) with CD4+α4β7+CCR9+ lymphocytes, and IL-1β, TNF-α and IL-10 secretion

Homing Small Bowel T Cells and FD

- Cytokine release and CD4+α4β7+CCR9+ lymphocytes correlated with symptom intensity pain, cramps, nausea, vomiting

- Delayed gastric emptying correlated (r=0.78, p=0.02) with CD4+α4β7+CCR9+ lymphocytes, and IL-1β, TNF-α and IL-10 secretion

Paediatric Studies and Duodenal Eosinophilia – FD

- Confirmation of duodenal eosinophilia in pediatric FD in the absence of macroscopic (endoscopy) or routine histology findings

- Duodenal eosinophilia should be considered as a therapeutic target in paediatric FD

<table>
<thead>
<tr>
<th></th>
<th>FD CASES (N= 36)</th>
<th>CONTROLS (N= 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (%)</td>
<td>20 (56)</td>
<td>19 (53)</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean age (± SD)</td>
<td>13.6 (± 3.1)</td>
<td>10.5 (± 4.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Personal Hx atopy (%)</td>
<td>14 (39)</td>
<td>9 (25)</td>
<td>0.21</td>
</tr>
<tr>
<td>Psychological co-morbidity (%)</td>
<td>19 (53)</td>
<td>14 (39)</td>
<td>0.24</td>
</tr>
<tr>
<td>Family Hx functional GI disorder (%)</td>
<td>10 (28)</td>
<td>1 (3)</td>
<td>.003</td>
</tr>
<tr>
<td>Median duodenal IEL counts per 100 enterocytes (IQR)</td>
<td>10 (8-13)</td>
<td>12 (8-18)</td>
<td>0.12</td>
</tr>
<tr>
<td>Median duodenal eosinophils counts per mm² (IQR)</td>
<td>151 (118-207)</td>
<td>76 (60-106)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>
CHILDHOOD RECURRENT ABDOMINAL PAIN IS ASSOCIATED WITH DUODENAL EOSINOPHILIA REGARDLESS OF H. PYLORI INFECTION

L. Wauters¹, P. Harris², C. Serrano², A Villagrán², I Duarte³, G Rakhra⁴, MP Jones⁵, NJ Talley⁶, JE Crabtree J⁷, MM Walker⁶

- 72 RAP, 29 controls from Chile
- No significant differences in demographics, clinical symptoms, H. pylori and endoscopic findings between cases and controls
- Median (IQR) duodenal eosinophils /5HPF were 86 (62-114) in cases and 49 (31-88) in controls (***p< 0.001)
- Children with a clinical diagnosis of RAP have duodenal eosinophilia, independent of H. pylori infection, suggesting the role of unknown infectious or allergic triggers in the pathogenesis of functional gastrointestinal disorders in childhood
• Innate immune alteration in intestinal mucosa Ξ bronchial mucosa in asthma

• FD increased duodenal eosinophils

• IBS increased mast cells in duodenal and colonic mucosa.

• Asthma is exacerbated by infection - PI- IBS described

• Atopy characterised by imbalance of the stress axis response - neurogenic inflammation with a cytokine TH2 cytokine bias leads to exacerbation of atopic disease Ξ stress implicated in IBS

## Traditional Pharmacologic Strategies for FD

<table>
<thead>
<tr>
<th>Therapeutic intervention</th>
<th>Efficacy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em> eradication</td>
<td>36% vs 30% placebo; NNT 15</td>
<td>Meta-analysis of 17 RCTs</td>
</tr>
<tr>
<td>PPIs</td>
<td>33% vs 23% placebo; NNT 10</td>
<td>Meta-analysis of 10 RCTs</td>
</tr>
<tr>
<td><strong>H₂-receptor antagonists – a paradox!</strong></td>
<td></td>
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<tr>
<td></td>
<td>More efficacious than placebo for epigastric pain/postprandial fullness</td>
<td>Meta-analysis of 11 RCTs; NNT 7</td>
</tr>
<tr>
<td></td>
<td>Higher response than PPIs (more heterogeneous data)</td>
<td><em>Why are H₂ blockers better as less effective at acid suppression?</em></td>
</tr>
<tr>
<td>Antidepressants – TCAs</td>
<td>NIH FDDT trial <em>(Talley)</em></td>
<td>Modest efficacy (SSRIs, SNRIs NO efficacy)</td>
</tr>
<tr>
<td>Antacids</td>
<td>No better than placebo</td>
<td>1 RCT only</td>
</tr>
<tr>
<td>Bismuth salts</td>
<td>No better than placebo</td>
<td>Meta-analysis of 5 RCTs</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>No better than placebo</td>
<td>Meta-analysis of 2 RCTs</td>
</tr>
</tbody>
</table>

Talley & Ford, NEJM. 2015.
Duodenal Eosinophils Suppressed on PPI – 10 Adult Patients, 10 Age and Sex Matched Controls

Duodenal Eosinophil Count

P=0.03

Duodenal Eosinophils Suppressed on PPI – Not Just Acid!

