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Inflammation and the Biopsychosocial Model in Pediatric Dyspepsia

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1. Introduction

1.1. Diagnostic criteria

In the late 1980s, a group of experts met in Rome to establish symptom-based diagnostic criteria for functional gastrointestinal disorders (FGIDs). This first set of “Rome criteria,” published in 1989, focused exclusively on adults [1]. In 1999, when these criteria were revised, a pediatric committee established a parallel set of diagnostic criteria for FGIDs in children and adolescents [2]. The Rome II pediatric subcommittee defined four pediatric disorders related to abdominal pain: functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine, and functional abdominal pain. With Rome II, FD was defined as persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus) that was unrelated to a change in stool frequency or form and not exclusively relieved by defecation. Further, there had to be no evidence of an inflammatory, anatomic, metabolic, or neoplastic process to explain the patient’s symptoms. Importantly, the committee determined that mild, chronic inflammatory changes on mucosal biopsies should not preclude the diagnosis of FD. Similar to the adult criteria on which they were based, the Rome II pediatric criteria for FD included 3 subtypes: 1) ulcer-like, in which pain was the predominant symptom; 2) dysmotility-like, in which discomfort (e.g., bloating, early satiety, postprandial fullness) was the predominant symptom; and, 3) unspecified.

In 2006, the same process of expert committees again revised the criteria, yielding the current Rome III criteria [3,4]. In adults, the previous FD subtypes were eliminated while two new subtypes were identified based on new studies generally utilizing factor analysis. The first subtype, postprandial distress syndrome, was defined as bothersome postprandial fullness occurring after ordinary sized meals and/or early satiation that prevents finishing a regular

meal. The second subtype, epigastric pain syndrome, was defined as intermittent pain or burning localized to the epigastrium (i.e., not generalized or localized to other abdominal or chest regions) and of at least moderate severity. The Rome III pediatric subcommittee also eliminated the old subtypes, but did not adopt the new adult subtypes because of a lack of existing data to support their existence in children and adolescents. However, recent evidence suggests that the adult subtypes actually may have meaningful associations with mucosal inflammation and psychosocial functioning in pediatric FD [5].

1.2. Prevalence and presentation

Most pediatric gastroenterologists may not routinely use Rome criteria and differences exist in how the criteria are interpreted. Nevertheless, there is agreement that a strong majority of children with chronic abdominal pain presenting to pediatric gastroenterology practices fulfill criteria for an FGID, with the two most common being FD and IBS [6-9]. Community prevalence for FD is estimated at 3.5-27% in children/adolescents compared to 20-30% in adults [3,4].

In both pediatric and adult gastroenterology practices, FD frequently overlaps with IBS or gastroesophageal reflux [7,10]. Adult IBS overlap is associated with more psychological dysfunction including anxiety and depression, compared to “pure” FD, but this association does not appear to be present in pediatric overlap [11,12]. Pediatric FD is associated with lower quality of life, increased functional disability, and increased likelihood of meeting criteria for an anxiety disorder relative to healthy children [13]. In adults with FD, the association with anxiety appears to be specific to patients with postprandial distress syndrome, with this relationship also apparent in children/adolescents with symptoms consistent with postprandial distress syndrome [5,14].

1.3. Etiology

FD, like all FGIDs, is probably best understood through a biopsychosocial model (see Figure 1). This model states that symptoms are likely the result of varying contributions from, and interactions between, biological/physiological factors (e.g. inflammation, mechanical disturbances, hypersensitivity), psychological factors (e.g. anxiety, depression, somatization), and social factors (e.g. interactions with parents, teachers, or peers). Within this model, there is less emphasis on the “cause” of symptoms than on “contributors” to its emergence and maintenance. This model would suggest that there is value in identifying and targeting all of the factors which might be contributing to symptom generation in children with FD. It also would suggest that there is value in understanding the mechanisms by which the factors interact with one another, as these mechanisms represent additional opportunities for clinical intervention.

2. The role of inflammation in functional dyspepsia

Inflammation has the potential to contribute to the development of FGIDs via the release of specific mediators that impact mechanisms known to play a role in the pathogenesis of these conditions. Acute gastrointestinal inflammation and injury are associated with both peripheral

