Pediatric Health, Medicine and Therapeutics

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REVIEW

An Update on the Assessment and Management of Pediatric Abdominal Pain

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Abstract: Chronic abdominal pain is very common in children and adolescent and results in high personal and social costs. Most youth with chronic abdominal pain fulfill criteria for a functional abdominal pain disorder (FAPD) as defined by Rome criteria. These are complex conditions with a wide array of biological, psychological, and social factors contributing to the experience of pain. The purpose of the current review is to provide an overview of the pathophysiology of FAPDs and an up-to-date summary of the literature related to FAPDs in children and adolescents, with additional focus on several areas (eg, diet and probiotics) where patients and families frequently have questions or implement self-directed care. We also provide an approach to the assessment and treatment of pediatric FAPDs focusing on the robust literature regarding psychological interventions and much sparser literature regarding medication treatment.

Keywords: abdominal pain, functional abdominal pain disorders, functional dyspepsia, irritable bowel syndrome, biopsychosocial model

Introduction

Chronic abdominal pain is very common in children and adolescent and results in high personal and social costs.[1] It is associated with reduced health-related quality of life (QOL) comparable to organic gastrointestinal diseases.[2] The worldwide prevalence has been estimated at 13.5% with comparable rates across continents.[3] It is more common in females with a peak prevalence in the early teens.[3]

Most youth with chronic abdominal pain fulfill criteria for a functional gastrointestinal disorder (FGID) as defined by Rome criteria.[4] Within the relatively broader category of FGIDs, there are four recognized functional abdominal pain disorders (FAPDs) including irritable bowel syndrome (IBS), functional dyspepsia (FD), abdominal migraine, and functional abdominal pain syndrome, with IBS and FD being the two most common.[5,6] (See Table 1 for criteria) Criteria for FGIDs in pediatrics were first adopted by expert consensus in 1999 (Rome II).[7] They were revised in 2006 (Rome III) and again in 2016 (Rome IV).[4,7] They have remained largely consensus-based, having never been fully validated or shown to predict treatment response. Particularly, for IBS and FD, transition to Rome IV brought significant changes resulting in different prevalence estimates and creating doubt on whether existing research utilizing Rome III criteria can be extrapolated to patients currently defined by Rome IV.[8] Lastly, there are additional challenges in that the criteria are inconsistently applied, and diagnoses differ in comparing parent- and patient-reported symptoms.[9,10] Despite these challenges, there is value in the

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Received: 22 April 2021
Accepted: 15 July 2021
Published: 6 August 2021

Table 1 Rome IV Criteria for Functional Abdominal Pain Disorders in Children and Adolescents

Functional Dyspepsia*: 1. Postprandial fullness 2. Early satiation 3. Epigastric pain or burning not associated with defecation
Irritable Bowel Syndrome*: 1. Abdominal pain in association with at least one of the following: • Related to defecation • A change in stool frequency • A change in stool form 2. In children with constipation, the pain must not resolve with resolution of the constipation
Abdominal Migraine: at least 2 episodes of all of the following, fulfilled for at least 6 months: Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting at least 1 hour 1. Episodes separated by weeks to months 2. Pain is incapacitating and interferes with normal activities 3. Stereotypical pattern and symptoms in the individual patient 4. Pain is associated with 2 or more of the following: • Anorexia • Nausea • Vomiting • Headache • Photophobia • Pallor
Functional Abdominal Pain*: 1. Episodic or continuous abdominal pain that does not occur during physiologic events (eg eating, menses) 2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia or abdominal migraine

Notes: *Must occur at least 4 times per month for 2 months. For all: After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition. Data from Hyams et al.[4]

clinician being familiar with the criteria as they represent the classification used in nearly all treatment trials. In addition, it has been demonstrated that providing the patient with a positive diagnosis may enhance treatment outcomes.[11]

While FAPDs are precisely defined, it should be recognized that patients can fulfill criteria for more than one FAPD. There are a significant number of youths with chronic abdominal pain who fulfill criteria for both IBS and FD, and overlap has significantly increased with institution of Rome IV criteria.[12] Further, overlap of FAPDs with other health issues is common. Specifically, youth with FD have been shown to have high rates of both gastroesophageal reflux and overactive bladder symptoms.[13] Additionally, there can be significant symptom heterogeneity within a specific diagnosis. Nausea, which occurs in high proportions of patients with either FD or IBS, may be of particular importance. Nausea has been associated with worse abdominal pain and gastrointestinal symptoms, somatic symptoms, sleep disturbances, depression, anxiety, disability, poor school and social functioning, school absences, and poorer QOL.[14–17] Nausea also predicts a higher rate of persistence of gastrointestinal and somatic symptoms, anxiety, and depression into adulthood.[14] As such, nausea may be an important treatment target in FAPDs.

The purpose of the current review is to provide an up-to-date summary of the literature related to FAPDs in children and adolescents, with additional focus on several areas (eg, diet and probiotics) where patients and families frequently have questions or implement self-directed care. We also provide an approach to the assessment and treatment of pediatric FAPDs focusing on the robust literature regarding psychological interventions and much sparser literature regarding medication treatment.

Biopsychosocial Model

It has become abundantly clear that the development of chronic abdominal pain is a complex process. The biopsychosocial model has long-been recognized within the context of chronic abdominal pain and recognizes that symptoms arise through numerous pathways that include biologic factors (eg, genetics, dysmotility, visceral hypersensitivity, inflammation, sleep disturbances, dysbiosis), psychologic factors (eg, anxiety, depression, dysfunctional coping), and social factors (eg, poor relationships with parents, peers, or teachers) which interact with each other. All these factors can contribute to the initiation or maintenance of pain as well as the severity and frequency of on-going symptoms, and all have been reported in FAPDs. Although the model remains relevant, it continues to evolve recognizing a much greater complexity within FAPD pathophysiology. Biologic factors can now be broken down into three main systems- neurologic, immunologic, and endocrinologic- which all communicate readily with each other and the psychologic system. Likely, other factors in the initial biopsychosocial model also are comprised of influential and interacting systems. Improved understanding of these will increase the complexity of screening and evaluation, but also provide more tailored treatment options given the somewhat unique combination of contributors believed to underlie each patient's presentation.

