All Roads Lead to Rome, But You Can’t Get There From Here: Confident Diagnosis and Management of Chronic Abdominal Pain

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Objectives – Illustrated with a Case

1. All Roads Lead to Rome but You Can’t Get There from Here: Looking for Red Flags in the Evaluation of Chronic Abdominal Pain and Using Rome Criteria to Diagnose Functional GI Disorders
2. Using what is known about the physiology of functional gastrointestinal disorders to convey diagnostic confidence and set the stage for recommending therapies
3. Implementing pharmacologic, non-pharmacologic, and dietary therapies for functional gastrointestinal disorders

Rome Criteria

• Symptom-based guidelines by which child and adolescent functional gastrointestinal disorders (FGID) can be diagnosed
• Combination of evidence and expert clinician consensus
• 2016: Rome IV

Disclosures

• None
Rome Criteria

Childhood Functional Gastrointestinal Disorders: Child/Adolescent

Jeffrey S. Hyams,1,2 Carlo Di Lorenzo,2,4 Miguel Saps,2 Robert J. Shulman,3 Annamaria Staiano,1 and Miranda van Tilburg5

Gastroenterology 2016; 150: 1456-1468

Part 1
Case – 15 year old female

Differential Diagnosis

- Functional Gastrointestinal Disorder
- GERD
- EoE
- Celiac
- IBD
- Gastroparesis
- SIBO
- Eating Disorder
- Endometriosis
- Biliary Disease

Case – 15 year old female

- Chief complaint: Generalized (sometimes upper) Abdominal Pain.
- Present for at least the last 6 months. Happens almost every day.
- In the upper abdomen. Feels “kinda like bloating, kinda like burning.” Some nausea, no vomiting.
- Though it can be present any time, it is most often made worse by oral intake. She tends to feel very full. There is no relation to bowel movements, which are soft and regular. No blood in the stool.
- No weight loss.
- Missing at least 2 days of school every week.
- Normal CBC, CMP, ESR, CRP, TTG-IgA. Negative Stool H pylori. Normal stool calprotectin.
- No response to proton pump inhibitor.
What’s NOT going on here

<table>
<thead>
<tr>
<th>Table 2. Potential Alarm Features in Children With Chronic Abdominal Pain*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease</td>
</tr>
<tr>
<td>Persistent right upper or right lower quadrant pain</td>
</tr>
<tr>
<td>Dysphagia</td>
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<tr>
<td>Odynophagia</td>
</tr>
<tr>
<td>Persistent vomiting</td>
</tr>
<tr>
<td>Gastrointestinal blood loss</td>
</tr>
<tr>
<td>Nocturnal diarrhea</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Perirectal disease</td>
</tr>
<tr>
<td>Involuntary weight loss</td>
</tr>
<tr>
<td>Deceleration of linear growth</td>
</tr>
<tr>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Unexplained fever</td>
</tr>
</tbody>
</table>

Gastroenterology 2016; 150: 1456-1468

Can you make a diagnosis?

Rome IV - Functional Dyspepsia

H2a. Diagnostic Criteria* for Functional Dyspepsia

Must include 1 or more of the following bothersome symptoms at least 4 days per month:

1. Postprandial fullness
2. Early satiation
3. Epigastric pain or burning not associated with defecation
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Rome IV - Irritable Bowel Syndrome

H2b. Diagnostic Criteria* for Irritable Bowel Syndrome

Must include all of the following:

1. Abdominal pain at least 4 days per month associated with one or more of the following:
   a. Related to defecation
   b. A change in frequency of stool
   c. A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

*Criteria fulfilled for at least 2 months before diagnosis.
**Rome IV – FAP-NOS**

H2d. Diagnostic Criteria® for Functional Abdominal Pain–NOS

Must be fulfilled at least 4 times per month and include all of the following:

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses)
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition

®Criteria fulfilled for at least 2 months before diagnosis.

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**Now can you make a diagnosis?**

- No Red Flags
- History could certainly be consistent with Functional Dyspepsia
- Appropriate Evaluation?

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**Appropriate Evaluation?**

- The most appropriate evaluation is the one that allows:
  - Provider to be satisfied with the diagnosis
  - Patient and family to be satisfied with the diagnosis

  *Satisfied = Able to tolerate the remaining uncertainty and move forward with non-specific therapies to target symptoms of functional disorders rather than continuing to perseverate on/wonder “what’s wrong?”

