TITLE: A Comprehensive Review of Functional Dyspepsia in Pediatrics

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Abstract (250 words):

Functional gastrointestinal disorders have been known as a diagnosis of exclusion since the Rome Foundation first created these criteria in 1990. Since that time, a large amount of research and clinical data has better clarified the mechanisms and treatment options for these. Functional dyspepsia is caused by physiologic, genetic, environmental, and psychological factors, as well as various functional abnormalities such as increased sensitivity to acid, increased sensitivity to duodenal lipids and low-grade inflammation. This disorder has significant symptom overlap between other functional disorders such as irritable bowel syndrome and gastroparesis but has differential criteria and two new subclasses: postprandial distress syndrome and epigastric pain syndrome. Diagnosis of functional dyspepsia should be based upon appropriate clinical evaluation in tandem with Rome IV criteria. In recent years, many treatment measures for functional dyspepsia have been studied, such as pharmacologic intervention, behavioral therapy, or alternative therapy, an example being hypnotherapy. These treatment measures and have proven to be effective in symptom reduction in pediatrics. Though this disorder is functional, it has been shown to cause a significant impact on pediatric patients' quality of life continuing into adulthood.

Key Words (4-6):

Functional Dyspepsia. Pediatrics. Gastrointestinal Disorders. Treatment. Rome IV Criteria.

Introduction

Functional disorders have been known as a class of diagnosis based on exclusion of other disease processes rather than testing protocol. The Rome Foundation first developed criteria for diagnosing functional gastrointestinal disorders (FGID) in 1990. These criteria were created by the committee to reflect the most recent literature review and give guidelines for approaching functional disorders. The Rome Foundation has since redefined FGID three times until most recently with the Pediatric Rome IV criteria created in 2016 [1].

The Rome IV criteria for diagnosing functional dyspepsia (FD) states that the child must experience at least one of the following bothersome symptoms for greater than 4 days per month and have had the symptoms for longer than two consecutive months. The symptoms include postprandial fullness, early satiation, or epigastric pain or burning not associated with defecation. The diagnosis no longer requires abdominal pain to be the chief complaint. Since this is a functional disorder, a major criterion for diagnosis is that after appropriate evaluation, the symptoms cannot be explained by another medical condition. Rome IV criteria also created two subtypes of FD: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). PDS includes bothersome postprandial fullness or early satiation which prevents the child from finishing meals. This also includes symptoms of abdominal bloating, postprandial nausea, or excessive belching after meals. EPS, on the other hand, focuses on a bothersome pain or burning sensation in the epigastric region that does not localize to other abdominal or chest regions. Also, this sensation should not be relieved by defecation or flatulence. The pain can be induced or relieved by eating meals and may occur while fasting. Turco R, et al**.** [2] reported that the two distinct FD subtypes are identifiable in the pediatric population. They reported 17% classified as EPS, 47% as PDS, and 36% had an overlap between the two subtypes. After six months, 19% of the PDS group changed to EPS group, and 19% changed to the overlap group respectively. Off the initial 36% in the overlap group, 30% changed to PDS and 19% to EPS group after 6 months. There is a high percentage of overlap and variation of subtypes overtime.

Epidemiology

FGID impacts anywhere between 1-30% of the pediatric population worldwide across all age groups and various functional disorders [3]. Utilizing Rome IV criteria, FD is prevalent in roughly 10% of individuals. Children with a

FGID have about a 1-in-3 chance of continuing to have symptoms of FGID into adulthood despite treatment. The transition of care from a pediatric to adult gastrointestinal provider is crucial to ensure these patients continue to have their FGID managed properly. Adult care tends to focus more on patient autonomy rather than pediatrics which tends towards growth and family [4]. It is necessary for the pediatric provider to evaluate the patient's readiness to transition to adult practice. Though there is limited data on the difference of disease prevalence between males and females in pediatric populations, Sun Kim and Kim conducted a review of adult FD prevalence and found that the female-to-male ratio of uninvestigated by gastroduodenoscopy, FD across all geographic regions in the world was 1.24:1 [5]. The study found that a significantly higher number of females met the Rome IV criteria for FD in all age groups from 18 to 65+ years old. The studies reviewed by this article also found that females tend to have a lower quality of life associated with FD.

The prevalence of FD (functional dyspepsia) has been reported as 2.8% among teenagers between the ages of 10-15 years in Japan. These patients have been found to have impaired sleep and eating habits, and frequent symptoms of comorbid orthostatic dysregulation and headaches [6]. There is also a high prevalence of FGID found among pediatric patients with persistent asthma. These patients have poor asthma control and increased anxiety [7]. Obese and overweight children are more likely to develop FD than normal weight peers. FD was found to be 23% more prevalent in obese pediatric patients versus 7% in normal weight controls [8]. There is a link between excess body fat and anxiety in children. There is an effect of food and nutritional substances, gut microbial environment, and psychological factors associated with obesity. Furthermore, FD has been significantly associated with the presence of migraines in children and adolescents. FGID's have been reported in 30-70% of patients with Autism spectrum disorders (ASD). In a retrospective study of children and adults, it was found that a third of ASD patients had FGID's. Moreover, the presence of FGID's in these patients was significantly associated with intellectual disability, sleep disorders, and with behavioral problems [9]. The incidence of FD in ASD patients is unknown. These children may benefit from having an interdisciplinary medical team that can diagnose and treat FGID's and often associated medical conditions [10] .