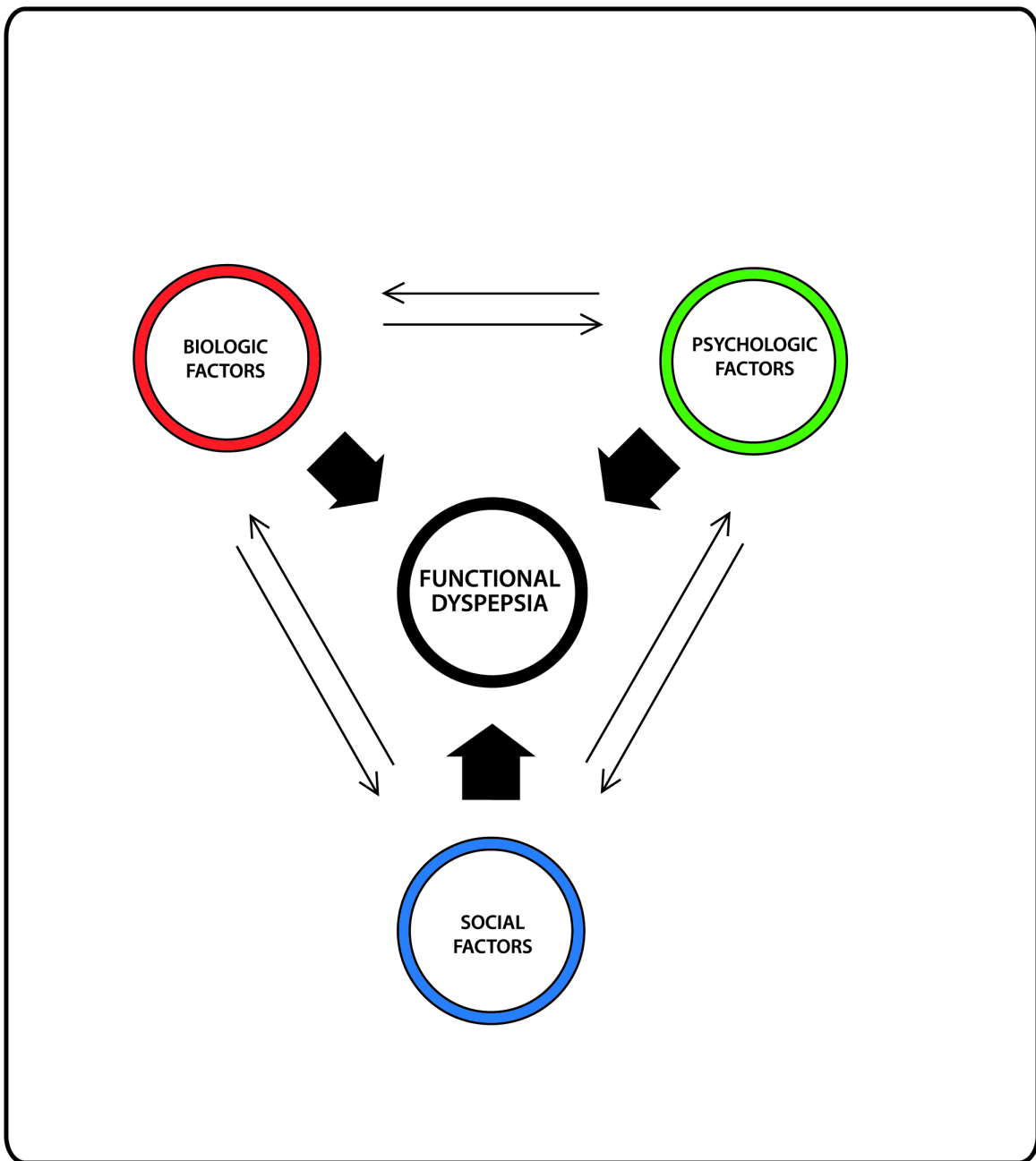


Figure 1. The Biopsychosocial Model of FD

and central sensitization of the nervous system, which results in visceral hyperalgesia [15]. Neuroplastic changes may occur that affect the response thresholds of enteric nerves, thereby negatively impacting both sensitivity and motility [16]. Both motility and sensitivity responses to acute inflammation in adults generally are reversible; however, animal model responses suggest that, if inflammation occurs in neonates, neuroplastic changes and sensitivity may persist into adulthood [17,18]. Visceral sensitization may be even more relevant in instances where there is chronic inflammation with ongoing mediator release, as there may be subsequent effects on visceral sensitivity that compound and prolong the issue.

The role of inflammation in FD has historically been controversial. However, emerging evidence supports its role as a contributing factor in the biopsychosocial model of FD. In fact, inflammation may be of particular importance in this model, as it interacts with a number of other factors and may actually mediate the relationship between psychologic and physiologic factors. The remainder of this chapter focuses on examination of inflammation within the biopsychosocial model of FD, laying out the current evidence for its prevalence, mechanisms of action, relationship with other important factors, and implications for evaluation and treatment.

2.1. Chronic inflammation

Upper endoscopy is commonly performed in children with chronic abdominal pain in general and children with functional dyspepsia in particular. Histologic inflammation is common in these patients. In children with chronic abdominal pain, esophagitis is common and would implicate gastroesophageal reflux as a contributor or cause of pain [19]. In one study of children with FD, specifically, histologic esophagitis was found in 18%, gastritis in 21%, and duodenitis in 13% [10]. Higher prevalences for gastritis, ranging from 43% to 71%, have been reported by others [20,21]. For the broader group of children with chronic abdominal pain, histologic inflammation has been documented in up to 79%, with an increase in mononuclear cells (indicative of chronic inflammation) in the antrum of 55% and in the duodenum of 16% of these children [19].