While a discussion of all known factors and their interactions are beyond the scope of this paper, it is useful to provide some examples of how factors interact (Figure 1). There appear to be four main interacting systems which readily communicate with each other: psychologic, neurologic, immunologic, and endocrinologic. Most known pain triggers interact with one or more of these systems starting a cascade resulting in the experience of abdominal pain. Visceral hyperalgesia, an exaggerated response to a potentially painful occurrence (such as bowel distension) is believed to be one of the central mechanisms in FAPDs. Sensitivity to stretch has been shown in youth with recurrent abdominal pain and, specifically, in IBS.[18–20] In adults, infusion of acid into the stomach or duodenum can result in pain and infusion of acid or lipid into the duodenum can increase gastric sensitivity to distension, providing one mechanism by which diet may induce pain.[21–26] Diet will be discussed more later. FAPDs are associated with aberrant motility although it has been difficult to link dysmotility to specific symptoms or symptom severity.[27] Also within this biologic realm, there is mounting evidence implicating inflammation in FAPDs, particularly mast cells in IBS and both mast cells and eosinophils in FD.[28–30] An important mechanism by which stress can trigger symptoms is through activation of mucosal mast cells, which in turn, release mediators transmitting a pain message, or which sensitize nerves resulting in hyperalgesia.[31,32] There is an association between mucosal mast cells and/or eosinophils with anxiety and depression in youth with FD and IBS.[33,34]

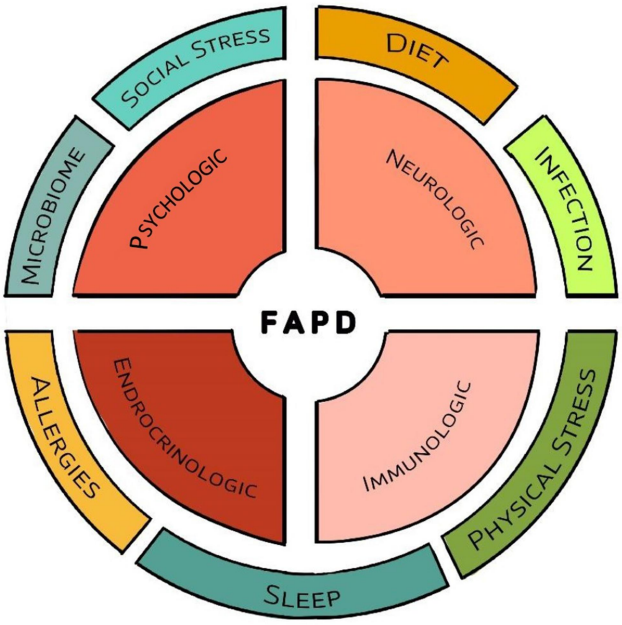

Figure 1 Overview of factors involved in the pathophysiology of functional abdominal pain disorders. Central to this process are four interacting systems with a variety of factors which interact with these systems and in some instances, with each other.

There is also increasing recognition of an altered intestinal microbiome and an interrupted intestinal barrier having a role in FAPD pathogenesis. Although there is great variability regarding the specific bacteria altered, IBS, in particular, is associated with an altered microbiome composition and possibly more importantly, an altered milieu of bacterial metabolic products.[35,36] Bacteria can directly affect visceral sensation and alter expression of tight junction proteins allowing increased passage of antigens, prompting an immunologic reaction.[37] Likewise, the intestinal barrier can also be disrupted by stress and inflammation.[38] Barrier dysfunction has been reported in 37–62% of adults with diarrhea-predominant IBS (IBS-D) and 4–25% of those with constipation-predominant IBS (IBS-C).[39] All four pediatric studies assessing the intestinal barrier in patients with IBS have demonstrated barrier dysfunction, which is associated with abdominal pain, symptom severity, depression, and anxiety.[39]

Psychologic disturbances frequently co-exist and interact with biologic factors, cutting across FAPD diagnoses, and are associated with abdominal pain severity.[40] Pediatric FAPDs are associated with increased anxiety and depression, both of which are associated with increased abdominal pain severity and disability.[40,41] The presence of psychologic dysfunction predicts worse outcomes and persistence into adulthood.[41,42] In addition, coping style can significantly affect symptom severity and outcomes.[40,41] While anxiety and depression appear to be triggers for abdominal pain, it also appears that abdominal pain is a trigger for anxiety and depression.[43]

Lastly, considerable evidence now implicates sleep disturbances (SD) in FAPDs which are associated with more severe gastrointestinal symptoms, more emotional disturbances, hyperalgesia, and upregulation of inflammatory cytokines.[44–50] Difficulties related to sleep onset and maintenance, the most common SD followed by excess somnolence, are equally distributed across FAPDs, more common in adolescents, and associated with increased functional disability.[47] In children and adolescents, the total sleep hours and the number of night awakenings predict the prevalence of pain the following day.[48] Additionally, sleep disturbance is associated with worse clinical outcomes in youth with FAPDs.[42]

Table 2 Alarm Signs and Symptoms for Youth with Chronic Abdominal Pain with Suggested Initial Evaluation

Alarm Sign or Symptom	Evaluation
Weight loss Deceleration of growth Delayed Puberty	Complete blood count, C-reactive protein, stool calprotectin (or lactoferrin), and celiac serology
Excessive vomiting Right upper quadrant pain	Liver function tests, amylase, lipase, urinalysis, and abdominal ultrasound
Hematemesis or hematochezia Right lower quadrant pain Severe chronic diarrhea Perianal disease Systemic symptoms such as unexplained fever or arthritis Family history of inflammatory bowel disease or celiac disease	Complete blood count, C-reactive protein, stool calprotectin (or lactoferrin), celiac serology, and endoscopy
Dysphagia	Barium swallow and endoscopy

While the previous description of the biopsychosocial model and FAPD pathophysiology represents only a very small portion of the literature, we hope it gives a sense of the complexity of FAPDs. More importantly, the goal is to give a useful working knowledge of the model as patient and family education on the construct represents a vital first step in treatment and has a positive effect on treatment outcomes.[51] What patients and their family understand about FAPDs, their complex physiology, and treatment has a significant impact on engagement, adherence, and outcomes.[52] This model forms the basis for seeking to identify the multiple factors operating in any given patient and the rationale for recommendations targeting biologic and psychologic processes.

