Functional abdominal pain and irritable bowel syndrome in children and adolescents

Functional abdominal pain (FAP) and irritable bowel syndrome (IBS) are both associated with recurrent abdominal pain and are among the most commonly diagnosed medical problems in pediatrics. The majority of patients with mild complaints improve with reassurance and time. For a distinct subset of patients with more severe and disabling illness, finding effective treatment for these disorders remains a challenge. Based on the biopsychosocial model of functional disease, the Rome III criteria have helped frame FAP and IBS in terms of being a positive diagnosis and not a diagnosis of exclusion. However, the lack of a single, proven intervention highlights the complex interplay of pathologic mechanisms likely involved in the development of childhood FAP and IBS and the need for a multidisciplinary, integrated approach. This article discusses the epidemiology, proposed mechanisms, clinical approach and therapeutic options for the management of FAP and IBS in children and adolescents.

KEYWORDS: biopsychosocial model ■ cognitive behavioral therapy ■ dietary interventions ■ functional abdominal pain ■ functional gastrointestinal disorders ■ irritable bowel syndrome ■ pharmacotherapy ■ psychosocial interventions ■ recurrent abdominal pain

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Functional abdominal pain (FAP) and irritable bowel syndrome (IBS), both of which typically present with recurrent abdominal pain (RAP), are common complaints in the pediatric population. In general, RAP accounts for approximately 2–4% of all pediatric visits [1] and 25% of referrals to tertiary gastroenterology clinics [2]. Although it is usually a benign problem, parents may be worried, the child may be in distress and the practitioner may be concerned about ordering tests to avoid missing serious occult disease. In most patients, the RAP is functional in etiology – that is, without evidence of a defined pathologic condition, such as an anatomic, metabolic, infectious, inflammatory or neoplastic disorder [3].

Historically, a variety of different terms have been used to describe recurring abdominal pain in childhood: including FAP, RAP, idiopathic pain, psychosomatic pain and chronic nonspecific pain. All of these labels refer to abdominal pain without a clear organic cause. The term RAP has been most widely used. It was first introduced in the landmark study by Apley and Naish in 1958 and was defined as RAP occurring at least three times over a period of at least 3 months, with attacks severe enough to affect activity [4]. Since then, it has been agreed that RAP is not a single diagnosis, but more of a description that includes children with a variety of functional gastrointestinal disorders (FGIDs) as well as other organic diseases. Efforts have subsequently been made to standardize the diagnostic criteria for various FGIDs, which are defined as a variable combination of chronic or recurrent gastrointestinal (GI) symptoms not explained by structural or biochemical abnormalities [5]. The Rome criteria were initially published in 1999 (Rome II) and more recently revised in 2006 (Rome III). These criteria were designed to be used as diagnostic tools by the clinician in an office-based setting. We can now classify abdominal pain into four FGIDs in children: FAP, IBS, functional dyspepsia and abdominal migraine [5]. Despite their prevalence, FGIDs are the subject of many misconceptions in both the healthcare and lay communities [6,7], which often leads to a delay in formal diagnosis [8]. The focus of this article will be on the epidemiology, proposed mechanisms, clinical approach, diagnosis and management of FAP and IBS in children and adolescents.

Population-based studies have estimated the prevalence of weekly abdominal pain in school-aged children to range from 11 to 38%, with up to 3.2% reporting abdominal pain on a daily basis [9–11]. In a school-based study, Saps *et al.* found that 23% of children reported missing school for abdominal pain, with complaints persisting for at least 8 weeks in 24% [11]. In terms of FGIDs, one systematic review reported the prevalence of FAP to range from 0.3 to 19% in Western countries [12], while other studies

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have estimated the prevalence of IBS to range between 6 and 14% in children and between 22 and 35.5% in adolescents [9,13,14]. The wide ranges in reported prevalence are likely due to differences in definitions as well as the diagnostic criteria for FGIDs used in research. The development of the Rome III criteria will hopefully bring standardization not only for research purposes, but clinically as well.

Functional abdominal pain and IBS have been associated with significant impairment in children and adolescents and can have considerable impact on parents and families as well. Children with FAP have lower self-reported quality-of-life scores compared with healthy children and are comparable to children with inflammatory bowel disease [15]. Compared with healthy children without abdominal pain, children with daily pain have more school absences as well as non-GI symptoms, such as headache [16]. Adolescents with frequent abdominal pain are at increased risk of depressive symptoms and social isolation, in addition to missing more school [10]. Besides worrying about their child's health, parents have to handle increased costs of healthcare use, lost wages for time taken off from work and disruptions to family plans and activities. Although the economic costs related to FGIDs in childhood are not precisely known, they are likely to be substantial, considering the frequent need for multiple medical visits and evidence of increased healthcare utilization into young adulthood [17]. It is estimated that approximately US$30 billion are spent each year for healthcare costs and lost wage costs related to adults with IBS alone [18].