Pathophysiology

The pathophysiology of FD consists of multiple mechanisms such as physiologic, genetic, environmental, and psychological factors. Functional abnormalities, such as impaired accommodation, delayed gastric emptying, and

hypersensitivity, are described as well. Some duodenal abnormalities such as increased sensitivity to acid, increased sensitivity to duodenal lipids and low-grade inflammation may be implicated in the pathophysiology of FD in adults [11]. The gastrointestinal (GI) tract is one of the most diverse and complex organs of the human body. It is involved in activities from digestion, absorption, and excretion, to endocrine and immune functions. Most of these functions are dependent on highly coordinated sensory mechanisms. This results in highly coordinated interactions among the components of gut neuromuscular comprising the enteric nervous system (ENS), which is the intrinsic nervous system of the GI tract and is present along its entire length, the smooth muscle coats, and the Interstitial Cells of Cajal. The ENS is organized as plexuses in both the large and small intestine, present in both the outer myenteric plexus that is between the inner circular and outer longitudinal muscle layers, and the inner submucosal plexus between the mucosa and the inner circular layer. In rat models, there is evidence that the enteric neuronal development is not completed at birth i.e., changes in the number of neurons and the morphology of the plexus has been reported between the first four weeks of life [12]. There is data lacking in the maturation of the ENS in children, however it has been reported that the number of cell bodies within ganglia appears to change according to the age of the individual between one day of age and 15 years [13]. The enteric muscle coat is organized into three discrete muscle layers: the innermost muscularis mucosa, the inner circular muscle layer, and the outer longitudinal muscle layer. In between these muscle coats lies the ENS. These muscle layers work in concert and result to execute peristalsis and aboral propulsion of GI luminal contents. The Interstitial Cells of Cajal are established as the pacemakers and mediators of enteric motor neurotransmission. Their loss and reduction have been implicated in motility disorders.

Apart from genetics, key influences on the ENS come from the central nervous system (CNS), and autonomic nervous systems (ANS), endocrine system, immune system, intestinal microbiota, and connective tissue. In children this is further complicated by development and growth of the gut, in addition to influences of environment and diet. Therefore, there are a wide range of etiologies that could result in gut motility disorders. Sensory functions of the GI tract are important in understanding of functional disorders. Most of the information originating from the GI tract does not reach conscious perception, but rather is processed in the brain stem. However, sensations such as hunger, fullness, satiety, bloating, and the need to defecate reach the cortex. The ANS consisting of the parasympathetic and sympathetic branches affect GI motility. Extrinsic innervation of the GI tract is through vagal, spinal visceral (sympathetic cause), and sacral nerves. These nerves transmit information (afferent fibers) from the viscera to the

CNS, and efferent fibers transmit information from the CNS to the gut. The ANS promotes secretion and peristalsis. Disorders of the ANS are related to disturbances in GI motility and sensing. Furthermore, abnormally heightened visceral hypersensitivity is considered a central pathophysiological mechanism of FGID. Visceral hypersensitivity is defined as the increased perception of visceral sensation. FD is a model of a brain-gut disorder. The presence of food in the stomach signals the brain via neurohormonal pathways. The coexistence of hypersensitive fundic and antral distention with FD symptoms triggered by meal ingestion and sensitivity of the stomach in the post-prandial state has been demonstrated in adult studies [14] . This kind of hypersensitivity can be central or peripheral. Visceral sensations can be transmitted from the gut to the brain via afferent nerves. Alterations of the mechanisms of pain transmission from the stomach to the brain could explain the presence of hypersensitivity to gastric distension seen in FD patients. Moreover, with defective sensory filtering, the brain may inappropriately perceive normal sensory signaling from the GI tract. For example, this defective sensory filtering may impair food intake regulation and increase perception of physiological stimuli as being painful. Acidic hypersensitivity of the duodenum has also been shown to cause FD symptoms in adults [15]. Hypersensitivity is also present after lipid infusion and fatty meals. Moreover, in adults the prevalence of developing FD after infectious gastroenteritis was higher compared to the control population [16]. This is likely, due to the association with abnormal activation of the immune system causing increased incidence of FD in patients with acute infectious gastroenteritis. Other risk factors include genetic factors and smoking. Tobacco use is an important factor for providers to consider when evaluating pediatric patient symptoms and lifestyle associated with an FGID because in 2020, 6.7% of middle school aged and 23.6% of high school aged children in the United Stated reported using some form of tobacco product [17].