Evaluation

As previously stated, most children and adolescents with chronic abdominal pain will fulfill criteria for a FAPD. The great majority will not have a specific "organic" disease or will have findings (particularly on endoscopy) which are of unknown clinical significance.[53] FAPDs are intended to be positive diagnoses based on symptom profiles that do not require a work-up to rule out other conditions to establish the diagnosis. However, Rome criteria contain the caveat that they are diagnosed "after appropriate evaluation" which is largely undefined.[4] No evidence-based guidelines exist to direct evaluation and there is wide variability in testing performed across pediatric gastroenterologists.[9]

It is common practice to search for "red flag" or alarm symptoms and to use non-invasive laboratory testing to identify patients needing additional evaluation before diagnosing an FAPD, and in the absence of these alarm symptoms, to make a diagnosis of an FAPD without testing. Alarm symptoms are symptoms that generally are infrequent in FAPD or at least, indicative of greater severity. Table 2 contains signs and symptoms which have been utilized as alarm symptoms to indicate a potential need for further testing. While these are utilized in practice, there is limited evidence supporting their validity. Differentiating IBS from inflammatory bowel disease (IBD) is of particular importance when evaluating youth with chronic abdominal pain. Fortunately, literature is strongest in this area. Specifically, alarm symptoms of hematochezia and weight loss (or problems gaining weight) have been shown to be helpful in differentiating Crohn's disease from FAPDs.[54] Selecting patients for further evaluation for IBD also may be aided by laboratory assessment. The presence of anemia increases the likelihood of IBD.[54] Serum C-reactive protein (CRP) and stool calprotectin or stool lactoferrin also have utility in indicating IBD including in children and adolescents.[55–60]However, results must be interpreted with caution. While a low calprotectin decreases the chances of IBD (particularly in combination with a low CRP), it does not eliminate IBD from the diagnosis; similarly an elevated calprotectin does not necessarily indicate IBD, particularly in patients with diarrhea-predominant IBS.[55,58,61] While most studies do not support a relationship between celiac disease and pediatric

FAPDs, one Italian study found a 4-fold increase in celiac (4.4% vs 1%) in youth with IBS and another study found a borderline increase.[62,63] Both the American Gastroenterological Association (AGA) and the pediatric Rome committee have recommended celiac screening in IBS.[4,64] Evidence for screening laboratory evaluations in FAPDs other than IBS are limited.

Special mention should be made of the role of endoscopy as it is costly and somewhat controversial in terms of its necessity and value in the context of FAPDs. Endoscopy is generally performed to identify pathology or conversely to rule-out an organic disease to establish the diagnosis of an FAPD. The diagnostic yield of esophagogastroduodenoscopy (EGD) has been widely studied, with histologic inflammation (esophagitis, gastritis, duodenitis) and/or the presence of *Helicobacter pylori* being present in 23–93% of patients.[53] While the disease prevalence appears high, the clinical significance of these findings is not well-established. The role of endoscopy may be shifting from a "search for disease" to a "search for biologic contributors" within the biopsychosocial model, particularly the presence of eosinophils and mast cells. Although there are not well-established criteria for histologically defining eosinophilic gastroenteritis, and norms have not been established for mucosal mast cell densities, both have been extensively studied. Eosinophils and mast cells have been implicated in FD, while mast cells have been implicated in IBS pathogenesis.[28–30]

Current evidence, albeit limited, and recommendations support minimal initial diagnostic testing in youth with suspected FAPDs. Therapeutic interventions are the initial approach with diagnostic testing reserved for patients with alarm symptoms. Further evaluation should also be considered for patients not responding to treatment, searching not only for less common diseases (eg, cholelithiasis or renal anomalies with ultrasound) but potentially also for biological contributors (eg, mast cells and eosinophils with endoscopy).

Treatment

Diet

There has been a great interest in the role of diet in patients with FAPDs. Over 90% of youth with FAPDs identify at least one food that they associate with worsening of gastrointestinal symptoms.[65,66] As compared to healthy controls, youth with FAPDs avoid foods more frequently and more often implement diet strategies.[65,66] While adverse food reactions could be related to allergies, malabsorption, or anticipation of symptoms, there has also been an interest in the effects of specific dietary components interacting with components of the brain-gut axis.

FODMAPS

Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are common dietary components which have been implicated in FAPDs, particularly IBS. The low FODMAP diet is presumed to result in a decrease in gas production and subsequently a decrease in distension with a decrease in pain. The diet also results in improved barrier function and decreased inflammation.[67,68] A systematic review of the low FODMAP diet in functional abdominal pain concluded that the diet may be effective in adults but that more data was needed to assess its efficacy in pediatrics.[69] Long-term effectiveness of a low FODMAP diet has been reported in 57% of adults with IBS.[70] As in adults, there is a subset of pediatric FAPD patients who demonstrate increased pain with fructan (a FODMAP) ingestion.[66,71,72] In a cross-over trial in children with IBS, Chumpitazi and colleagues demonstrated that fructans increased pain frequency and the severity of bloating and flatulence with increased production of hydrogen gas.[72] A double-blind cross-over trial comparing the low FODMAP diet to the "the typical American childhood diet" found decreased abdominal pain with the low FODMAP diet.[73] Efficacy of the diet appears to be related to the baseline microbial composition.[73–75] Although short-term studies suggests efficacy, studies assessing whether a low FODMAP diet results in long-term benefit are needed in children. The diet places a high burden on the patient and family and has potential for adverse effects including decreased fiber and calcium intake, as well as a decrease in potentially beneficial bacteria.[76] A small adult study suggests that this latter effect can be overcome by supplementation with Bifidobacteria-containing probiotics but more studies are needed, particularly in children.[77]

Particularly in IBS, as recommended by AGA IBS guidelines, an empiric trial of a low FODMAP diet appears to be a reasonable initial intervention although not yet a strong recommendation in children and adolescents. The low FODMAP diet is instituted in 3 phases: restriction, reintroduction, and personalization.[78] If initial restriction is beneficial, eliminated foods are reintroduced sequentially to determine specific foods associated with symptoms followed by personalization where only the

specific symptom-causing foods are eliminated. The resulting diet should be evaluated by a dietician to ensure adequate intake of fiber, vitamins, and both macro- and micronutrients.