Most of these patients have chronic inflammation of which the clinical significance is unknown. Chronic gastritis is not associated with electrogastrographic abnormalities, delayed gastric emptying, or psychologic dysfunction in children with FD [5,22]. Despite this, chronic active gastritis (manifest as lymphocytic and neutrophilic inflammation) has been associated with a higher prevalence of nocturnal pain [21]. Chronic gastritis has been associated with an increased prevalence of postprandial pain [5].

2.2. Mast cells

Increased mucosal mast cell density has been demonstrated in the gastric corpus and antrum in adults with FD [23,24]. In adults with gastritis, mast cell density is significantly increased and generally correlates with the intensity of the inflammation [25]. Though findings have been variable, increased mast cell density appears isolated to the stomach in adults with FD; increased duodenal mast cell density is more associated with IBS [24,26]. In addition, increased mast cells in the proximal stomach in adults with FD have been associated with hypersensitivity; these mast cells will degranulate with balloon distension of the proximal stomach [27].

Due to a lack of normal control data, it is not known if gastric mast cells are elevated in pediatric FD. However, antral mast cells do appear to be actively degranulating in children with FD, with a mean degranulation index of 67% and greater than 50% degranulation in over 80% of patients [28]. In children with FD, mast cell density positively correlates with slower gastric emptying and increased gastric dysrhythmia (primarily preprandial bradycardia) in children with FD [28]. Further, this dysrhythmia is associated with increased postprandial pain [29].

2.3. Eosinophils

Ethical considerations preclude undertaking studies that assess eosinophil density in healthy pediatric controls. However, the available pediatric literature indicates that it is reasonable to consider eosinophil densities $\geq 10/\text{hpf}$ in the antrum and $>20/\text{hpf}$ in the duodenum to be abnormal. In a pediatric autopsy study, eosinophil density was $<10/\text{hpf}$ in the antrum of all subjects and $\leq 20/\text{hpf}$ in the duodenum of 82%, even though symptoms could not be documented [30]. Another study reviewed biopsies from 682 presumably symptomatic children referred for endoscopy, documenting eosinophil density $\leq 10/\text{hpf}$ in the antrum in 90% and $\leq 20/\text{hpf}$ in the duodenum in 93% [31].

While certain cut-off points for density seem reasonable, eosinophil density may not be completely informative. Eosinophil biologic activity occurs through mediator release or degranulation, and the effects are generally concentration-dependent. Important to consider is the fact that density and activation are not correlated events [32]. In one study involving 20 children with FD, eosinophil density $>20/\text{hpf}$ was present in only 15%; however, moderate to extensive degranulation was demonstrated by electron microscopy in 95% [33].

Adult population studies have demonstrated increased duodenal eosinophil density in those with dyspepsia compared to controls, whereas antral eosinophils did not differ between the groups [34,35]. Higher eosinophil density and a higher prevalence of duodenal eosinophilia (as defined by application of the cut points outlined above) have been specifically associated with the postprandial distress syndrome subtype of FD in adults [36]. Duodenal biopsies from adults with FD also have revealed more extensive degranulation, including documentation of extracellular major basic protein; this corresponds to a similar finding of degranulation and release of major basic protein previously demonstrated in pediatric patients with FD [33,35].

Although no information is available for healthy children, tissue eosinophilia has been evaluated in the broad group of children with chronic abdominal pain, which provides some limited basis for comparison. In a study of 1191 children with chronic abdominal pain, eosinophilia was identified in the antrum or duodenum in 11.4% [37]. In another study, gastric eosinophilia was reported in 19% and duodenal eosinophilia in 32% of children with unspecified chronic abdominal pain [19]. In contrast, duodenal eosinophilia has been demonstrated in 79% of children specifically fulfilling FD criteria [38].

Antral eosinophil density does not appear to have any direct relationship to gastric electro-mechanical function in children with FD [28]. However, in patients with elevated mucosal eosinophils, antral CD3⁺ cell density does correlate with preprandial tachygastria, indicating that it may result from the interaction between different cell types [28].

3. Specific Conditions Associated with Mucosal Inflammation

There are a number of triggers or inciting events which may initiate an inflammatory response in the gastrointestinal tract, particularly with regard to recruitment and activation of mast cells

and eosinophils. These include stress/anxiety, infection (including *H. pylori*), and allergy, as detailed below.