Disaccharidase deficiency, although typically thought to cause diarrhea, can also cause abdominal pain and FD. Disaccharidase deficiency should be considered as a possible diagnosis when evaluating a child with symptoms consistent with FGID. Chumpitazi, et al. demonstrated that in chronic FD almost half of the children (47.5%) had underlined disaccharidase deficiency [18]. However, a correlation between disaccharidase level and the severity of symptoms has not been found. If the deficiencies are identified, it can lead to better treatment outcomes for affected patients. Many genes have been associated with disaccharidase deficiency. This includes the rare congenital sucrase-isomaltase deficiency. The prevalence of congenital sucrase-isomaltase deficiency varies by population. It is estimated to occur in 1 in 5,000 people of European descent, but in the populations of Greenland, Alaska, and Canada, it is believed to be 1 in 20 people. Diagnosis can be made by breath testing and, if undergoing an

esophagogastroduodenoscopy (EGD), by tissue analysis for disaccharidases. These should be considered in the differential for children presenting with FD.

Gastric accommodation is defined as the ability of the stomach to distend appropriately during a meal when there is an increase in gastric volume in the absence of increased gastric pressure; it is considered a motor abnormality responsible for symptoms in patients with FD. Scintigraphy and ultrasonography studies have shown abnormal intragastric distribution of food with preferential accumulation in the distal stomach. In adults the impaired accommodation is suggested to be in the proximal stomach [19]. The cause of impaired accommodation is related to abnormalities of the vagovagal reflex, of the intrinsic inhibitory innervation or alteration in the smooth muscles of the proximal stomach in adults [20]. Friesen, et al. reported of the 30 pediatric patients studied with FD, 50% had an abnormal electrogastrogram (EGG) and 47% showed slow gastric emptying [21]. The predominant EGG abnormality was dysrhythmia with bradygastria being present in the fasting state and tachygastria in the postprandial state. The stomach plays a central role with abnormal motor function such as impaired gastric accommodation, delayed gastric emptying, and antral hypomotility associated with varied intragastric concentrations of solid and liquid food. Haag, et al. reported that there were no differences in gastric emptying between adult subgroups EPS and PDS of FD [22]. Delayed gastric emptying occurs in 20% to 50% of adult patients with FD [23].

Wauters, et al. [24] performed a retrospective study in which 72 children who underwent EGD with normal pathological findings were evaluated. Those children who met criteria for FD diagnosis showed a significantly higher duodenal eosinophil count than those of controls [24]. These findings suggest that increased duodenal eosinophil density can be used as a predictive measure for diagnosing FD in patients with otherwise normal histologic EGD pathology.

There is increasing evidence that FGID can result from immune system dysregulation or gut microbiota dysbiosis. Cows' milk allergy (CMA) occurs in 2-3% of children, likely during the first months of life. This allergy is associated with GI inflammation and dysbiosis therefore is likely linked with FGID in later life. Dietary treatment for CMA often includes extensively hydrolyzed casein formula (EHCF) along with probiotic supplements such as *Lactobacillus rhamnosus* GG (LGG). Nocerino, et al. studied the relationship between pediatric patients with CMA treated with EHCF, EHCF+LGG, and a healthy population used as a control. Each patient was evaluated for a FGID using Rome criteria after treatment. The rate of FGID in those treated with EHCF+LGG was significantly lower

than those treated with EHCF alone. Further, the rate of FGID in the healthy population was similar to those treated with EHCF+LGG indicating that the addition of a probiotic supplement significantly reduced the effects of dysbiosis and, therefore, the occurrence of FGID in children with CMA [25]. There is a paucity of data in support of microbial regulation of gastric function. The administration of Prebiotic Arabino Xylo Oligosaccharide in healthy adult volunteers was not associated with changes in gastric sensitivity, compliance, accommodation despite increased colonic fermentation [26]. It has not been discerned whether associations of microbial mechanisms impair gastric or small intestinal motility, and/or other factors such as chronic acid suppression and opioid analgesics can cause FD

Clinical Presentation

Many patients present with a variety of symptoms making it difficult to determine what disease or disorder is causing the issues. For functional disorders, this is more difficult because there is no specific testing that an individual can have to confirm or rule out a diagnosis. The diagnosis of FD requires careful history taking and physical examination to rule out red flags which can include diarrhea, bloody stools, weight loss, fevers, nocturnal awakening from pain or diarrhea. On examination concerning findings include pallor, rashes, abdominal distension, guarding on abdominal exam, joint pain, stiffness or swelling, and anal lesions. Functional abdominal disorders carry many similar symptoms such as pain or abnormal stooling as shown in Figure 1. Schurman, et al. conducted 3 and 4-factor statistical analysis to determine overlap between FD, IBS, and other abdominal complaints in children. In 4-factor analysis, the Rome IV subtypes of FD, PDS and EPS, correlated significantly and strongly according to Cohen's conversion. Additionally, the correlation between each of the FD complaint clusters showed a comparable correlation with IBS and these did not differ statistically [27]. Though this data suggests that the symptoms within the subtypes of FD as defined by Rome IV are not significantly different in patients, the classification has been shown to impact clinical management. Specifically, children with PDS also can be associated with greater gastric mast cell density and higher self-reported anxiety and depression scores [28]. Many pediatric complaints center around headaches and abdominal pain. Friesen, et al. conducted a consecutive study of pediatric patients with these complaints to determine their occurrence in patients with FD. Of those patients studied, 86% met Rome IV criteria for FD. Almost 74% of the patients diagnosed with FD also reported symptoms of headaches compared to only 45% of patients reporting headaches that did not meet criteria for FD. In this study, all patients underwent an EGD as