Gluten

In pediatrics, the only clear entity where gluten has a documented adverse effect is celiac disease, where gluten induces an immunologic reaction. While one study found an increased prevalence of celiac disease in pediatric IBS and another found a borderline association, most studies have not supported an association between celiac disease and FAPDs in children.[62,63] A few studies, mostly in adults, suggest that a gluten-containing diet may induce symptoms in some patients with IBS.[79] In adults, 7–15% of the population report that wheat induces gastrointestinal symptoms but only 1 of 6 are confirmed with a double-blind wheat challenge.[80] Randomized controlled trials to assess the effects of gluten have produced mixed results.[81] In adults with refractory FD, 35% responded to a gluten-free diet but only 18% of these recurred on a double-blind challenge.[82] Pediatric data is sparse. In a study of 1114 children with chronic gastrointestinal symptoms, only 3.3% exhibited symptoms correlated with wheat ingestion.[83] Of these, 39% were positive on a double-blind gluten challenge.[83]

The mechanisms by which gluten and/or wheat may induce symptoms is not well understood. Gluten/wheat can induce inflammation, increase mast cell density, and alter the microbiome as seen in FD and IBS.[84–86] It is also possible, and even likely, that symptoms are induced by other components of wheat such as FODMAPs.[79,87] When adults reporting non-celiac gluten sensitivity were given diets with fructans, gluten, or placebo, only fructans induced symptoms.[88]

While gluten or other components of wheat may contribute to symptoms in some patients, gluten restriction should not be viewed as routine management and should only be undertaken after celiac serologic testing. Like other restrictive diets, if the patient deems the diet to be beneficial and decides to remain on it, a dietician should be consulted to ensure the nutritional adequacy of the restricted diet.

Disaccharides/Sugars

Disaccharidase deficiencies appear to be common in youth with FAPDs. [El-Chammas; Chumpitazi; Colombo] However, the clinical significance of deficiencies is not well established. These deficiencies are not associated with specific symptoms or symptom severity.[89–91] This should not be surprising as there are several factors involved in symptom generation including the degree of deficiency, the amount of sugar consumed, microbiome composition, intestinal motility, and psychosocial functioning.[92] If diarrhea is present, the Rome working group recommends a 7–10-day trial of restriction of lactose, fructose, and poorly absorbed sugars such as sorbitol. Three sugars have drawn particular attention: fructose, lactose, and sucrose.

Fructose is a common dietary sugar present in fruits, fruit juices, some vegetables, honey, table sugar, and obviously, high fructose corn syrup. Fructose malabsorption is common in children with FAPDs but has been demonstrated in a higher percentage of healthy controls.[93] It has been demonstrated that clinical symptoms correlate with symptoms experienced during a fructose breath test, but not with measures of malabsorption.[94] Fructose restriction has been shown to be helpful in a subset of children with FAPDs.[94–97]

Seventy percent of the population develop very low lactase levels.[90] Although lactase deficiency is common in pediatric FAPDs, symptoms experienced during a lactose malabsorption test are more specific for lactose intolerance than are measures of malabsorption.[98] In most but not all studies, lactose restriction does not lead to relief of symptoms even in patients with demonstrated malabsorption.[92,99–101] The effects of lactose malabsorption may be more complex and persist after restriction as lactose malabsorption is associated with increased colonic lymphocytes, eosinophils, and mast cells as well as visceral hypersensitivity, which may represent secondary therapeutic targets if symptoms persist after lactose elimination.[102–105]

There has been recent interest in a possible role for sucrase deficiency in FAPDs. The sucrase-isomaltase enzyme accounts for virtually all sucrase and isomaltase activity as well as 80% of maltase activity indicating an important role in starch digestion as well as sucrose digestion.[106] Sucrase deficiency, whether measured by mucosal assay or sucrose breath test, is common in pediatric FAPDs.[89,90,107] Sucrase deficiency is not predicted by any specific symptom or symptom complex.[91,107] Hypomorphic SI gene variants as seen in congenital sucrase-isomaltase deficiency (CSID) are increased in IBS and predict non-response to a low FODMAP diet.[108,109] In adults with IBS, a sucrose and starch restricted diet resulted in significant improvement in both gastrointestinal and non-gastrointestinal symptoms.[110,111]

As recommended by the Rome committee, empiric restriction of fructose, lactose, and poorly absorbed sugars such as sorbitol is a reasonable early step in managing IBS. A trial of sucrose and starch restriction is also reasonable. There is no need to undertake tests of malabsorption as they are not predictive of response.

Lipids

Increased small intestinal lipid sensitivity has been demonstrated in adults with both FD and IBS.[112,113] Two-thirds of FD patients demonstrate sensitivity.[114] Duodenal lipids lead to fullness, bloating, and nausea, and enhance sensitivity to distension.[114] In adults with FAPD, high fat meals induce greater pain, nausea, and sensitivity than do high carbohydrate meals.[113,115] When unblinded, cognitive perceptions of fat can alter symptoms and brain activity following lipid intake.[116] Whether dietary restriction of fat is useful is largely unknown, but care should be taken to not overly restrict fats particularly in growing, developing children.