- IL-13 increases Eotaxin-3 in immortalised EoE epithelial cells
- Omeprazole (PPI) blocks IL-13 induced Eotaxin-3 release
- PPI can decrease inflammation e.g. IL-8, VCAM

Montelukast in FD and Eosinophilia (Paediatrics)

- N=40 children (6-18 yr) dyspepsia & duodenal eosinophilia
- Double blind, randomized, placebo-controlled, cross-over study monteleukast 10 mg vs identical placebo once daily
- Evaluated on day 14 for symptomatic responses

Global Response

Montelukast in FD and Eosinophilia (Paediatrics)

- Competitive antagonist of the cys LT\(_1\) receptor
- n=24; 83% a positive clinical response to montelukast
- 50% a complete or nearly complete clinical response
- Unrelated to systemic drug exposure or to mucosal drug concentration
- No significant changes in eosinophil density, eosinophil activation, or serum cytokines

Future Studies

• Anti-eosinophil treatment in early satiety and eosinophilia
  – Montelukast
  – Budesonide
  – IL-5 antibody
  – IL-13 antibody

• Functional?
An Overarching Disease Model of Functional Dyspepsia

Post-infectious FD & IBS

- Rotavirus infection leads to transient delayed gastric emptying
- Giardia intestinalis produces mainly post infectious FD
- Salmonella spp. and Campylobacter jejuni cause terminal ileitis and colitis, associated equally with both postinfectious FD and postinfective IBS

- Overlap of FD with reflux symptoms
- PDS at baseline: 4.5 fold increased risk of incident GERS 10 years later (not EPS)
- Duodenal eosinophils
- PDS & impaired fundic accommodation* increased TLESRs*
- Gastro-oesophageal reflux disease (GERD)

Patients with IBS have a different microbiome to healthy controls

1.5-fold decrease in numbers of Bifidobacterium

But no “signature”
The Brisbane Aseptic Biopsy Device (AGIRA) allows for contamination-free sampling of the MAM. This device has enabled detailed characterisation of the duodenal MAM, which is dominated by Streptococcus.

**Bacterial community profiles, grouped by biopsy device.** Each coloured bar represents a bacterial genus as assessed by 16S rRNA gene sequencing followed by taxonomic assignment.

**Most abundant genera are:**
1. Streptococcus
2. Prevotella
3. Lactobacillus
4. Veillonella
5. Neisseria
6. Porphyromonas

Translation into practice: Recommended Treatment Algorithm for Patients with a Provisional Diagnosis of Functional Dyspepsia

Epigastric pain or burning, early satiety, or postprandial fullness

Alarm symptoms present?

Yes

Urgent upper EGD

Abnormal

Treat relevant underlying organic pathology

No

Normal

Local H. pylori prevalence ≥10%?

Yes

Non-invasive testing for H. pylori

Positive

H. pylori eradication therapy

Success

No

Negative

Failure†

Discharge

Discharge, and try drug holiday in 3 months

Empirical acid suppression therapy for 4-8 weeks

Yes

Prokinetic e.g. acotiamide, where locally available, domperidone, or metoclopramide‡

Success

Failure†

Discharge, and try drug holiday in 3 months

Postprandial distress syndrome present?

Yes

Discharge

Failure†

Avoid opiates

Consider:

Psychological therapy

Combination therapy using >1 pharmacological agent

Complementary or alternative therapies

No

Failure†

Discharge, and try drug holiday in 3 months

*Via C13 urea breath test or stool antigen off PPI for ≥1 week

†Re-evaluate and reconsider the diagnosis at each step via further investigation, if necessary:

EGD if not performed within the last 5 years

Abdominal ultrasound, particularly if severe, intermittent pain episodes

Celiac serology

Gastric scintigraphy or C13 acetic or octanoic breath test to assess gastric emptying if symptoms severe/resistant, or vomiting and weight loss prominent

‡Limited RCT data, start at a low dose due to cardiac and neurological toxicity

Functional GI Disorders (FGIDs)?

- FGIDs – variable combinations chronic or recurrent GI symptoms do not have an identifiable pathophysiology
- Is this concept current? NO! Identifiable pathology!!!
- IBS, inflammation/cytokines, bacteria
- FD & eosinophils, homing T cells

Disorders of GI function or gut-brain/brain-gut disorders

Mast cells in IBS - POPCOL (CD117 immunostaining) – Walker & Talley.