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**Can you make a diagnosis YET?**

- Rome III: “no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explain the subject’s symptoms”
- Rome IV: “after appropriate medical evaluation, the symptoms cannot be attributed to another medical condition”
- Paradigm shift from a diagnosis of exclusion to diagnosis in a positive fashion based on clinical criteria.

Gastroenterology 2016; 150: 1456-1468
"...it seems clear that technology will perform the routine tasks of medicine for which algorithms can be developed. Our value as physicians will lie in the gray-scale space, where we will have to support patients who are living with uncertainty — work that is essential to strong and meaningful doctor–patient relationships."

Summary 1

- Identification of Red Flags is helpful in the evaluation of chronic abdominal pain.
- Functional Gastrointestinal Disorders can be diagnosed in a positive fashion based on clinical criteria.
- An appropriate evaluation is one that allows the provider and the patient to tolerate the uncertainty inherent in a functional diagnosis and move forward with therapy.
**Concepts in Pathophysiology**

- Disordered gut-brain axis
  - Abnormalities in 5-hydroxytryptamine (5-HT) metabolism.
- Dietary effects
- Genetic factors
- Infections and disturbances in the intestinal microbiota
- Low-grade mucosal inflammation
- Immune activation
- Altered intestinal permeability
- Disordered bile salt metabolism

**Limited Knowledge Based**

Crohn’s: 318.5/100,000 = 0.3%

Pain-Predominant FGID: 15%

- Functional -28 hits
- Ped. Crohn’s 128 hits

**But there’s still A LOT we know**
**PAG: Relevance to Chronic Pain**

- Area of the brain known to have an important role in pain processing
- Since 2001, differences in periaqueductal gray matter activity and/or connectivity have been associated with:
  - irritable bowel syndrome
  - primary dysmenorrhea
  - migraine
  - chronic low back pain

*Gastroenterology 2001;120:369-376
Neurogastroenterol Motil 2017;29:e13060*

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**PAG: Relevance to Chronic Anxiety**

- PAG has significant functional connections to the bed nucleus of the stria terminalis (BNST)
- BNST seems to have an important role in stress response and in anxiety and addiction
- Anxiety and FGIDs are commonly co-morbid

*Neuropsychopharmacology REVIEWS 2016;41:126-141*

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**Disordered Brain-Gut Axis: Starts with PAG**

*Gastroenterology 2001;120:369-376
Brainstem Periaqueductal Gray Matter*
Summary 2

- Periaqueductal Gray is important in pain processing and signaling.
- Visceral pain shares some CNS signaling pathways with chronic anxiety (through the PAG).
- There may be a bidirectional relationship between anxiety, depression, and chronic GI pain.

Pharmacologic Therapy

- Cyproheptadine
- Amitriptyline
- Citalopram
- Peppermint Oil

Cochrane Database Syst Rev 2017 Review conclusion: “...There is currently no convincing evidence to support the use of drugs to treat RAP in children. Well-conducted clinical trials are needed to evaluate any possible benefits and risks of pharmacologic interventions...”

Cyproheptadine Use in Children With Functional Gastrointestinal Disorders

Retrospective, Single Center, Single Clinician

Conclusion: cyproheptadine effective for improving symptoms of FGIDs

JPGN 2016;62:409-413
Antidepressants

TCA and SSRI are effective in adults

Am J Gastroenterol 2014;109:1350–1365
Neurogastroenterol Motil 2014;26:1642–1650

Amitriptyline

- RCT: AMI vs Placebo
- Primary Outcome: QoL
- AMI > Placebo

J Pediatr 2008;152:685-9

- RCT: AMI vs Placebo
- Primary Outcome: Pain
- Significant improvement in sx over time
- No difference between AMI and placebo

Gastroenterology 2009;137:1261–1269

Citalopram

RCT: CIT vs Placebo
Primary Outcome: Pain
Difference not significant, both groups improved

Neurogastroenterol Motil 2014;26:1642–1650

Peppermint Oil

RCT: Peppermint Oil vs Placebo
Primary Outcome: Pain
Significant Difference with improvement in peppermint oil group

J Pediatr 2001;138:125-128

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Much worse</th>
<th>Worse</th>
<th>No effect</th>
<th>Better</th>
<th>Much better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint oil</td>
<td>Frequency</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Percent</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>Frequency</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Percent</td>
<td>10</td>
<td>19</td>
<td>28</td>
<td>43</td>
</tr>
</tbody>
</table>

*P < .002.
Non-Pharmacologic Therapy

- Meditation/Mindfulness
- Hypnotherapy
- Cognitive Behavioral Therapy
- *Cochrane Database Syst Rev* 2017 Review conclusion: “...data from trials to date provide some evidence for beneficial effects of CBT and hypnotherapy in reducing pain in the short term in children and adolescents presenting with RAP... there were insufficient data to explore effects of treatment by RAP subtype.”