Spicy Foods

In adults with IBS, higher consumption of spicy foods is associated with more symptoms.[117] In an adult population, frequent consumption of spicy foods was associated with an increased prevalence of IBS but only in women.[118] In adults with IBS as compared to healthy controls, spicy meals significantly increased abdominal pain and burning, while oral burning was similar.[119]

Most studies have evaluated the effects of capsaicin, a component of red pepper which stimulates TRPV1. Oral capsaicin increases symptoms in approximately 50% of adults with FD and symptoms in this group increase more than in patients with IBS or healthy controls.[120–123] In adults with IBS, rectal capsaicin application results in a dose-dependent increase in urge and pain perception.[124] Increased pain perception was most evident in those with visceral hyperalgesia and was associated with anxiety.[124]

It is reasonable for patients to self-evaluate reactions to spicy foods as the symptoms should occur rapidly, and then only restrict if spicy foods exacerbate symptoms.

Fiber

Studies evaluating fiber as a treatment for FAPDs have largely been confined to evaluation of fiber supplements and not increasing dietary fiber. Benefits are probably most related to water retention stimulating peristalsis and slow fermentation to produce short-chain fatty acids which in turn, preserve the intestinal barrier, promote anti-inflammatory actions, inhibit mast cell activation, and may decrease visceral sensitivity.[125–127] A meta-analysis of adult studies found that soluble fiber improved symptoms and abdominal pain scores, while there was no evidence for efficacy of insoluble fiber.[128] Adult IBS clinical guidelines recommend a trial of soluble fiber, but not insoluble fibers such as bran.[64,129]

There have been five controlled studies of fiber in pediatric FAPDs.[130] One involved treatment with corn fiber which is insoluble and resulted in a decrease in pain attacks.[131] The other four studies utilized various soluble fibers. No benefit was shown for glucomannan or ispaghula husk.[132,133] Psyllium has been shown to decrease pain episodes without altering breath hydrogen or methane production, intestinal permeability, or microbiome composition.[134] Partially hydrolyzed guar gum was shown to improve bowel habits, but improvement in abdominal pain did not reach statistical significance.[135]

Supplementation with soluble fibers is a reasonable early intervention in IBS. Whether increasing dietary fiber, which is often a combination of both soluble and insoluble fiber, is helpful is not known with the exception that bran appears to have little treatment value.

Food Allergies

There is a well-established association between IBS and atopic conditions.[136,137] The association of IBS with mucosal mast cells and FD with mucosal mast cells and eosinophils might also suggest a possibility of allergen-induced inflammation.[28–30] There is not conclusive data implicating IgE-mediated reactions to food as identified by skin prick testing.[137,138] Based on studies utilizing colonoscopic allergen provocation test (COLAP), it appears that patients may have local allergic reactions within the mucosa without systemic symptoms and which are not identified by skin prick testing or food-specific IgE testing.[139–141] These findings cast doubt on the ability of standard allergy testing to provide a list of safe foods based on negative results. Aguiler-Lizarraga have proposed that these localized reactions may represent part of a spectrum of reactions with systemic reactions to foods at one end of the spectrum.[139]

There may also be a role for environmental allergens. Indeed, environmental pollen exposure has been shown to have as strong or stronger influence on pain occurrence in youth with FAPDs than does negative affect or hours of sleep.[48] Birch allergy has been particularly studied. In

adults with birch allergy, during birch allergy season, mucosal eosinophils and mast cells are increased compared to out-of-season and frequently associated with oral allergy syndrome with birch-associated foods.[142,143] Cecal COLAP utilizing Bet v-1, the active allergen in birch pollen which cross-reacts with foods, demonstrated an association between positive reactions and a history of pollinosis and reactions to birch-associated foods but no correlation with skin prick testing.[140]

Although controversial, there are some studies implicating IgG or more specifically, IgG4-mediated food reactions. IgG and IgG4 food reactions are generally increased in IBS patients as compared to healthy controls.[144–146] These may represent food exposures in patients with impaired barriers as opposed to immunologic reactions contributing to symptoms, as resolution of food allergies is generally associated with development of increased food-specific IgG and IgG4 levels.[147,148] On the contrary, several studies have shown improvement in symptoms on elimination diets based on food-specific IgG testing with a prompt decrease in food-specific IgG in one study.[145,149,150]

In the absence of a systemic allergic reaction or oral allergy syndrome, routine allergy testing is not recommended in the absence of a clear relationship between a food and symptoms. It should be remembered that the reaction may be local to the mucosa and not identified by standard skin prick tests or food-specific IgE. There may be value in testing for cross-reacting foods or empirically eliminating cross-reacting foods when allergies to specific pollens are identified.

Diet Conclusion

Although there are no interventional studies evaluating a healthy diet, there is no reason not to recommend a normal, healthy diet in patients with FAPDs.[79] Recommending good hydration, eating regularly and slowly, limiting excessive fat intake, and watching for symptom exacerbations with spicy foods or any specific foods also seems to make common sense given the current state of the literature.[151] If a food appears to exacerbate symptoms, it should not be assumed that the reason is known (eg, allergy, gluten content), especially if that leads to other excessive restrictions, as foods have many components that could potentially increase pain. In patients with IBS, an empiric trial of a low FODMAP diet (as recommended in AGA guidelines) or of fructose, lactose, and poorly absorbed sugars (as recommended by the Rome committee) are reasonable but should be followed by reintroduction and personalization. If a restricted diet is used for long-term management, consultation with a dietician would be appropriate to ensure nutritional adequacy of the diet.

Probiotics

Probiotics are living microorganisms which provide health benefits when consumed. Probiotics are used to alter the microbiome composition and/or metabolic activity modulating inflammation and permeability, and possibly altering susceptibility to food allergy.[38,137,152] To our knowledge, there have been 13 randomized trials of probiotics in youth with FAPDs.[153–165] Benefit has been demonstrated in at least some patient groups in eleven of these studies. Benefit has been demonstrated in 4 of 6 studies utilizing *Lactobacillus reuteri*, 5 of 6 studies utilizing *Lactobacillus GG*, and in 3 studies utilizing *Bifidobacteria* species, *Bifidobacteria* and *Lactobacillus* species, or a combination of *Bacillus coagulase* and a prebiotic, respectively.[153–165] Benefit has occurred most commonly in patients with IBS, to a lesser degree in FAP, and less often in FD. Benefit is most often reflected by improvement, but not resolution, in pain frequency and/or intensity. Studies comparing probiotics are lacking as are studies identifying reliable predictors of response. Despite this lack of data, probiotics are a reasonable early intervention in IBS.