Although the majority of children with FAP eventually have improvement of pain with physician reassurance and time, long-term follow-up studies have shown that a significant number continue to experience symptoms after 5 years or even beyond into adulthood [19–21]. Furthermore, adults with a history of pediatric abdominal pain are more likely to meet criteria for a lifetime and current history of anxiety disorders compared with healthy controls [20]. Not surprisingly, those with more severe, disabling or persistent illness often present a diagnostic as well as management challenge for both the primary physician and pediatric gastroenterologist.

Biopsychosocial model of functional disorders

The biopsychosocial model of illness is based on the complex interplay of genetic, environmental, physiological and psychosocial factors and their influence on symptoms and illness. It is the cornerstone to understanding the etiology of FGIDs [22]. Physicians must take into account the role of the patient's own perception of illness and well-being. Furthermore, helping parents to accept their child's FGID as a biopsychosocial disease has also been shown to affect disease prognosis favorably [2]. Each patient's background of risk factors and perceptions may interact via the brain–gut axis with GI factors, such as motility, visceral hypersensitivity, altered mucosal immunity or permeability, and may contribute to the development of active versus maladaptive coping skills [23].

Genetic factors

Genetic factors in the development of FGIDs have long been suspected based on the observation of symptom and diagnosis clustering within families and twins [24–26]. In children, having a mother with a FGID appears to be an especially strong predictor of also developing a FGID [25,26]. The specific genes that may be responsible for a predisposition towards developing a FGID are unknown, but genes encoding serotonin-related proteins, proteins involved in noradrenergic signaling and immune-mediated cytokines are being investigated [27]. Ultimately, the relative lack of data does not yet allow any conclusion to be made regarding the genetic factors associated with FAP or IBS in children. Moreover, clustering of FGIDs in families does not necessarily implicate a genetic basis, but could also result from environmental exposures shared in a household, including diet or lifestyle behaviors, exposure to adverse life events within the family, learned cognitions about disease and illness behavior or even shared exposure to microorganisms [27].

Early childhood stress

Indeed, various aspects of physical and social environment have been linked with the development of FAP and IBS in childhood. Stress during early childhood is thought to lead to the development of hypersensitivity or altered stress response later in life. Some of the strongest evidence for this comes from the association between prior childhood abuse and the development of FGIDs later on in life [28,29]. The risk of developing IBS also appears to increase following other traumatic experiences in early childhood, such as neglect or loss of a parent [30]. Animal models have found an association between neonatal noxious stimuli, inflammatory stimuli and maternal deprivation and long-term consequences on GI

functions [31]. However, the minimum degree of stress or pain that can result in long-term health implications is not clear. Furthermore, it is not known what makes some children more vulnerable than others and at what age children are most susceptible; for example, children with a history of neonatal nasogastric suctioning were reported to have higher rates of abdominal pain in adolescence compared with their siblings [32]. During the first year of a child's life, irregular sleeping and eating, as well as maternal and paternal anxiety, have been associated with subsequent development of FAP [33].

Social learning

Parental factors have been the subject of several investigations and speak towards the complex interplay between shared genetics and the role of the parent–child relationship. Several studies have found an association between pediatric FGIDs and maternal history of anxiety, depression, somatoform disorders, IBS and migraine [34–36]. Family functioning, especially within the context of abdominal pain, may have a direct influence on the child's pain experience or functional disability. According to social learning theory, parental modeling and reinforcement of the sick role increases the likelihood of pediatric functional GI symptoms that may persist into adulthood [37]. Parents may inadvertently reinforce illness behaviors in their children when attempting to be protective and nurturing. In a study by Walker *et al.*, children's symptom complaints nearly doubled when parents paid attention to the symptoms but were reduced by half when they were instructed to distract their child [38].

Psychiatric comorbidities

The relationship between FGIDs and psychiatric comorbidity has also been extensively studied in pediatric patients themselves. Indeed, the rising prevalence of FAP and IBS in adolescence and shift in gender ratio from equal in childhood to a female dominance in adolescence parallels the epidemiology of anxiety and depressive symptoms and disorders [12,39]. Patients with FAP are more likely to be diagnosed with anxiety and depressive disorders, as well as report a history of outpatient psychiatric treatment compared with healthy children [40–42]. The exact relationship between internalizing symptoms, FAP and IBS, however, remains unclear. On the one hand, there is evidence to show that anxiety and depressive disorders are likely to precede abdominal complaints [40], which suggests that these psychological comorbidities may predispose to heightened attention to pain and lead to negative coping mechanisms. On the other hand, it has also been proposed that psychological disorders and FGIDs may share a common underlying risk factor or are simply different manifestations of a singular causal process. Regardless of the mechanisms responsible, physicians should have a high index of suspicion for undiagnosed psychiatric disorder, particularly anxiety or depression, in children and adolescents with FAP or IBS. In addition, emotional disorders in the child or parents may interfere with management of their abdominal complaints, either in the form of decreased motivation for participating in treatments or heightened anxiety leading to the desire for unnecessary and invasive testing. Addressing an emotional disorder may thus prove beneficial to the treatment plan. Finally, the link between FGIDs and emotional disorders suggests that treatments effective for anxiety or depression, such as cognitive behavioral therapy (CBT) or antidepressants, may be helpful for treating symptoms of FAP or IBS.