### Meditation

**Mindfulness-Based Stress Reduction for the Treatment of Irritable Bowel Syndrome Symptoms: A Randomized Wait-list Controlled Trial**

RCT: mindfulness program vs waitlist
Primary Outcome: IBS symptom scale
Clinically meaningful decrease in symptom severity

### Hypnotherapy

**Hypnotherapy for Children With Functional Abdominal Pain or Irritable Bowel Syndrome: A Randomized Controlled Trial**

RCT: Gut-directed hypnotherapy vs standard care
Outcomes: Pain intensity score, frequency score
*Significant improvement in pain freq and intensity*
*Gastroenterology* 2007;133:1430-1436

### Cognitive Behavioral Therapy

**Internet-Delivered Cognitive Behavior Therapy for Adolescents With Irritable Bowel Syndrome: A Randomized Controlled Trial**

RCT: iCBT vs waitlist control
Outcome: IBS symptom scale
*Statistical Improvement in symptom scale over time in the treatment group*
*Am J Gastroenterol* 2017;112:152-162
Dietary Interventions

• Low-FODMAP Diet

• Probiotics

• Cochrane Database Syst Rev 2017 Review conclusion:
“...moderate to low quality evidence suggesting that probiotics may be effective in improving pain in children with RAP...there was no convincing evidence that fibre-based interventions improve pain in children with RAP...future trials of low FODMAP diets...are also required.”

Low FODMAP Diet

• FODMAP = Fermentable oligosaccharides, disaccharides, monosaccharides and polyols

• As a result of poor absorption, these carbohydrates may contribute to gastrointestinal symptoms.
  - Luminal Distension (osmotic)
  - Rapid Fermentation

• Low FODMAP diet comprehensively limits consumption of fermentable carbohydrates.

• Evidence for efficacy in Adults

Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome

• Randomized cross-over design with 7 day washout period.
• FODMAP group: 1.1/day
• TACD group: 1.4/day P < 0.05
• Modest, significant improvement

Probiotics

Multiple RCTs.
Multiple different strains/products used.
Favorable pooled analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotic Events</th>
<th>Placebo Events</th>
<th>Odds Ratio M vs. F (95% CI)</th>
<th>Odds Ratio M vs. F (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 2015</td>
<td>11</td>
<td>25</td>
<td>1.10 (0.89, 1.35)</td>
<td></td>
</tr>
<tr>
<td>Overall 2016</td>
<td>15</td>
<td>40</td>
<td>0.64 (0.32, 1.30)</td>
<td></td>
</tr>
<tr>
<td>Overall 2017</td>
<td>25</td>
<td>52</td>
<td>1.20 (0.74, 1.95)</td>
<td></td>
</tr>
<tr>
<td>Overall 2018</td>
<td>25</td>
<td>52</td>
<td>1.15 (0.64, 2.05)</td>
<td></td>
</tr>
<tr>
<td>Overall 2019</td>
<td>25</td>
<td>52</td>
<td>1.15 (0.64, 2.05)</td>
<td></td>
</tr>
<tr>
<td>Overall 2020</td>
<td>44</td>
<td>59</td>
<td>1.03 (0.60, 1.73)</td>
<td></td>
</tr>
<tr>
<td>Overall 2021</td>
<td>27</td>
<td>45</td>
<td>1.26 (0.96, 3.33)</td>
<td></td>
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<tr>
<td>Overall 2022</td>
<td>44</td>
<td>59</td>
<td>1.03 (0.60, 1.73)</td>
<td></td>
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<tr>
<td>Overall 2023</td>
<td>27</td>
<td>45</td>
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<td></td>
</tr>
<tr>
<td>Overall 2024</td>
<td>44</td>
<td>59</td>
<td>1.03 (0.60, 1.73)</td>
<td></td>
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<tr>
<td>Overall 2025</td>
<td>27</td>
<td>45</td>
<td>1.26 (0.96, 3.33)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>361</td>
<td>361</td>
<td>1.63 (1.67, 2.47)</td>
<td></td>
</tr>
</tbody>
</table>
Weaknesses of the Literature