3.1. Stress/Anxiety

The involvement of inflammation in the biopsychosocial model is best illustrated by examining the stress response. Corticotropin releasing hormone (CRH), produced by the hypothalamus (as well as immune cells including lymphocytes and mast cells) is a major mediator of the stress response in the hypothalamic-pituitary-adrenal axis and, subsequently, within the brain-gut axis. CRH has central nervous system (CNS) effects which may alter central processing of nociceptive messages, leading to anxiogenic and depressive effects. The stress response also results in physiologic effects which may be relevant to FGIDs, including inflammation and alterations of sensorimotor function such as altered gastric accommodation, gastric dysmotility, and visceral hypersensitivity.

The relationship between the CNS and gastrointestinal pathophysiology appears bidirectional. In a rodent model, gastric irritation in the neonatal period induces a long lasting increase in depression- and anxiety-like behaviors. This, in turn, is associated with an increased expression of CRH in the hypothalamus and increased sensitivity of the hypothalamic-pituitary-adrenal axis to stress [39]. CRH stress systems may be activated by afferent nerves from inflamed sites or via cytokines including TNF- α , IL-1, IL-6, and IL-12 [40]. The majority of studies support an enhanced hypothalamic-pituitary-adrenal axis in at least some adults with IBS, although results have been variable [41-45].

Corticotropin releasing hormone receptors are widely expressed including within the gastrointestinal tract and immune cells. Mast cells express both CRH1 and CRH2 receptor subtypes at their surface [46]. Most of the inflammatory cell actions, including those on mast cells, occur via CRH2 receptors. Once mast cells are activated, they release mediators which recruit and activate eosinophils. Both of these cell types are interactive in a bi-directional fashion with T helper cells (Th; see Figure 2).

In addition to this indirect pathway, there also may be a direct effect for CRH on eosinophils. In a rodent model, psychologic stress results in eosinophils expressing CRH [47]. CRH is not expressed on eosinophils in the intestines of the mice except under psychologic stress and decreases after the stress is removed, with the reversion requiring longer periods of time as the length of the stressor increases [47]. A high correlation exists between anxiety scores and mucosal eosinophil density in children with FD [48]. Antral mast cell density also correlates with anxiety scores in children with FD [5]. Stress appears to shift the relative proportion and trafficking of T helper lymphocytes towards a Th2 or "allergic" phenotype [40]. This shift is driven by central and peripheral CRH, catecholamines, and histamine via H2 receptors. The Th2 phenotype is associated with release of IL-4, IL-10, and IL-13, which stimulate growth and activation of mast cells and eosinophils [40]. Shifting from a Th1 to a Th2 response may be the mechanism through which low grade inflammation leads to visceral sensitivity and motility disturbances; eosinophils and mast cells represent the key effector cells [49].