Environmental factors

Environmental factors are also important determinants in the biopsychosocial model of FGIDs and are also thought to affect changes in gut flora and its homeostasis. In a recent pediatric, multicenter study, children exposed to acute bacterial gastroenteritis were significantly more likely to subsequently develop a FGID compared with controls [43]. A cohort study that followed children after a large outbreak of acute gastroenteritis secondary to *Escherichia coli* and *Campylobacter* species in Walkerton, ON, Canada, also found a significant increase in IBS among exposed subjects compared with controls, with female gender identified as an independent predictor for development of IBS [44]. Finally, although viral causes of gastroenteritis have been similarly associated with increased cases of IBS following exposure in adults, the effects appear to be more transient compared with bacterial infections [45]. In children, exposure to rotavirus infection did not appear to increase the risk of FGIDs at long-term follow-up greater than 2 years [46].

GI factors

Understanding the relationship between infection and gut function may ultimately help to shed light on the role of other biological factors that could be involved in the pathogenesis of

FAP and IBS, such as mucosal inflammation, dysregulation of intestinal immunity, gut flora homeostasis and gut permeability. Indeed, evidence of increased GI permeability and higher levels of fecal calprotectin (a proposed surrogate marker for intestinal inflammation) have been found in children with FAP and IBS compared with controls [47]. Small intestinal bacterial overgrowth (SIBO), which is characterized by an abnormally high bacterial population in the small bowel (exceeding 10^5 organisms/ml [48]), is thought to occur when the indigenous microbial population extends proximally from the colon into the small intestine. Suspected consequences of SIBO include abnormal production of microbial gases secondary to fermentation, altered motility and sensation and immune activation. Children with FAP and IBS have been found to have a higher prevalence of abnormal microbial fermentation based on breath testing compared with healthy controls [49,50]. However, the causal mechanisms that lead from SIBO to symptoms in FAP and IBS have not yet been elucidated. Moreover, further studies are needed to evaluate the efficacy of SIBO decontamination on IBS and FAP symptoms in children.

In addition to enteric infections, there may be other triggers for intestinal inflammation and alteration such as undiagnosed food allergies, which could lead to IBS or FAP. There are adult data that suggest that activated mast cells in proximity to nerve endings in the gut wall are increased in IBS patients and may be correlated with abdominal pain complaints via alterations in visceral perception [51,52]. Moreover, use of the mast cell stabilizer ketotifen has been shown to decrease visceral hypersensitivity and improve abdominal pain in adult IBS patients [53].

Visceral hypersensitivity

Ultimately, it is believed that the interaction of psychosocial factors and altered gut physiology via the brain–gut axis results in the different phenotypic presentations of FGIDs [54]. Abnormalities in the enteric nervous system and its interactions with the CNS may lead to abnormally heightened reactions to physiological stimuli (e.g., meal, gut distension and hormonal changes), noxious stressful stimuli (e.g., inflammation and allergic reaction) or psychological stress (e.g., parental separation and anxiety) [55]. The concept of visceral hypersensitivity or hyperalgesia has been proposed to play a major role in unexplained abdominal pain. Heightened perception of experimental visceral stimuli has been observed in children with FGIDs [56–59]. However, visceral hypersensitivity identified in experimental situations has yet to be validated as a biomarker of FGIDs. The clinical translation from these experimental models of visceral hypersensitivity using a visceral barostat or water load tests to actual symptoms remains controversial. In one study, the sensory threshold for pain determined by rectal barostat examination was lower in children with IBS and FAP compared with control subjects [60]. However, in another study, differences in laboratory visceral pain thresholds between patients with IBS versus controls were explained by an increased tendency to report pain rather than increased neural sensitivity [61]. This suggests that symptoms in FAP and IBS may have more to do with abnormal amplification of physiologic or minor stimuli, rather than true neurosensory hypersensitivity.

Alterations in GI motility

Alterations in GI motility have been among the earliest proposed mechanisms for FGIDs. While various moderate abnormalities of small bowel [62–64] and colonic [65–67] motor activity have been demonstrated in patients with FAP or IBS, none appear to be specific [68]. Subsequent research has failed to establish a strong correlation between contractile abnormalities and abdominal pain or symptoms perceived by patients. In fact, many of the motor events described in patients with IBS and FAP are also found in healthy subjects with lower frequency, but without any associated concomitant symptoms, again suggesting that there may be role for heightened visceral sensation in the perception of these motor events.