well. The duodenal mast cell density was significantly higher in the population reporting headaches than those without this complaint [29]. This data suggests that those with an unremarkable EGD but have elevated mast cell density on biopsy possibly could have FD. Nausea is another frequent symptom associated with FD which has shown to exacerbate symptoms, quality of life, and functioning in adolescents. Kovacic K, et al. reported in a study of 112 adolescents, 71% recorded chronic nausea. Patients with nausea compared to no nausea had statistically significant worsened quality of life and greater disability, in addition to non-statistically significant reported higher anxiety. Comorbidities were more associated in the nausea group with concentrating difficulties, chronic fatigue, and sleep disturbances all statistically significant [30]. FD has been associated with migraines. Le Gal J, et al. reported up to 32% of children and adolescents with FGID have migraines compared with 18% in the control group [31]. Consequently, in the control group less than 1% had FD, compared to 6% with FD in the migraine group.

Because functional disorders cannot be indicated by organic causes, it is important to consider other exacerbating factors. Depressive symptoms have been known to worsen GI symptoms and show a strong correlation to symptoms continuing into adulthood. A study of 392 children, with 162 meeting criteria for FGID, a child with a Children's Depression Inventory (CDI) score of 12, the minimum cut-off for clinical depression, was three times more likely to continue to have FGID symptoms into adulthood than those who did not have a CDI score linked with depression [32]. In another study, approximately 50% of children and adolescents with FD showed elevated and anxiety scores [33]. Stress is associated with activation of the hypothalamus which releases the corticotropin-releasing factor with significant response including inflammation (mast cell activation), sympathetic nervous system activation, altered gastric accommodation, gastric dysmotility, and visceral hypersensitivity in adults [34].

Diagnosis and Treatment

Organic disease rule out:

Dyspepsia can be divided into 2 main categories: "organic" and "FD". Organic causes of dyspepsia in children are peptic ulcer, gastroesophageal reflux disease, celiac disease, upper gastrointestinal Crohn's disease,

pancreatic or biliary disorders, intolerance to food or drugs, other infectious diseases such as giardiasis, infiltrative diseases such as eosinophilic gastroenteritis or systemic diseases.

Testing and then treatment of *Helicobacter pylori* (*H. pylori*) infection is reasonable to do in FD patients. Although eradication may only help a minority of patients, it may have long-term benefits such as those found in adults [35]. Furthermore, *H. pylori* is important to eradicate in order to reduce the risk of peptic ulcer disease in the future. The treatment of *H. pylori* risk-to-benefit ratio shows that it is beneficial to treat it, therefore if an infection is found, it should be treated with a patient tested for cure 1 month after treatment. A trial assessing the benefit of eradication therapy showed that it was more beneficial in treating EPS symptoms instead of PDS symptoms in adults [36]. Spee, Madderom et al. reported in a meta-analysis that children who presented with abdominal pain in the epigastric area had a significantly higher prevalence of *H pylori* infection when they had short term recurrent abdominal pain (2 weeks to 3 months) but not when they had recurrent abdominal pain [37]. The joint ESPGHAN/NASPGHAN guidelines for the treatment of *H pylori* in children and adolescents state that the decision to investigate and treat the infection should be supported by a clear benefit for the individual child [38]. Therefore, they recommend that in children fulfilling the Rome IV criteria for FAP diagnostic testing (noninvasive or invasive) for *H pylori* infection should not be undertaken. However, since EPS has been shown to be significantly associated with *H pylori* infection in children [37], the authors recommend non-invasive testing in this group of patients.

For many GI diseases such as gastritis or reflux, an EGD is indicated as the gold standard for diagnosis. Because functional disorders are considered a diagnosis of exclusion, in the past it was almost always necessary for patients to have an EGD prior to diagnosis of a functional disorder which may present with similar symptoms as gastritis. Data regarding the need for an EGD has been analyzed by the Rome Foundation, and the conclusion is that there is not compelling evidence to require an EGD for the diagnosis of FD in children [39]. Figure 2 shows a workup plan to rule out possible organic disease causes of dyspeptic symptoms in children.