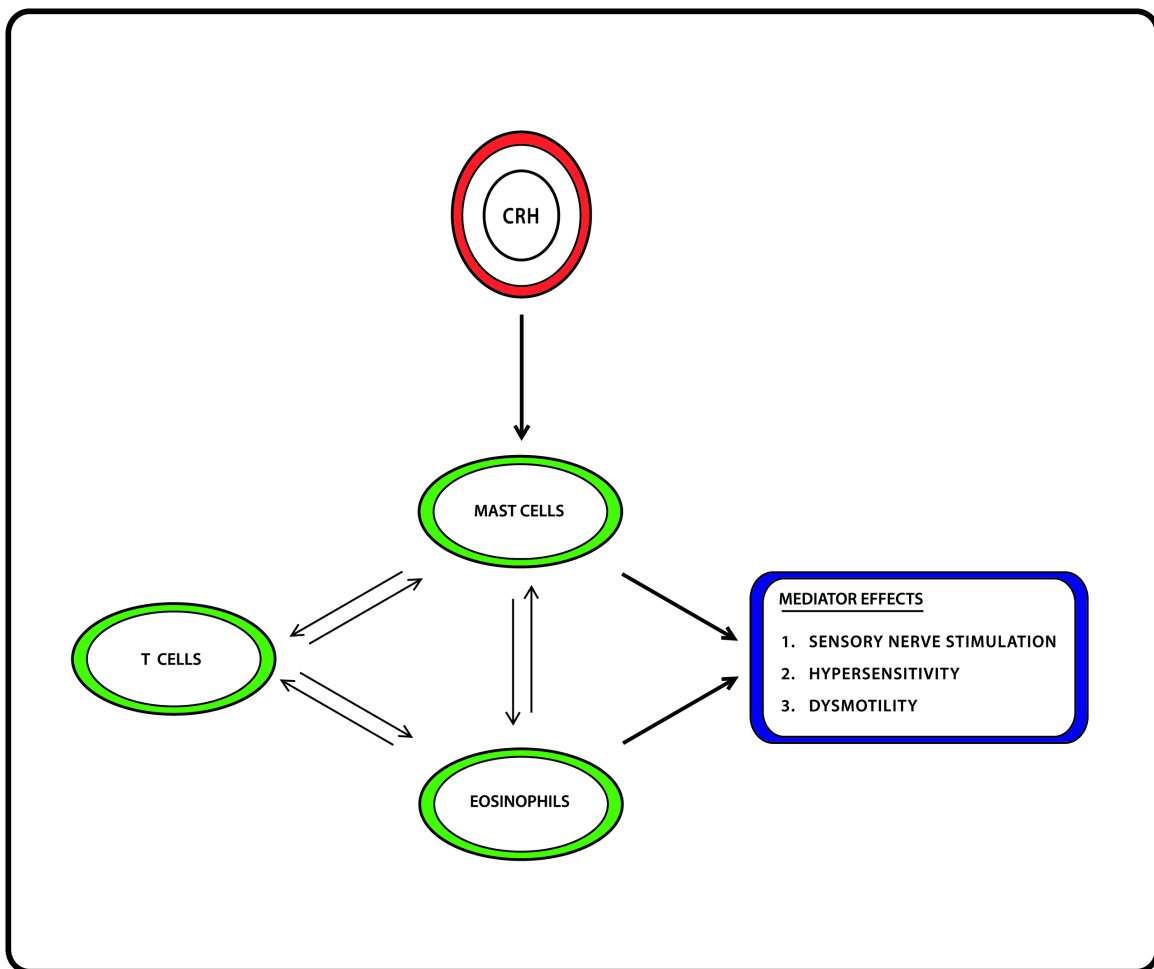


Figure 2. The Relationship between CRH Activation and Inflammatory Cells in FD Symptom Generation

Once activated by CRH, mast cells may release pre-formed and newly synthesized cytokines, including interleukins (IL-4, IL-5, IL-6) and tumor necrosis factor (TNF- α) among others [50,51]. In adults, there is selective luminal release of tryptase and histamine from jejunal mast cells under cold stress; the magnitude of release is similar to that induced by antigen exposure in food allergic patients [52]. Once released, mast cell and eosinophil mediators can stimulate afferent nerves sending a “pain” message, sensitize afferent nerves resulting in visceral hypersensitivity, and alter electromechanical function (see Figure 2). Histamine also can stimulate afferent sensory nerves via H₂ receptors [53]. Consistent with this, experimental anxiety decreases gastric compliance and accommodation and increases epigastric symptom scores during a standard nutrient challenge [54].

3.2. Infection

FD has been reported at a higher prevalence following both bacterial and parasitic infections [55]. It seems likely that FD may also be induced by viral gastroenteritis similar to what has been reported with IBS. In a large cohort of adults that were evaluated 8 years after bacterial

dysentery, an increased prevalence of FD was found compared to non-infected controls [56]. Consistent with the biopsychosocial model, anxiety and depression were independent risk factors for developing post-infectious FD [56]. In another study, 82 adults were identified with persistent abdominal symptoms following *Giardia* infection; 24.3% of these met criteria for FD, while 80.5% met criteria for IBS [57]. Over half of these patients reported exacerbation due to specific foods and nearly half reported exacerbations with physical or mental stress [57]. Rates of post-infectious FD appear similar in pediatric populations. In a study of 88 children with a previous positive bacterial stool culture, FD was present in 24% and IBS in 87% [58]. Fifty-six percent of these patients reported the onset of abdominal pain after the acute infection.

Post-infectious FD appears to represent an impaired ability to terminate the inflammatory response after the offending pathogen has been eliminated, but also may involve neuroplastic changes in visceral and central afferent pathways as it is associated with impaired accommodation and increased sensitivity to distension [59-61]. Post-infectious FD patients frequently demonstrate histologic duodenitis, with a severe grade in 57% [62]. Post-infectious FD is associated with increased macrophages and may be associated with increased CD8+ cells [62, 63]. Findings regarding CD8+ cells however have been variable [62,63]. Duodenal eosinophilia has also been described in post-infectious FD [49]. In addition, gastric mast cells are significantly increased in post-infectious FD as compared to healthy controls [64]. Post-infectious FD is associated with increased gastric release of histamine and 5HT, as well as increased number of mast cells within 5 μ m of nerve fibers as compared to healthy controls or patients with FD that is not post-infectious [64].

H. pylori. The role of *Helicobacter pylori* (*H. pylori*) in FD remains incompletely defined and, as such, deserves particular attention within the scope of infectious organisms. Given that most people never demonstrate symptoms at all when colonized with *H. pylori*, it is possible that *H. pylori* has little to no contributory value for a significant subset of the population with FD. However, it is possible that *H. pylori* may generate symptoms as a primary chronic infection or, alternatively, patients may experience post-infectious FD once *H. pylori* has cleared in the much the same way as seen in other bacterial and parasitic infections.