Symptom-based diagnosis & therapeutic approach

In general, the approach to a child or adolescent with chronic or RAP should begin with the establishment of an effective patient–physician relationship, which is based on compassion, acknowledgement of the distress associated with the painful condition and maintenance of an objective and observant stance [69]. Even when a functional diagnosis, such as FAP or IBS, is suspected it is important that the physician validates the patient's symptoms as real and takes any concerns or complaints seriously. The physician should adopt an 'active listening approach' and an enthusiastic, positive and encouraging attitude towards treatment [70].

Performance of a clinical history should elicit key features of the abdominal pain, including the frequency, severity, location and association

with bowel disturbance or abnormalities of defecation. Although these features do not necessarily help distinguish between functional and organic causes, it is a starting point as to potential etiology. Comorbid psychological factors, family history, dietary considerations and precipitating and exacerbating factors may also be useful. General physical examination for signs of systemic disease should be followed by abdominal and rectal examination, although significant abnormalities are usually absent. Symptoms of abdominal pain that meet Rome III criteria for FAP or IBS (Box 1) in the presence of a normal physical examination and growth curve with the absence of red-flag signs or symptoms (Box 2) substantiates a positive diagnosis [5]. Red flags are not validated warning signs, but they may be clinically useful to help direct specific diagnostic testing for other causes of abdominal pain. In the absence of red-flag signs, extensive diagnostic studies are usually unjustified not only because they are not indicated clinically, but also because they are expensive and tend to impair the physician–patient relationship and the therapeutic alliance. They may send a message to the patient or parent that the physician is uncertain of the positive diagnosis of FAP or IBS and reduce overall patient confidence in the plan of care.

Although there is no evidence to evaluate the predictive value of blood tests in general or in the face of red flags to distinguish between organic and functional disease [71], a limited and reasonable screening may include a complete blood cell count, erythrocyte sedimentation rate or C-reactive protein, urinalysis and urine culture. Other biochemical profiles, screening for celiac disease and diagnostic tests (Table 1) can be performed at the discretion of the clinician, based on the presence of red-flag signs, the child's predominant symptoms, degree of impairment, parental anxiety or failure to respond to empiric therapy of a presumed FGID [5]. Setting up an expectation for normal results to laboratory testing or investigations, when appropriate, may assist in establishing acceptance of a functional disorder diagnosis. In general, the evidence for the usefulness of more invasive investigations or imaging in FAP or IBS is lacking. When abdominal and pelvic ultrasound was performed in children with RAP without red-flag symptoms, abnormalities were found in fewer than 1% [72]. Likewise, there is insufficient evidence that demonstrates that use of endoscopy or esophageal pH monitoring in the absence of red-flag signs or symptoms has a significant yield for organic disease [71]. Moreover, the presence or absence of endoscopic or histopathologic inflammation has not been shown to predict prognosis for children with RAP, which is generally favorable [73].

In summary, the physician should provide reassurance that the positive diagnosis of FAP or IBS is not a failure to identify an organic illness, while educating the patient and family about the pathophysiology of visceral pain and associated complaints. A confident diagnosis, confirmation and explanation of pain experience and reassurance can by itself be therapeutic [74]. It is important to offer frequent support and to explain that treatment response is often gradual. Patient and family expectations should be aimed at 'care' rather than 'cure', with realistic goals, as such increased tolerance of symptoms and maintenance of normal daily living activities [75].

Box 1. Diagnostic Rome III criteria for childhood functional abdominal pain and irritable bowel syndrome.

Diagnostic criteria for childhood functional abdominal pain

- Must include all of the following criteria, fulfilled at least once per week for at least 2 months prior to diagnosis:
  - Episodic or continuous abdominal pain
  - Insufficient criteria for other functional gastrointestinal disorders
  - No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms

Diagnostic criteria for childhood irritable bowel syndrome

- Must include both of the following criteria, fulfilled at least once per week for at least 2 months prior to diagnosis:
  - Abdominal discomfort or pain associated with two or more of the following at least 25% of the time:
    - Improvement with defecation
    - Onset associated with a change in frequency of stool
    - Onset associated with a change in the form (appearance) of stool
  - No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms

Box 2. Red-flag signs and symptoms.

- Persistent right upper or right lower quadrant pain
- Dysphagia
- Persistent vomiting
- Gastrointestinal blood loss
- Nocturnal diarrhea
- Family history of inflammatory bowel disease, celiac or peptic ulcer disease
- Pain that wakes from sleep
- Arthritis
- Perirectal disease
- Oral lesions
- Skin rashes
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty
- Unexplained fever

Table 1. Approach to diagnostic testing.