- Few controlled trials
  - Small sample sizes
  - Not reproduced
- Heterogeneous populations
  - All use Rome criteria
  - Some include all pain-predominant syndromes
- Heterogeneous outcomes
  - Most are reported by the subject
- No comparisons of interventions

Summary 3

- There are many safe pharmacologic, non-pharmacologic, and dietary interventions that can be considered to treat functional gastrointestinal disorders.
- All have been studied in small scale and generally have relatively small effect compared to placebo.
- Few to none have been studied on a large scale or reproduced.
- And if you were paying attention to some of those graphs...

Placebo

<table>
<thead>
<tr>
<th>Study name</th>
<th>Improvement rate (%)</th>
<th>Placebo rate and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christensen et al.</td>
<td>62.5</td>
<td>37.7 (21.8, 73.6)</td>
</tr>
<tr>
<td>Feldman et al.</td>
<td>26.9</td>
<td>13.4 (5.2, 21.6)</td>
</tr>
<tr>
<td>See et al.</td>
<td>12.0</td>
<td>3.9 (0.2, 21.7)</td>
</tr>
<tr>
<td>Kline et al.</td>
<td>33.3</td>
<td>16.8 (5.7, 45.3)</td>
</tr>
<tr>
<td>Baussman et al.</td>
<td>40.0</td>
<td>23.0 (9.7, 36.0)</td>
</tr>
<tr>
<td>Gawriniska et al.</td>
<td>44.2</td>
<td>31.5 (23.6, 39.4)</td>
</tr>
<tr>
<td>Bahar et al.</td>
<td>2.8</td>
<td>0.2 (0.0, 3.2)</td>
</tr>
<tr>
<td>Sadeighan et al.</td>
<td>39.7</td>
<td>15.7 (8.2, 43.7)</td>
</tr>
<tr>
<td>Sapi et al.</td>
<td>52.3</td>
<td>37.7 (16.7, 66.3)</td>
</tr>
<tr>
<td>Guiraudet et al.</td>
<td>49.0</td>
<td>36.7 (23.8, 60.0)</td>
</tr>
<tr>
<td>Alghamdi et al.</td>
<td>17.0</td>
<td>6.9 (0.7, 20.0)</td>
</tr>
<tr>
<td>D. Nanto et al.</td>
<td>52.0</td>
<td>33.1 (10.0, 73.2)</td>
</tr>
<tr>
<td>Komario et al.</td>
<td>6.7</td>
<td>1.7 (0.0, 22.2)</td>
</tr>
<tr>
<td>Horvath et al.</td>
<td>46.5</td>
<td>32.3 (16.7, 61.7)</td>
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<tr>
<td>Poumpoukhaldas et al.</td>
<td>38.4</td>
<td>12.8 (0.7, 43.8)</td>
</tr>
<tr>
<td>Kuranangiyake et al.</td>
<td>59.5</td>
<td>44.3 (23.7, 71.2)</td>
</tr>
<tr>
<td>Zbych et al.</td>
<td>56.0</td>
<td>24.4 (10.0, 70.0)</td>
</tr>
<tr>
<td>Pooled</td>
<td>40.9</td>
<td>33.8 (26.7, 43.9)</td>
</tr>
</tbody>
</table>

41% of patients improve with placebo!

Placebo studies also reveal the value of social interaction as a treatment for pain...researchers studied patients in pain from irritable bowel syndrome and found that 44 percent of those given sham acupuncture had adequate relief from their symptoms.

If the person who performed the acupuncture was extra supportive and empathetic, however, that figure jumped to 62 percent.”

- NY Times, 1/9/2016
Grand Summary

• Though our understanding of their physiology is incomplete, Functional Gastrointestinal Disorders should be diagnosed in a positive fashion.
  - Objective evaluation should target tolerance of the uncertainty inherent in a functional diagnosis.

• There is evidence to suggest that there are difference in neurological signaling (brain-gut interaction) between people with and without FGIDs.

• There are many safe pharmacologic, non-pharmacologic, and dietary therapies that can be considered for treatment of FGIDs.
  - Ultimately our time, validation, and empathy may be just as important as any of them

References