Several studies have demonstrated efficacy in reducing FD symptoms with *H. pylori* eradication; however, others have found only a moderate (but statistically significant) effect or no clinical benefit to eradication at all [65-69]. A Cochrane review concluded that eradication was significantly better than placebo [69]. Response rates may be dependent on the specific symptom. For example, one study documented a positive response to *H. pylori* eradication, but only for the symptoms of epigastric pain and burning, indicating that efficacy may be restricted to patients with the epigastric pain syndrome subtype of FD [67]. A large number of patients with FD continue to experience symptoms following *H. pylori* eradication. These may be patients in whom *H. pylori* had no pathologic role, or may represent a group of patients who should be classified as post-infectious FD given that complete resolution of submucosal inflammation requires a prolonged period [70].

H. pylori colonization is generally associated with gastric and duodenal histologic inflammation. Histologic duodenitis has been associated with more severe symptoms when histologic gastritis also is present [71]. However, this finding has not been consistent, with others actually

reporting an inverse relation between severity of symptoms and gastric inflammation [72]. *H. pylori* colonization in children is associated with increased mucosal lymphocytes, plasma cells, neutrophils, and eosinophils, which decrease with eradication [20]. *H. pylori* colonization may also be associated with increased antral mast cell density, though this may be *H. pylori* strain specific [73]. In the setting of nodular gastritis associated with HP colonization, eosinophils may be of particular significance. Nodularity is associated with the presence and density of eosinophils [74]. Patients with nodular gastritis have a higher incidence of FD symptoms which resolve with eradication therapy and improvement of gross endoscopic appearance [70]. Even in the absence of nodularity, *H. pylori* colonization is associated with increased antral eosinophils, as well as increased gastric fluid eosinophil cationic protein indicating eosinophilic activation [20,75,76]. These findings suggest a possible pathophysiologic role for eosinophils in contributing to symptoms in patients with *H. pylori* colonization or possibly following eradication.

Similar to post-infectious FD, *H. pylori* may be associated with electromechanical dysfunction which, in turn, can contribute to FD symptom generation. Though studies are conflicting, *H. pylori* has not consistently been associated with delayed gastric emptying or visceral hypersensitivity [77]. However, treatment with a prokinetic was found to be as effective as eradication at 12 months [78]. *H. pylori* also has been associated with an abnormal electrogastrogram that normalized in 83% with eradication [79]. *H. pylori* does not appear to have any effect on accommodation [60].

3.3. Allergy

The role of allergy in the development of FD has not been greatly studied. However, allergy may be important given the observed increases in, and activation of, mast cells and eosinophils in FD. FGIDs occur more commonly in children with a history of cow's milk allergy as infants [80]. In children with FD in association with cow's milk allergy, mucosal application of cow's milk is associated with increased eosinophils and mast cells, as well as rapid degranulation, within 10 minutes of application [81]. In addition, cow's milk exposure is associated with increased mast cells within 5 μm of nerves [81]. Adult FD patients with a history of allergy have increased duodenal eosinophil density [36]. In addition, lymphoid hyperplasia is significantly more frequent in children with abdominal pain associated with food allergies [19]. Lymphoid hyperplasia is associated with food hypersensitivity although this reaction may be local reactivity only as it is associated with normal skin prick tests and normal serum IgE levels [82,83].

Food allergy, similar to post-infectious FD and *H. pylori* colonization, also may cause electromechanical dysfunction. Exposure to cow's milk in allergic FD children resulted in increased bradygastria [81]. In infants with cow's milk allergy, exposure results in gastric arrhythmias and delayed gastric emptying [84].

Whether food allergy accounts for a substantial portion of children with FD is not clear. One study found no significant increase in immunoreactivity to common food allergens in FD children with duodenal eosinophilia, although it is possible that the reaction was localized to the mucosa [85]. It is also possible that environmental allergens may be playing a role. Antigen

exposure in adults with birch pollen allergy results in an increase in mucosal major basic protein positive eosinophils and IgE-bearing cells, as well as in FD symptoms, in the majority of patients [86]. Information in this area remains quite limited.

4. Implications for Care

4.1. Evaluation

The current approach to the pediatric FD patient has not been thoroughly studied. Based on existing small studies in children and large studies in adults, however, it appears reasonable to treat empirically with acid reducing medications and proceed with endoscopy with biopsies for non-responders. There may be value in evaluating mucosal biopsies for eosinophil density, particularly those obtained from the duodenum. A reasonable standard would be to consider antral eosinophil density $>10/\text{hpf}$ and duodenal eosinophil density $>20/\text{hpf}$ as abnormal. Despite current information implicating a role for mucosal mast cells, particularly in the antrum, it is less clear if there is value in determining mast cell density. The latter would require special immunohistochemical stains and the standard for normal is even less well defined than for eosinophils.