Diagnostic test	Diagnosis/findings
Basic laboratory tests	
Complete blood cell count	Anemia, thrombocytosis, leukocytosis
Erythrocyte sedimentation rate or C-reactive protein	Systemic inflammation (e.g., inflammatory bowel disease)
Albumin and total protein	Nutrition and inflammation
Tissue transglutaminase IgA, total IgA	Celiac disease
Urinalysis and urine culture	Hematuria, urinary tract infection
Stool guaiac	Inflammation
Additional laboratory tests/imaging/other testing to consider	
Basic metabolic panel, including blood urea nitrogen/creatinine	Electrolyte disturbance, renal insufficiency
Aspartate aminotransferase/alanine aminotransferase, γ-glutamyl transpeptidase	Hepatobiliary inflammation or obstruction
Amylase, lipase	Pancreatitis
Stool culture and staining for ova and parasites	Infectious colitis, giardiasis
Breath testing for carbohydrate malabsorption	Lactose or fructose intolerance
Other symptom-guided diagnostic testing: abdominal ultrasound; contrast and other imaging studies; endoscopy/colonoscopy	To be performed only if indicated by history, physicial examination findings or screening laboratory tests

Treatment & management

The overall management of a patient with FAP or IBS should be tailored to the patient's specific symptoms and identifiable triggers. The biopsychosocial model for FGIDs, which highlights the importance of the child's physical and social setting as well as psychological comorbidities, forms the foundation for a multidisciplinary approach. Regardless of the specific therapeutic interventions that are employed, physicians need to be cognizant of the potential power of the placebo effect. In several studies of FAP and IBS, the failure of an intervention to demonstrate significant benefit was not because of an absolute lack of improvement, but may have been due to the observation of a strong placebo effect. For example, in a study by Saps *et al.*, 58% of patients who received placebo reported feeling better at the end of the study, compared with 63% of patients who received amitriptyline [76]. Clearly, engaging in a positive patient–physician relationship is very important and should be the foundation for promoting a therapeutic response to all treatments for FAP and IBS. The four major therapeutic approaches that will be reviewed here include: dietary, psychosocial, pharmacologic and complementary/alternative medicine interventions.

Dietary interventions

Restrictive diets

Lactose intolerance has long been implicated as a possible factor in IBS, especially for patients with predominant symptoms of diarrhea. A diagnosis of lactase deficiency is unlikely in younger children since brush border lactase activity peaks at around 3 years of age, but it can be considered for older children and adolescents. However, there is no data to support empiric recommendation of a lactose-free diet. In a double-blind, crossover trial, Dearlove *et al.* placed 21 children with RAP on an empiric, 2-week lactose-free diet, but found no differences in pain symptoms or relief when the subjects were subsequently given lactose versus placebo [77]. Lebenthal *et al.* studied 21 children with abnormal results on lactose tolerance testing and also found there was no significant difference in pain frequency when they were given cows-milk formula compared with lactose-free soy formula [78].

Malabsorption of other carbohydrates, such as fructose, has also been implicated in the pathogenesis of chronic abdominal pain. Persistence of fructose in the GI tract, especially in the form of high-fructose corn syrup, is postulated to cause an osmotic diarrhea as well as serve as substrate for fermentation by colonic bacteria resulting in the production of gas. Gomara *et al.* found that higher doses of fructose administered in a breath hydrogen test were associated with increased GI symptoms, such as nausea, bloating and abdominal pain [79]. In the uncontrolled study, children who had abnormal breath test results reported a rapid improvement in the GI symptoms when subsequently placed on a fructose-restricted diet.

Dietary fiber

Many physicians routinely recommend the use of bulking agents or dietary fiber to produce more regular bowel movements and to decrease

abdominal pain associated with FAP or IBS. These agents are thought to help by softening stool and enhancing colonic transit. In a meta-analysis, the benefit of dietary fiber for adults with IBS was limited to psyllium hydrophilic mucilloid (ispaghula husk); wheat bran and corn bran were no better than placebo [80]. In children, the data on dietary fiber is even more sparse. Children with RAP have been found on average to have significantly lower intake of fiber compared with healthy controls [81]. On the other hand, in one randomized, double-blinded, placebo-controlled study of children with RAP, the group that received ispaghula husks (66% fiber) reported no significant difference in the mean number of pain episodes compared with the group who received placebo (2% fiber) [82]. The benefit of dietary fiber in the treatment of RAP and IBS in children is unclear, but given the encouraging results in adult studies, an empiric trial of psyllium fiber may be reasonable, especially if there are associated symptoms of constipation.