Because postprandial distress and early satiation is a predominant symptom with FD, gastric scintigraphy may be indicated to rule out gastroparesis which can have similar symptoms as well. In addition, water load test can be used to gauge gastric accommodation and hypersensitivity in pediatric patients [40]. In a study done by Ozaki, et al., water load testing was performed on patients age 4-14 with a FGID. This study showed that patients with FD had a maximum water intake roughly 45% less than those with FGID of irritable bowel syndrome or functional abdominal

pain (FAP) [40]. This suggests that gastric compliance and visceral hypersensitivity may be a differential component of FD. However, data collected regarding the patient's daily diet intake did not indicate a significant decrease in food or nutrient intake when comparing patients with FD, IBS and FAP.

An objective test in FD that assesses meal-related symptoms is the nutrient test meal. From an adult study, after an 8-hour fast, provide 200 mL of a standardized enteral feeding solution (e.g., Ensure®, Abbott Laboratories, Illinois, USA) every 5 minutes up to a cumulative volume of 800 mL; following each 200 mL drink, five key symptoms are assessed (fullness, abdominal pain, retrosternal/abdominal burning, nausea, and regurgitation) using a standardized instrument on visual analogue scales (0 to 100), and the cumulative symptom score across all symptoms calculated [41].

Other tests that are mainly used for research purposes include single-photon emission computed tomography, antroduodenal manometry, or EGG to test electrical activity.

Treatment options:

When treating FD, the most important measure of treatment is patient and parents' education. It is important to explain the pathophysiology of the condition, provide reassurance that it is a functional disorder without any anatomical abnormality, and discuss long-term prognosis of the condition. The goal of the treatment is to improve symptoms rather than treating any underlying cause. Both non-pharmacological treatments and pharmacological treatment options should be explained to the patient. Various treatment options are discussed further in the list below

- **Lifestyle**
    - Diet: Many diets exist to help alleviate functional disorder symptoms. For FD, recommendations include eating smaller meals slowly, as well as avoiding triggers such as spicy foods, acidic foods, or caffeinated beverages.
    - Exercise: Obesity and stress are correlated with increased symptoms as explained above. Findings from a pediatric based meta-analysis suggest that physical activity interventions can improve adolescents' mental health [42]. However, in an adult population based study it was found that patients with FD tend to have lower exercise levels [43]. Moreover, moderate exercise and

weight loss has been shown to reduce symptoms in children, and should be a part of all treatment plans [44].

- Sleep Hygiene: Studies have shown that melatonin, a naturally occurring hormone produced by the onset of darkness by the pineal gland, acts as a gastroprotective agent in children [44]. It has been shown to regulate GI motility and sensation and elicits anti-inflammatory responses. Poor sleep hygiene can cause decreased melatonin levels and, therefore, increases symptoms from FD. Sleep hygiene includes sleep quality, sleep latency, nighttime waking, daytime drowsiness, and the exposure to artificial light during the night. Improving these factors in pediatric patients with FD can reduce symptoms and overall improve the patient's quality of life. However, in a randomized controlled trial to evaluate therapeutic effects of melatonin, it was not found to be superior to placebo in children [45].
- Cognitive behavioral therapy (CBT): The impact of an FGID on a patient's life can be directly correlated with the management of psychosocial factors. The psychosocial factors may influence the symptoms of the FGID through association with symptom onset or disability associated with FGID. CBT has been shown to be effective at treating symptoms and disability associated with FD. This form of therapy allows patients to learn strategies for identifying and changing thoughts, emotions, and behavioral responses to help manage symptoms both in children and adults [46]. Though some physicians may be uncertain when psychosocial therapy is needed in a patient, Reed-Knight, et al. asserts that all patients can benefit from this therapy due to its ability to disrupt progress towards increased disability and distress associated with the functional disorder [46].

- Mind-Body Therapy: This class of therapy stems from CBT and includes activities such as mindful meditation, clinical hypnosis, and yoga. There are several studies showing that gut-directed hypnotherapy decreases pain symptoms in children with FAP [47]. Though these studies have small sample sizes, and FAP is not strictly FD, the efficacy and safety of these options suggest that it is a likely beneficial treatment modality for FGID, including FD.