4.2. Treatment

Medications targeting mast cells or eosinophils could offer benefit by decreasing either cell density or activation. Such agents include corticosteroids and mast cell stabilizers. In addition, medications potentially could provide relief by targeting receptors for specific mediators once released by either cell. Although there is no current means for identifying the specific mediators generating symptoms in a particular patient, antagonists are available for some mediators, such as histamine, cysteinyl leukotrienes, and TNF- α . Finally, other treatments exist that may provide relief by targeting other factors, such as CRH, that may play an important role in activation and/or maintenance of inflammation. Consistent with a biopsychosocial model, combining treatments that address inflammation from different perspectives ultimately should be most beneficial.

Corticosteroids. Corticosteroids have not been evaluated in treating FD, but are commonly used in the treatment of eosinophilic gastroenteritis, although there are no placebo-controlled studies evaluating efficacy. The extensive side effect profile represents a significant draw back in considering their use long term. Budesonide may represent a safer alternative. Budesonide is a synthetic corticosteroid with high topical activity and substantial first pass elimination, limiting systemic exposure [87]. The literature regarding budesonide and eosinophilic gastroenteritis is limited, consisting of only case reports where budesonide therapy has been reported to be effective against eosinophilia in the duodenum and jejunum [88-90].

Mast Cell Stabilizers. Mast cell stabilizers, including cromolyn and ketotifen, would represent an attractive potential therapy given data implicating mast cells in the generation of FD symptoms as previously discussed. These agents would have the potential to prevent release

of a variety of mediators with downstream effects. In one open-label observational study of children with FD in association duodenal eosinophilia, resolution of pain was demonstrated with use of oral cromolyn in 89% of patients who had previously failed to respond to H2 and combined H1/H2 antagonism [91]. There have been no other pediatric or adult studies on the use of mast cell stabilizers in patients with FD. Benefit has been demonstrated in adults with IBS and may be related to blocking allergic or immunologic reactions to foods [92-94]. Ketotifen, specifically, has been shown to significantly decrease pain in adults with IBS and to increase the threshold for discomfort in patients with visceral hypersensitivity [95]. Ketotifen also acts as an H1 antagonist, so the effects may not be directly, or completely, related to mast cell stabilization.

Antihistamine Medications and Proton Pump Inhibitors (PPI). Acid reduction remains the most common treatment prescribed empirically by pediatric gastroenterologists for children with FD [9]. While there are numerous adult studies to support this practice, pediatric studies are limited. In children with chronic abdominal pain, famotidine (H2 receptor antagonist - H2RA) was superior to placebo in global improvement, with clear benefit to those with FD [96]. In a large pediatric study, omeperazole was shown to have a very modest advantage in the relief of all symptoms as compared to either famotidine or ranitidine; however, there was no significant difference between the three with regard to resolution of abdominal pain, epigastric pain, nausea, or vomiting specifically [97].

In adults, H2 antagonism has been shown to improve at least some symptoms associated with FD, including abdominal pain, indigestion, belching, and gastroesophageal reflux symptoms [98,99]. H2 antagonists have been shown to be superior to prokinetic medications and short term use of an anxiolytic [100,101]. A meta-analysis evaluating the use of PPIs in adult FD determined that they were superior to placebo in symptom reduction [102]. Studies of omeperazole, lansoprazole, and pantoprazole have demonstrated a modest superiority to placebo in symptom reduction which is limited to patients with ulcer-like or reflux-like FD [103-105]. Whether PPIs are superior to H2 antagonism is not completely clear. Omeperazole was found to have a modest increase in efficacy as compared to ranitidine at 4 weeks (51% vs. 36%), but there was no additional benefit at 6 months [101].

Given the response to PPIs, it would appear that at least some of the clinical improvement from H2 antagonism or PPIs is related directly to acid suppression. A significant portion of responders may derive benefit from treatment of overlap GERD, or possibly from peptic gastritis or duodenitis. Conversely, the benefit may be due to removing exposure to acid in patients with acid hypersensitivity. PPIs do not appear to have other benefits with regard to gastric emptying or myoelectrical function [106].

The benefit of H2 antagonism may be unrelated to acid reduction, at least in part. Histamine has direct gastric myogenic actions, modulates afferent enteric nerve excitability, and acts as an immunomodulating agent [53,107-111]. There may be additional benefit from H1 antagonism, as well. Combining an H1 antagonist with an H2 antagonist has been reported to relieve symptoms in 50% of children with FD associated with duodenal eosinophilia and in 79% of adults with FD associated with increased antral mast cell density who had previously failed to respond to acid reduction therapy [91,112]. H1 receptors affect smooth muscle contraction

and visceral sensitivity [53]. In addition, some benefit from H1 antagonism may be due to an anxiolytic effect [113].