Psychologic Treatment

Although an association between abdominal pain and psychologic dysfunction does not mean cause-and-effect in either direction, once present, psychologic dysfunction likely contributes to symptoms and thus becomes an important therapeutic target. A significant proportion of children with FAPDs have clinically relevant anxiety or depression.[166] In addition, one study found that 35–45% of children with FAPDs have subclinical elevations in anxiety.[167] This latter group presents some challenges as they would likely benefit from psychological intervention but do not have a diagnosable psychologic condition. Psychologic features impact clinical outcomes and are associated with increased symptom severity and disability.[41] In addition to the broad categories of anxiety and depression, response to treatment is influenced by response to several pain-specific targets including catastrophizing, parent-perceived disease threat, and avoidance behaviors.[41,168,169]

Aligning psychologic and medical care allows more comprehensive treatment of the patient but requires regular communication.[170] In addition, educating the patient and family on the biopsychosocial model and incorporating psychologic care at the beginning decreases resistance to behavioral healthcare.[170,171] Lastly, simply instructing the patients and families to find a therapist is unlikely to be an adequate approach.[170] An AGA expert review defined best practices to include the medical provider knowing the features of the most common psychologic interventions and establishing a relationship involving direct referral and on-going communication with 1–2 mental health providers while continuing to be involved in the on-going care team.[172] Below, we discuss some of the more common and most supported psychologic interventions including cognitive behavioral therapy, hypnotherapy, biofeedback-assisted relaxation training, and mindfulness-based treatment.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a short-term psychotherapy which aims to alter maladaptive thoughts, coping, and behaviors that contribute to symptom escalation or maintenance.[170,173] Patients are taught to recognize and challenge distorted thoughts, engage in positive coping, and change behaviors to promote well-being.[173] CBT also employs exposure-based exercises in which patients face sensations or situations that cause fear in order to gradually alleviate stress and decrease symptoms while improving quality of life.[170,173] CBT for children with FAPDs and their parents has been shown to decrease pain and severity of gastrointestinal symptoms while improving parental responses and decreasing solicitous behaviors.[170,174] Compared to a variety of controls including standard medical care, CBT has been shown to be effective in decreasing symptoms and increasing functioning in most, but not all, studies with demonstrated long-term benefit.[174–180] To improve access, CBT delivered by phone or internet has been evaluated in a substantial number of studies with findings very similar to in-person CBT.[181–187] Phone/internet CBT has been shown to decrease pain, activity limitations, catastrophizing, parental solicitousness, functional disability, missed school days, GI-specific anxiety, and avoidance behaviors while improving QOL.[181,183,185–187]

Hypnotherapy

Hypnotherapy is a form of medical hypnosis where post-hypnotic suggestions focus on abdominal discomfort to relax automatic reactions to symptoms and increase a feeling of self-efficacy in dealing with symptoms. It usually involves weekly sessions (6–12) led by a therapist with daily practice using audio recordings with guided imagery.[170,173] Hypnotherapy and guided imagery have been shown to decrease pain scores, pain-related disability, and missed activities with long-term benefit.[188–190] As with CBT, home-based audio-recorded guided imagery has been shown to be effective.[191,192] Overall, these therapies have resulted in success rates (pain reduction or resolution) in 50–85%.[188,189,191–193]

Biofeedback-Assisted Relaxation Training

Biofeedback is a technique where individuals are trained to relieve[170,173] physical and emotional symptoms utilizing physiologic data displayed visually or aurally.[194] When combined with relaxation training, it is termed biofeedback-assisted relaxation training (BART). BART addresses physiologic contributors to symptoms, providing concrete methods to cope with pain and stress, blunting the physical stress response and enhancing self-efficacy over pain.[170,194] BART generally requires 4–6 sessions. BART has been shown to be effective in children with FD and duodenal eosinophilia.[194] As compared to medications alone, medications combined with BART resulted in more rapid improvement in pain frequency and intensity.[194] In children with recurrent abdominal pain, biofeedback combined with fiber was shown to be superior to fiber alone and adding CBT or parental support did not enhance this effect.[195]

Mindfulness

Mindfulness utilizes meditation and non-judgmental awareness of the current moment without any attempt to change the current situation.[170,173] It requires training and practice. Mindfulness training has been shown to reduce stress and anxiety in adults and children and depression in adults.[170,196,197] Mindfulness-based treatment has been demonstrated to improve symptoms and quality-of-life (QOL) in adults with IBS, at least in part, by decreasing reactivity to gut-focused anxiety and catastrophizing with refocused attention.[198–200] There are no published studies of mindfulness-based treatment in youth with FAPDs.

Psychologic Treatment Conclusion

Psychologic therapies are vitally important in the treatment of children with FAPDs, addressing the numerous psychologic co-morbidities, decreasing disability, and increasing QOL. These interventions are also clearly

helpful in decreasing pain frequency and/or severity; however, pain is often only partially relieved, and patients will need additional interventions to fully resolve pain. Although CBT has the most empiric support, there are other interventions, particularly hypnotherapy, that are useful, and which may resonate better with individual patients. The goal should be to "fill the toolbox" of the patient and care-givers with a variety of positive coping skills to deal with pain, enhancing self-efficacy, and decreasing school and activity avoidance, in particular.