- **Pharmacology**

- Acid suppression therapy: medications including proton pump inhibitors (PPI) which block gastric acid secretion by irreversibly inhibit the hydrogen-potassium ATPase pump, and histamine-2 receptor antagonists (H2 blockers) which reduce basal acid secretion and pepsin production. These can be used in FD and have been shown to reduce symptoms when compared against a placebo group in adults [48]. In addition, a meta-analysis has shown that acid suppression medications are superior to placebo and can be used as first-line therapy for EPS type FD. Interestingly, H2 blockers have shown to be of higher benefit than PPI in adults [49]. While these are used widely and recommended often, only a minority of individuals respond to PPIs, and their long-term use can have adverse side effects. A Japanese trial showed that 15 mg lansoprazole, a PPI, was superior to a placebo for FD in adult patients, but only the EPS subtype responded to the drug [50].
- Prokinetic agents: medications that promote intestinal peristalsis, gastric emptying, reduce reflux, and decrease nausea through various mechanisms of action. Since in motility disorders gastric accommodation is impaired in FD, prokinetic agents can be used for its treatment. A meta-analysis of 24 studies demonstrated that prokinetics were more effective than a placebo in adults with FD [51]. Cisapride agonizes serotonin type-4 receptors (5-HT4) in the intestine to increase peristalsis, gastric emptying and decrease esophageal reflux. This medication is no longer available in the US due to its cardiac side effects causing prolonged QT interval and resulting in sudden death. However, it is available as an institutional investigational new drug (IND) for select patients. Mosapride acts similarly on 5-HT4 receptors. In a study of 60 children, Mosapride was found to be as effective as Pantoprazole, a PPI, in relieving FD dyspeptic symptoms [52]. However, Mosapride is not available for use in the United States though it is currently used in many Asian countries. These medications also can have metabolites that target serotonin type-3 receptors (5HT3) on the vagal nerve terminals in the GI system as well as the trigger zones of the CNS producing an antiemetic effect. Other medications such as Metoclopramide and Domperidone are dopamine-2 (D2) receptor antagonists which can function as prokinetic agents. Metoclopramide is used sparingly because of its questionable efficacy in FD, in addition to its black box warning of side effects such as irreversible tardive dyskinesia.

Domperidone is also not available in the US readily except through an Investigational New Drug (IND) protocol. Domperidone does not cross the blood-brain barrier. Itopride and Levosulpiride are also selected D2 antagonists that can be used as prokinetic agents in adults [53, 54]. Acotiamide, a muscarinic autoreceptor inhibitor and cholinesterase inhibitor, has also been proven effective at reducing FD symptoms and improving quality of life in controlled adult studies but has not yet been approved for use in the US [55].

○ Gastric accommodation: Cyproheptadine is effective in treatment of FD through its gastric accommodation effects. It is a first-generation antihistamine and is used for its serotonin and calcium channel blocking effects in FD. In a cohort of 151 children, cyproheptadine was effective in 73% of patients, resulting in complete improvement of FGID including FD [56]. Rodriguez, et al. investigated whether cyproheptadine would be a viable first line treatment option for children with FD. Of those studies, 55% reported a response to the therapy with females reporting better responses. However, after analyzing the data, the study found no association of therapy response and gastric emptying, antroduodenal manometry, FD, vomiting, and use of cyproheptadine as first therapy. Patients with symptoms of vomiting within an hour after meals or those that had retching status post a Nissen fundoplication did report excellent response rates to the medication. Only 2.5% of the patients reported symptoms of abdominal pain while on cyproheptadine. This suggests the medication potentially improves gastric accommodation or hypersensitivity. Therefore, it was concluded that cyproheptadine is safe and effective in treatment of FD in children [57]. Buspirone, an antianxiety agent, relaxes the gastric fundus through its action on serotonin type-1 receptors and in a randomized, cross-over clinical trial reduced PDS symptoms over placebo at a dose of 10 mg three times daily over 4 weeks in adults [58]. However, buspirone did not show any superiority over placebo in childhood FAP in a randomized pediatric clinical trial [59]. This could indicate that FAP may not be associated with disorders of fundic accommodation such as in FD.

○ Antidepressant: In a large randomized controlled trial which included 292 adult patients who were randomized to the low dose tricyclic amitriptyline (25 mg for 2 weeks, then 50 mg for 10 weeks), escitalopram (a selective serotonin reuptake inhibitor [SSRI] at 10 mg for 12 weeks) or

placebo, the rate of response was 53% with amitriptyline, 38% with escitalopram, and 40% with placebo [60]. Moreover, in another adult study, there was no benefit observed over placebo with the SSRIs or selective norepinephrine reuptake inhibitors (SNRI's) [61]. Antipsychotic class drugs were also superior to placebo [61]. Mirtazapine is a tetracyclic antidepressant with antinausea and weight gain properties. One trial suggested a trend towards symptom improvement compared with placebo in adult FD, but the results were not definitive [62].

- Alternative Therapy
  - Herbal supplements: Various botanical supplements have been studied in their impact on treating symptoms caused by FD. One in particular, Iberogast® (Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany), has been studied extensively and has been determined to be both safe and effective in reducing or treating FD. Iberogast® is a preparation of 9 extracts and has been shown to reduce acid production, increase mucin production, increase prostaglandin E2 release and decrease leukotrienes. This in turn prevents development of gastric ulcers and promotes gastric motility by increasing the motility index of antral pressure waves found in children [44]. Suziki et al. conducted a randomized clinical trial of Rikkunshito, a Japanese herbal medicine, to evaluate its effectiveness in relieving FD symptoms in adults. The study found that the efficacy of Rikkunshito was demonstrated at 4 weeks and at 8 weeks Rikkunshito showed a significant reduction in epigastric pain symptoms and tended to reduce postprandial fullness when compared with the placebo control group. However, this herbal medication did not show any significant improvement in epigastric burning or early satiation in adults [63]. Other research has shown Rikkunshito improves gastric emptying and accommodation thus can likely be used to improve gastric motility in FD patients.