Cysteinyl Leukotriene (cysLT) Antagonists. CysLTs are another potential therapeutic target. The pattern of eosinophil degranulation in pediatric FD is consistent with the release of major basic protein, which is known to enhance the synthesis of cysLT; cysLT, in turn, stimulates smooth muscle contraction and recruitment of eosinophils [114]. CysLTs have been shown to alter mast cell function. CysLTs can induce IL-5 and TNF- α production in primed mast cells, an effect blocked by cysLT inhibition [115]. Leukotrienes (LTs) have the potential to increase intestinal sensory nerve sensitivity during inflammation. CysLTs have been shown to stimulate enteric neurons and to have a pro-contactile effect on the esophagus, stomach, small intestine, colon, and gallbladder [116-123].

Montelukast, a cysLT receptor antagonist, was superior to placebo with regard to relief of pain in a double-blind, placebo-controlled, cross-over trial of children with FD associated with duodenal eosinophilia [124]. The response rate was 84% in patients with eosinophil densities between 20 and 29/hpf versus 42% receiving placebo. A second study confirmed this high response rate [125]. In the latter study, the short term clinical response did not result from a decrease in eosinophil density or activation. This suggests that the effect of montelukast may be mediated through an enteric nerve effect on motility or sensitivity, something that remains to be demonstrated.

Anti-TNF- α . TNF- α would represent another potential therapeutic target. Mast cells are an important source of intestinal mucosal TNF- α in humans. CysLTs induce TNF- α production. TNF- α can recruit and prolong survival of eosinophils, as well promote a Th2 response depending on other chemokines present in the microenvironment [126-128]. Serum TNF- α concentration prior to treatment correlates negatively with the subsequent clinical response to montelukast in pediatric FD associated with duodenal eosinophilia, indicating that TNF- α may represent an alternative pathway for symptom generation in these patients. Although there are no controlled studies, anti-TNF- α has been reported to be effective in a series of children with resistant eosinophil disease, including patients with FD [129].

Biofeedback-Assisted Relaxation Training. The biopsychosocial model and CRH physiology would suggest a potential role for CRH antagonism or for controlling CRH secretion by controlling anxiety and the stress response. There are no previous studies evaluating CRH-antagonists in FD. Stress management would have the potential to control CRH secretion and, thereby, decrease inflammation. Biofeedback is a technique where individuals are trained to relieve physical or emotional symptoms using signals from their bodies that are displayed visually or aurally. It can be paired with relaxation training to yield biofeedback-assisted relaxation training. Biofeedback-assisted relaxation training may be considered as a solo therapy or, consistent with the biopsychosocial model, a stronger effect may occur in combining relaxation with medications targeting biologic factors such as inflammation. The combination of biofeedback-assisted relaxation training and fiber is superior to fiber alone in children with non-specific abdominal pain [130]. The effect of biofeedback-assisted relaxation training on inflammation has not been studied directly, but biofeedback-assisted relaxation training has been studied as adjunctive treatment in children with FD in association with duodenal

eosinophilia [131]. Children receiving medication plus biofeedback-assisted relaxation training demonstrated better outcomes with regard to pain intensity, duration of pain episodes, and global clinical improvement as compared to children receiving medications alone [131].

5. Conclusions

Current evidence implicates inflammation, particularly mast cells and eosinophils, in the pathophysiology of FD. FD in adults is associated with an increase in antral mast cell density and an increase in duodenal eosinophil density; elevated duodenal eosinophil density is frequently present in children with FD. Active degranulation of both cell types in children with FD suggests a pathophysiologic role. In children with FD, higher antral mast cell density is associated with gastric electromechanical dysfunction, psychologic dysfunction, and symptoms consistent with the postprandial distress syndrome subtype of FD defined for adults. Duodenal eosinophil density appears associated with anxiety in children with FD, but relationships with electromechanical dysfunction appear less direct. Both mast cells and eosinophils may have key roles in conditions that are associated with FD, including anxiety, infection (including *H. pylori*), and allergy. Ultimately, inflammation appears to be of particular importance in FD. Inflammation interacts with a number of other factors and may even mediate the relationship between psychologic and physiologic factors.

There may be efficacy in utilizing medications directed at inflammation, particularly mast cells and eosinophils. Most reports on treatment response consist of case series using H1/H2 antagonists, mast cell stabilizers, and anti-TNF- α . Consistent with a biopsychosocial model, some evidence exists to suggest that combining treatments targeting different components of the model that may influence inflammation can increase rates of symptom resolution in pediatric FD. There remains a need for placebo-controlled trials of the various medications and other treatments targeting inflammation which have been suggested to have efficacy, both alone and in thoughtful combination. Treatment for pediatric FD must continue to evolve if we are to prevent the significant downstream costs to the individual and society and, in this goal, inflammation appears an important primary target.

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