Placebo

Both the placebo effect and spontaneous improvement are significant contributors to the therapeutic response to a -medication.[201] The placebo effect is subject to a wide variety of influences including the consistency of symptoms, dosing frequency, duration of treatment and the patient-provider relationship.[201–203] The placebo response rate has varied in adult FD trials (6–72%) and adult IBS trials (3–84%) with an overall response rate of 45%.[204] In a systematic review and meta-analysis of pediatric FAPD trials, the overall placebo response rate was 41%.[202]

Placebo may even be effective when the patient is aware that they are taking a placebo, likely dependent on the language utilized to introduce the placebo. In a trial of an open-label placebo versus no treatment in adults with IBS, the placebo resulted in increased global improvement, decreased symptom severity, and an increase in adequate relief.[205] In another study of adults with IBS, response to an open-label placebo was superior to no treatment and not significantly different from the response to a blinded placebo.[206] The response to placebo seems to support the idea that if a patient believes an intervention is likely to be helpful, this may have psychological benefits in reducing the impact of stress or promoting positive coping. Additionally, these findings underline the importance of placebo-controlled trials in this patient group.

Medications

Currently, regarding medications, it may not be possible to treat pediatric FAPDs in an evidence-based fashion. First, Rome II and Rome III FAPD diagnostic criteria form the basis for entry into most published studies and not only have these criteria evolved significant differences under Rome IV, but evidence suggests that these diagnoses are not assigned in a consistent fashion across clinicians.[10] Second, there is a relative paucity of pediatric placebo-controlled medication trials, often utilizing medications at doses below those that are used clinically. Third, FAPDs are complex conditions with widely varying contributors across the patient population which are not controlled for in most therapeutic trials.[207] Most currently prescribed medications have only a single published trial to support their use and when there is more than one trial, results may be conflicting.

While there are many medications used in clinical practice (particularly in adults), we will largely focus on placebo-controlled trials in youth with FAPDs.[208,209] To our knowledge, there have been 15 randomized placebo-controlled trials of medications for pediatric FAPDs.[158,210–223] We have summarized these studies in Table 3. The current data does not lend itself to the development of pediatric practice guidelines regarding medication treatment for pediatric FAPDs as have been developed for adult IBS.[64] Given the lack of high quality, replicated data, we offer treatment recommendations based on current pediatric literature, adult practice guidelines, and common usage among pediatric gastroenterologists who themselves are quite variable in how they utilize medications to treat this patient population.[9]

Functional Dyspepsia

It is common practice to treat patients with FD initially with acid-reduction therapy, which has the most literature support, albeit still meager.[9,215,224] Another medication to consider is cyproheptadine, which is supported by one-placebo controlled trial and 2 retrospective studies.[214,225,226] Cyproheptadine is an antagonist of specific serotonin receptors, histamine-1 receptors and muscarinic receptors which may be effective, at least in part, through improvement in gastric accommodation or gastric emptying.[225] Thus, it may be more effective in patients with early satiety but this remains to be proven. Buspirone, which may also increase gastric accommodation, has shown benefit in adults with FD.[227] Other medications to consider are prokinetics, as FD can be associated with delayed gastric emptying. A single trial of domperidone demonstrated benefit in patients diagnosed with FAPDs, but not those with FD specifically.[210] Another commonly prescribed medication for FD is amitriptyline; this medication has shown benefit in adults with FD, although a single trial found no benefit in pediatric FD patients.[221,228] The maximum dose utilized in that trial was 20 mg and it is possible that a better response may be seen at higher doses such as those commonly used in clinical practice. If considering amitriptyline, it is

Table 3 Summary of Placebo-Controlled Trials in Children and Adolescents with Functional Abdominal Pain Disorders

Author	Medication	N	Age	Diagnosis	Benefit vs Placebo for Abdominal Pain
Karunanayake[210]	Domperidone	100 (50 active drug)	5–12 years	FAP, IBS, FD	Yes in FAP only
Collins[211]	Rifaximin	75 (49 active drug)	8–18 years	CAP with SIBO	No
Zybach[212]	Melatonin	12 (cross-over)	8–17 years	FD	No
Badihian[213]	Buspirone	95 (48 active drug)	6–18 years	FAP	No
Sadeghian[214]	Cyproheptadine	29 (15 active drug)	4–16 years	FAP	Yes
See[215]	Famotidine	26 (12 active drug)	5–18 years	FD	Yes
Asgarshirazi[158]	Peppermint oil	80 (40 active drug)	4–13 years	FAP, FD, IBS	Yes
Kline[216]	Peppermint oil	42 (21 active drug)	8–17 years	IBS	Yes
Friesen[217]	Montelukast	40 (cross-over)	6–18 years	FD with eosinophilia	Yes
Narang[218]	Drotaverine	132 (66 active drug	4–12 years	RAP	Yes
Symon[219]	Pizotifen	16 (cross-over)	5–13 years	AM	Yes
Pourmoghaddas[220]	Mebeverine	115 (59 active drug)	6–18 years	FAP	No
Saps[221]	Amitriptylline	90 (46 active drug)	8–17 years	FAP, IBS, FD	No
Bahar[222]	Amitriptylline	33 (16 active drug)	12–18 years	IBS-D	Yes
Roohafza[223]	Citalopram	86 (43 active drug)	6–18 years	FAP	Yes

Abbreviations: FAP, functional abdominal pain; IBS, irritable bowel syndrome; FD, functional dyspepsia; CAP, chronic abdominal pain; SIBO, small intestinal bacterial overgrowth; RAP, recurrent abdominal pain; AM, abdominal migraine; IBS-D, diarrhea predominant irritable bowel syndrome.

https://doi.org/10.2147/PHMT.S287719

recommended to get, at least, a baseline electrocardiogram to evaluate for prolonged QT.[229,230] Benefit has been demonstrated for montelukast for FD patients with duodenal eosinophilia.

IBS

Psychologic treatment and trials of dietary restriction (particularly in patients with IBS-D) are a common initial approach but often medications have a positive role in the treatment of IBS. In addition, a trial of soluble fiber or probiotics are reasonable early treatments before beginning medications. Patients with suspected IBS-C should initially be treated with laxatives to ensure that pain does not resolve with normalization of stools (ie, that they do not have functional constipation rather than IBS-C).