    Hangekobokuto, a Chinese herbal medicine, also has been studied on its impact on FD symptoms. In an adult study, Oikawa et al. found that the abdominal gas volume score (GVS), measured by abdominal radiography, was significantly higher in FD patients than healthy volunteers. After 2 weeks of Hangekobokuto administration, the study found that the GVS was significantly reduced in the FD patients but not changed in the healthy adult group [64]. Further, the study showed that

FD symptoms of reflux, abdominal pain, indigestion, and constipation were significantly reduced after the administration of Hangekobokuto for 2 weeks.

Licorice root, which comes from the root of the plant *Glycyrrhiza glabra (G. glabra)*, is one of the world's oldest remedies for gastric inflammation. The mechanism of action is thought to be due to the inhibition of prostaglandin synthesis and lipoxygenase. In a small, randomized, double-blind, placebo-controlled study of 50 adults with functional dyspepsia as diagnosed by Rome III criteria, subjects were randomized to placebo or a 75 mg extract of *G. glabra* for 30 days. Symptoms were assessed with a 7-point Likert scale of dyspepsia symptom severity at day 0, 15, and 30. Compared to placebo, the licorice extract showed a significant decrease in total symptom scores ($p < 0.05$) and improvement in quality of life [65].

Ginger root, the rhizome of *Zingiber officinale*, has been used for treating symptoms of nausea, reflux, and FD. Ginger has shown to have antiplatelet properties so should be used in caution in patients with bleeding disorders. In children who are unable to swallow ginger root capsules, ginger candies, chews, and teas are often more palatable.

- Acupuncture: For reflux and FD, certain acupuncture points have been effective in improving reflux symptoms, nausea, and vomiting. There is minimal clinical data for pediatrics on this, though studies suggest less than 2 in 100 children would have adverse events from acupuncture indicating a safe alternative line of therapy [44].

- Surgical
  - Gastrostomy: Surgical intervention for functional disorders is often not indicated except in those patients who are not maintaining proper nutrition secondary to symptoms associated with eating. In these cases, a G-tube or GJ-tube may be placed to allow for supplemental nutrition administration.

Quality of Life and Symptom Burden

FD is the most expensive disorder to treat and manage. From 1997 to 2009 the cost for managing this disorder increased by 183.2% from $12,674 to $35,898. The cost burden from FD is due to the fact that an EGD is often

indicated during diagnosis to rule out other diseases such as gastroesophageal reflux, gastritis, or eosinophilic esophagitis. Similarly, other diseases, such as pancreatic or biliary disease, often present with similar symptoms as FD, thus, lab tests for serum amylase, lipase or aminotransferase may be indicated which add further costs to the diagnosis of FD in children [3].

In a study of 949 children, those with a FGID had a mean lower quality of life rating than those who did not meet criteria for an FGID. Further, mothers who met criteria for a FGID were more likely to have children meeting criteria for a FGID. In many cases, the symptoms reported by the child were similar to those reported by the mother if they both qualified for a FGID [66]. The lower quality of life for children is often correlated with a decrease in school attendance, frequent illness and decreased social interaction. These patients are more vulnerable to developing pain management and mental health issues adding to the lower quality of life. Patients with FGID such as FD demonstrate lower health-related quality-of-life (HRQOL) than healthy controls. Moreover, patients with FGID manifest lower HRQOL than those with organic GI disease. These children missed more school, spent more time in bed, needing care, greater healthcare utilization with parents who missed more workdays [67].

SUMMARY:

The natural history of FD is chronic and fluctuating, with periods of time when the patient is asymptomatic followed by episodes of symptom relapse. FD symptoms impair quality of life and treatment is indicated if simple measures such as reassurance and dietary restrictions fail. Medical therapy remains largely symptom driven. Despite the chronic nature of FD, there is no evidence seen in the adult community to suggest that it is associated with decreased survival [68]. Since children have less comorbidities than adults, we can extrapolate similar results for them.