Probiotics

Commensal bacteria of the GI tract are believed to play an important role in homeostasis, while alterations to these populations have been implicated in dysmotility, visceral hypersensitivity, abnormal colonic fermentation and immunologic activation [83]. Disruption of normal enteric bacteria is thought to play a role in post-infectious and post-antibiotic cases of IBS and is supported by the finding of significantly decreased populations of normal *Lactobacillus* and bifidobacteria in patients with diarrhea-predominant IBS [84]. Probiotics commonly contain *Lactobacillus*, bifidobacteria or other living microorganisms thought to be healthy for the host organism when ingested in sufficiently large amounts. Improvement in GI symptoms is hypothesized to result from restoration of the microbial balance in the gut through metabolic competition with pathogens, enhancement of the intestine's mucosal barrier or alteration of the intestinal inflammatory response [85]. Different methods, formulations, dosages and outcome measures have made it difficult to make conclusions about the efficacy of probiotics. A recent meta-analysis concluded that probiotics as a class seemed to be efficacious for adults with IBS, although the magnitude of benefit and most effective species, strain and dosing are not clear [86].

Data in pediatric studies have been equally conflicting. In a randomized, controlled trial of *Lactobacillus GG* (1×10^{10} CFU) versus placebo twice daily, Bausserman *et al.* found no significant difference in abdominal pain relief or other GI symptoms in children with IBS after 6 weeks of treatment, with the exception of decreased perception of abdominal distension for patients receiving *Lactobacillus* [87]. Gawronska *et al.* studied *Lactobacillus GG* (3×10^9 CFU) versus placebo twice daily in 104 children with either FAP, IBS or functional dyspepsia [88]. In the subset of patients with IBS, there was a significant decrease in the frequency of pain episodes as well as proportion of patients with no pain at the end of treatment compared with placebo. There was no benefit of *Lactobacillus* over placebo for patients with FAP or functional dyspepsia diagnoses. Finally, in a recent multicenter, randomized, placebo-controlled trial, children diagnosed with IBS according to Rome II criteria were given VSL #3®, a proprietary brand consisting of a mixture of eight different strains of lactic acid bacteria, versus placebo for 6 weeks [89]. VSL #3 was found to be superior to placebo in a global assessment of symptom relief, as well as specific complaints of abdominal pain, bloating and life disruption.

Overall, there is insufficient evidence to show that dietary carbohydrate restriction, fiber supplementation or probiotic supplementation are effective in the management of FAP and IBS. Further studies are needed to evaluate the role of dietary interventions; until then, these options may be considered on a case-by-case basis after careful discussion with the patient and family.

Psychosocial interventions

Acceptance of the biopsychosocial model of FGIDs has provided the basis for the use of psychosocial interventions, including parental education, family therapy, cognitive behavioral techniques, relaxation, distraction, hypnotherapy, guided imagery and biofeedback. Many of these strategies aim not only to have direct effects on somatic symptoms, but also promote the child's ability to self-manage symptoms. Meta-analyses and systematic reviews have found that, as a class, psychological treatments are effective in treating somatic symptoms in both adults and children with FGIDs [90,91].

Cognitive behavioral therapy

Cognitive behavioral therapy, the most common type of psychotherapy employed for FGIDs, is based on the complex interactions between thoughts, feelings and behaviors. The aims of CBT include learning better coping and problem-solving skills, identification of triggers and

reduction of maladaptive reactions to them. Specific techniques can include: keeping a diary of symptoms, feelings, thoughts and behaviors; adopting relaxation and distraction strategies; using positive and negative reinforcement for behavior modification; confronting assumptions or beliefs that may be unhelpful; and gradually facing activities that may have been avoided. Several studies that have included components of CBT in the treatment of pediatric FGIDs have yielded encouraging results.

Sanders *et al.* conducted a study of 44 children with RAP randomized to 8 weeks of cognitive-behavioral family therapy (CBFT) versus standard care and reassurance [92]. There were reductions in pain for both groups post-treatment, but the CBFT group had significantly higher percentages of pain-free subjects based on parental observation (70.6 vs 38.1%). However, there were no significant differences between groups on continuous measures of pain, pain-related behavior or other measures of coping or adjustment. Humphreys and Gevirtz randomized 64 children with RAP to either a combination of dietary fiber, biofeedback, CBT and parental support versus dietary fiber alone for 8 weeks [93]. A total of 72% of children in the combined, active-treatment groups reported being pain-free at the end of 8 weeks, compared with 7% in the fiber-only group. However, it is difficult to interpret which of the psychosocial interventions were responsible for this positive effect. Robins *et al.* also compared CBT to standard medical care in a randomized, controlled trial of 69 children with RAP [94]. At 6- and 12-months post-treatment, both groups reported improvements, but the CBT group had significantly lower scores on an abdominal pain index based on pain frequency and intensity. However, the standard deviations of these results were not provided and the clinical significance of these differences in scores is unclear. Duarte *et al.* studied 32 children with RAP in a randomized trial of CBT versus standard medical care [95]. After the study intervention, patients in the CBT group had significantly fewer episodes of abdominal pain per month compared with the control group, but there were no significant differences in other measures of pain.