In adults with IBS-C, osmotic laxatives are generally not helpful but chloride channel activators (eg, lubiprostone) and prokinetic drugs such as guanylate cyclase activators (eg, linaclotide) and 5-HT4 agonists (eg, tegaserod) are beneficial.[64] In a randomized trial of children with IBS-C, comparing a laxative to a laxative plus tegaserod, both improved constipation but pain only improved in the group receiving tegaserod.[231] Selective serotonin reuptake inhibitors (SSRI) anti-depressants have also been recommended in adults with IBS and may be most useful in IBS-C where tricyclic antidepressants can worsen constipation.[129] In a pediatric FAP study, citalopram was superior to placebo in pain reduction and global symptom severity improvement in the per-protocol analysis but not the intention-to-treat analysis.[223]

In adults with IBS-D, bile acid sequestration medication is generally not helpful but tricyclic antidepressants (TCAs), rifaximin, alosetron in certain patients, and mixed opioid agonists/antagonists are recommended.[64] There are mixed recommendations regarding antispasmodics such as dicyclomine and hyoscyamine.[64,129] Studies utilizing common antispasmodics are lacking in children with IBS-D and results of other antispasmodic trials are mixed.[218,220] Peppermint oil which has antispasmodic properties has demonstrated efficacy in two placebo-controlled trials in FAP and IBS.[158,216] Amitriptyline did not improve abdominal pain in a population with varying FAPDs including a sub-analysis of patients with IBS-D, but was likely underpowered for assessing this subgroup.[221] In a study of adolescents with IBS-D, amitriptyline demonstrated benefit in improving pain, diarrhea and QOL.[222]

Neurostimulation

Auricular neurostimulation is a relatively new non-pharmacologic treatment for FAPDs. The enteric nervous system connects with the gut endocrine and immune system, the microbiota, and to the CNS via the vagus nerve.[232] Auricular neurostimulation utilizing an FDA-cleared device targets these central pathways via branches of four cranial nerves including the vagus nerve.[233] Auricular neurostimulation alters CNS signal processing which in turn modulates inflammation, nociception, and autonomic functioning restoring sympathovagal balance.[234] In adults with FD, auricular stimulation has been shown to improve accommodation, increase the percentage of normal gastric slow waves, and stimulate vagal activity.[235] In the long-term, it improves dyspeptic symptoms, depression, and anxiety.[235] In adolescents with FAPDs, auricular neurostimulation decreases pain with sustained effects.[233] In adolescents with IBS, Krasaelap and colleagues found a 59% response rate with neurostimulation as compared to 26% in sham controls with lower composite and usual pain scores.[236]

Putting It All Together

Again, there are no established, evidence-based guidelines for the evaluation and management of pediatric FAPDs. We offer the following recommendations as a compilation of current evidence, adult guidelines (which are likely relevant to adolescents), and our experience with suspected FAPDs in the absence of alarm symptoms.

The approach should begin with the establishment of an FAPD diagnosis utilizing Rome IV criteria and this diagnosis should be shared with the patient and their caregivers. Treatment should begin with education, providing at least a brief overview of the biopsychosocial model, establishing the basis for recommendations.

All patients with FD or IBS should, at a minimum, be screened for anxiety, depression, and poor sleep and these targets, if identified, be intervened upon either in the context of a consultative relationship with a mental health provider in an integrated care setting or by a psychologist working independently. In the case of the latter, the referral should involve direct communication, clearly establishing goals to ensure the patient acquires positive coping skills even in the absence of a diagnosable mental health condition. Additionally, patients should be queried for sleep dysfunction. When

Table 4 Treatment Options for Constipation-Predominant IBS (IBS-C) and Diarrhea-Predominant IBS (IBS-D)

IBS-C	IBS-D
• Soluble fiber supplementation Lubiprostone • Probiotics (Bifidobacteria and Lactobacillus) Tegaserod	• Dietary restriction of fructose, lactose, and sorbitol • Low FODMAP diet Probiotics (Bifidobacteria and Lactobacillus) • Antibiotics (rifaximin or metronidazole) • Amitriptyline • Peppermint oil • Anti-spasmodics

delayed onset of sleep or frequent waking is present, behavioral sleep measures should be instituted.

For patients with FD, we recommend no initial diagnostic testing. Patients should initially be treated with an H2 blocker or proton pump inhibitor. If pain resolves (which may be by therapeutic effect or placebo response), we recommend treating for 8–12 weeks. In patients with no response after 2–3 weeks, cyproheptadine can be added. If there is no response to this medication after, 2–3 weeks, referral to a pediatric gastroenterologist for diagnostic evaluation should be considered.

For patient with IBS, initial evaluation including celiac serology and in the presence of diarrhea, stool calprotectin (or lactoferrin) is reasonable. For patients with suspected IBS-C, constipation should be initially treated with laxatives to establish the diagnosis. If pain resolves with resolution of the constipation, then the diagnosis is functional constipation and not IBS-C. The treatment approach then depends on whether symptoms are predominantly associated with constipation or diarrhea. We have summarized treatment options in Table 4. In the absence of alarm symptoms, IBS patients are probably best served by multiple intervention trials before undertaking further diagnostic testing, particularly colonoscopy. If patients are responsive to diet restrictions, they should be evaluated by a dietician to ensure the nutritional adequacy of the restricted diet.

Conclusion

As diagnostic evaluation of FAPDs can be costly and given that FAPDs are intended to be positive diagnoses not necessarily requiring tests to rule out disease, there is certainly a push to reduce "unnecessary" testing and contain costs. Ultimately, the cost of care must be weighed against the cost of inadequate evaluation and treatment, namely, impaired social, academic, and emotional functioning that is likely in the context of ongoing pain. Despite the high prevalence of FAPDs and a reasonably large body of scientific data, there remain significant questions to address, including which evaluations provide information that contributes to better patient outcomes. The issue is not just whether a test is costly, but whether the test provides value from the patient perspective, improving outcomes that justify the expense. There is also a need to study the commonly used medications and, to implement a precision therapeutics approach to determine which drugs work in which patients and at what dose and how to best combine biologic, psychologic, and social interventions tailored to the specific pain contributors of the individual patient. While we have attempted to provide an update across a wide number of important clinical areas for FAPDs, we suspect and hope there will be significant new developments over the next decade.

Disclosure

The authors report no conflicts of interest in this work.

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