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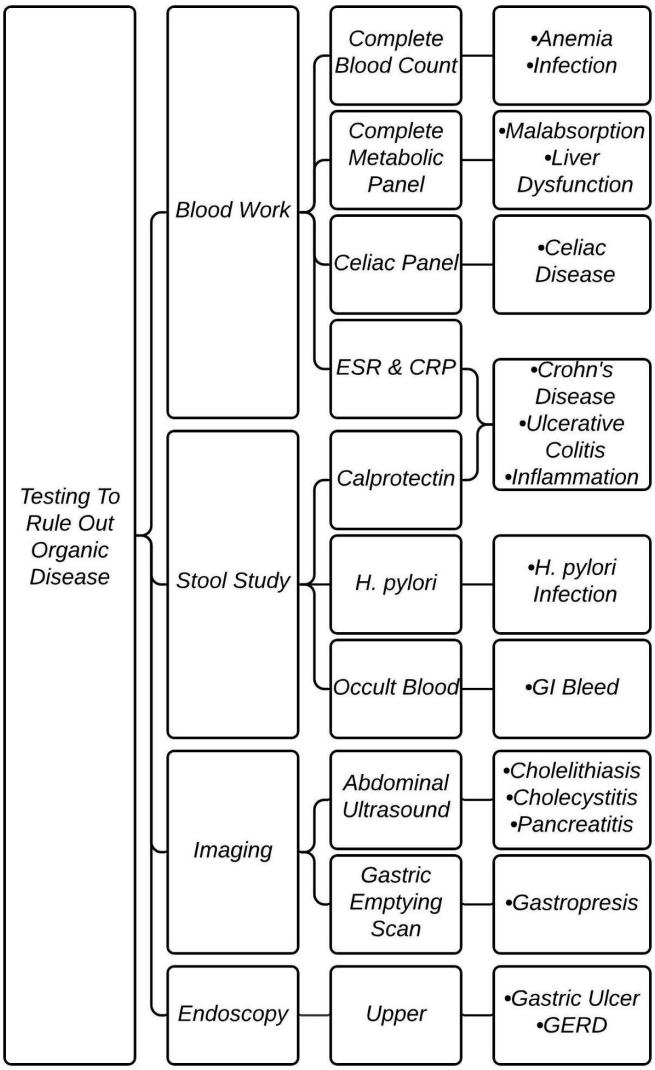

Figure 2: Possible lab testing, imaging studies or endoscopy analysis to rule out various organic diseases. This list is not comprehensive but does cover many diseases that have similar symptom presentations as FD.

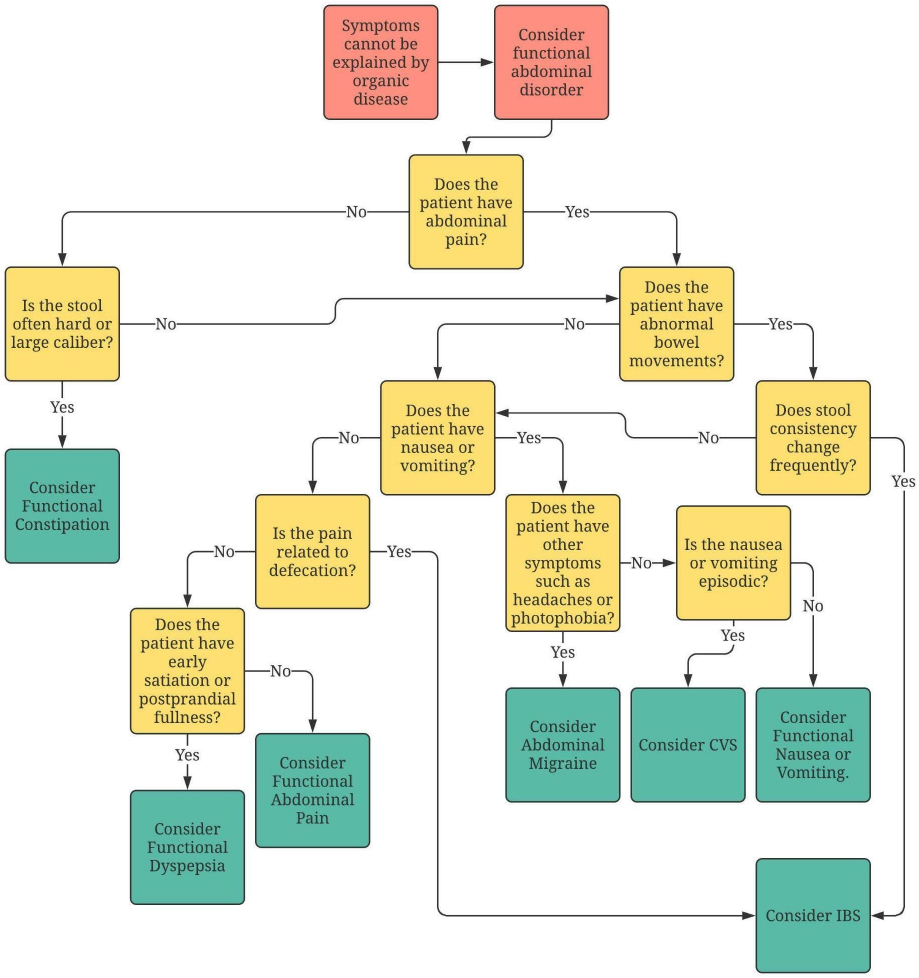

Figure 1: Decision making chart showing a possible differential diagnosis and overlap of symptoms for various FGID based on Rome IV criteria. Red color indicates low symptom specificity; yellow color indicates greater specificity; green color indicates high probability of diagnosis.