Most recently, Levy *et al.* studied 200 children with FAP as well as their parents and evaluated the effect of CBT versus educational support on children's pain complaints and parent's responses to their child's pain [96]. Children in the CBT group showed significantly greater decreases in GI symptom severity, while parents in the CBT group reported significantly greater decreases in solicitous responses to their child's pain. The results of this study appear to support the theory of social learning in pediatric FGIDs and suggest that parental responses to children's symptoms may play an important role in influencing child coping and dysfunction.

Guided imagery & hypnotherapy

Guided imagery is a specific form of relaxed and focused concentration whereby patients are taught to imagine themselves in a peaceful scene, in order to create an experience void of stress and anxiety. This can be combined with other relaxation techniques to produce a state of increased receptiveness to gut-specific suggestions and ideas, also known as 'gut-directed' hypnotherapy. Weydert *et al.* randomized children with RAP to four sessions of either breathing exercises alone or guided imagery techniques with progressive muscle relaxation [97]. The number of days with pain decreased more significantly in patients in the guided imagery group compared with those learning breathing exercises alone, but children in the guided imagery group also started with significantly more days of pain at baseline. More recently, van Tilburg *et al.* studied 34 children with FAP and randomly assigned them to 2 months of standard medical care either with or without home-based, guided imagery treatment using audio and video recordings [98]. Patients who participated in guided imagery treatment had significantly greater reductions in abdominal pain, disability and medical visits immediately after treatment as well as at 6-months' follow up compared with those who received standard medical care only. Vlieger *et al.* implemented a randomized controlled trial that compared gut-directed hypnotherapy to standard medical care for children with FAP or IBS [99]. In both treatment groups, pain intensity scores and pain frequency scores decreased significantly 1 year after therapy, but patients in the hypnotherapy group had significantly greater reductions in both pain intensity and frequency, and were more likely to be in clinical remission after 1 year when compared with standard medical therapy.

Other interventions

Other psychosocial interventions that may be employed, often in combination with CBT or other techniques, include psychoeducation, family therapy, relaxation and biofeedback. The goal of psychoeducation is to communicate information to patients and families about abdominal

pain and its connection with psychological triggers, as well as factors that may exacerbate pain, such as social reinforcement and school avoidance [100]. Family therapy targets family interactions and relationships rather than the individual patient in order to change maladaptive behaviors, increase tolerance of symptoms and encourage independent coping skills [101]. Relaxation is employed to reduce psychological stress by achieving a physiological state that is the opposite of how the body reacts under stress [100]. A variety of methods can be employed with effects such as decreasing heart rate, respiratory rate, blood pressure, muscle tension, oxygen consumption or brain wave activity [102]. Abdominal or deep breathing can stimulate the parasympathetic nervous system to increase feelings of calmness and relaxation. In progressive muscle relaxation, children are guided to systematically tense and relax each muscle group of the body. Patients are then encouraged to maintain attention on the relaxed feeling that results after tensing muscles. Biofeedback uses electronic equipment in combination with controlled breathing, hypnotic or relaxation techniques to generate a visual or auditory indicator of muscle tension, skin temperature or anal control, allowing the child to have external validation of physiological changes.

Overall, several psychosocial interventions have shown promise in the treatment of children with FAP and IBS. Specifically, the American Academy of Pediatrics subcommittee on chronic abdominal pain recently concluded that CBT may be useful in "improving pain and disability outcome in the short term" [103]. Limitations in several of these studies, such as small sample sizes, poorly defined comparison conditions, differences and lack of detail in intervention protocols and limited follow-up assessment, have made it difficult to draw any definitive conclusions. In general, incorporation of psychological treatments into the management of patients appears to be a reasonable consideration. Variability in the details of treatment protocols should be taken into account. Ultimately, additional studies are needed to elucidate the benefits of psychosocial interventions and understand the role of placebo effects in the pediatric FGID population.

Pharmacotherapy

Potential pharmacological treatments for FAP and IBS have been identified based on our emerging understanding of the interactions between the CNS, enteric nervous system and GI tract [104]. A significant degree of abdominal pain in functional disorders is believed to be associated with abnormal perception of visceral sensations or alterations in motility. Targets for modulation have therefore included smooth muscle cells of the GI tract, peripheral neurotransmitter receptors for various stimuli, interneurons of the spinal cord which transmit information bidirectionally and cortical areas responsible for the perception of pain [104]. Medications initially indicated for the treatment of depression, anxiety and seizures have also been adopted for the management of FGIDs owing to their effects on both the central and peripheral nervous systems.

Antidepressants

Antidepressants are among the most studied pharmacologic agents for FGIDs. Mechanisms of action are thought to include reduction of pain perception, improvement of mood and sleep patterns as well as modulation of the GI tract, often through anticholinergic effects. Antidepressants, such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), have been found to be beneficial for the treatment of FGIDs in adults [105]. However, use of antidepressant medications in children and adolescents has been recently tempered by concerns for increased suicidal thoughts and/or behavior, especially after the US FDA issued formal 'black-box' warnings in 2004. However, there has been no evidence that these suicidal thoughts or behaviors lead to an increased risk of suicide [106].

Tricyclic antidepressants act primarily through noradrenergic and serotonergic pathways but also have antimuscarinic and antihistaminic properties. Anticholinergic agents can slow transit in the GI tract, which may be beneficial for patients with IBS characterized by diarrhea, but may worsen constipation. A baseline ECG for evaluation of prolonged QT syndrome prior to initiating treatment is currently recommended by the American Heart Association, owing to the potential for inducing cardiac arrythmias [107]. The usual starting dose is 0.2 mg/kg and is increased to a therapeutic dose of approximately 0.5 mg/kg, given at bedtime owing to associated sedative properties.

Two recent pediatric trials studied the efficacy of amitriptyline, a tertiary amine tricyclic antidepressant, for the treatment of IBS and FAP. Bahar *et al.* studied 33 adolescents newly diagnosed with IBS according to the Rome II criteria and randomized them to 8 weeks of 10, 20 or 30 mg of amitriptyline based on weight versus placebo [108]. Compared with placebo, patients receiving amitriptyline were significantly more

likely to have an improvement in overall quality of life from baseline, but their baseline scores were also significantly lower to begin with. There was also an unusual negative placebo effect seen in the control group, which may have contributed to the statistically significant differences seen in comparisons between the two groups. Improvements in pain were inconsistent in terms of location and time of follow-up. There was no significant improvement in any other IBS-related symptoms.

In a multicenter study by Saps *et al.*, 83 children diagnosed with IBS, FAP or functional dyspepsia according to the Rome II criteria were randomized to 4 weeks of placebo or amitriptyline (10 or 20 mg daily depending on weight) [76]. The primary outcome was overall response to treatment based on the child's report of pain relief and sense of improvement. A substantial proportion of patients in both groups reported feeling better, but there was no significant difference between patients receiving amitriptyline versus placebo (63 vs 57.5%, respectively). Patients in the amitriptyline group had reduced anxiety scores ($p < 0.0001$), but there was no difference in improvement in pain, disability, depression or somatization scores during the 4-week trial. The authors postulated that the lack of significant findings may have been due to issues with insufficient statistical power, clinical heterogeneity of patients, relatively lower dosing of amitriptyline and shorter treatment duration (4 weeks), as well as the high placebo response observed.

Selective serotonin reuptake inhibitors act by blocking uptake of 5-hydroxytryptamine (5-HT), increasing its concentration at presynaptic nerve endings. In addition to its CNS effects on mood and anxiety, SSRIs may also be beneficial for GI complaints, since serotonin is an important neurotransmitter in the GI tract and greater than 80% of the body's stores are located in the enterochromaffin cells of the gut [104]. The exact role of serotonin in the GI tract has not been fully elucidated, but it has been implicated in the modulation of colonic motility and visceral pain in the gut.

Well-controlled, randomized pediatric trials on the use of SSRIs for either FAP or IBS are lacking. Campo *et al.* conducted a prospective, open-label, flexible-dose study of citalopram for children (ages 7–18 years old) with 'functional RAP' [109]. At the end of 12 weeks of treatment, 84% of subjects were classified as responders on a global illness improvement scale. Improvements in abdominal pain, anxiety, depression, other somatic symptoms and function were also reported [109]. Although these findings are promising, they need to be confirmed with additional clinical trials. In a recent randomized, placebo-controlled trial of citalopram for adult patients with IBS, there was no significant benefit after 8 weeks of treatment [110].

Monoamine uptake inhibitors, such as duloxetine and venlafaxine, represent a newer group of antidepressant medications with effects on serotonergic and adrenergic pain inhibition systems. These medications have shown evidence of analgesia in patients with fibromyalgia and diabetic neuropathy, but there have been no studies on the treatment of pediatric FGIDs [104].

Antispasmodics

Antispasmodic medications, such as peppermint oil and hyoscyamine, are thought to be helpful for FAP and IBS through their effects on decreasing smooth muscle spasms in the GI tract, which may be responsible for symptoms such as pain. In a recent meta-analysis, antispasmodics as a class were superior to placebo in the treatment of adults with IBS [80]. However, there was a significant amount of variability among included studies in terms of antispasmodic preparation, measured outcomes and overall methodological quality. Several agents included in the meta-analysis, such as otilonium, cimetropium and pinaverium, are not currently available in the USA.

Menthol, which is the active ingredient in peppermint oil, is a cyclic monoterpene with calcium channel blockade properties believed to be active on ileal and colonic smooth muscle. Reported side effects include rectal burning, esophageal pain or heartburn and allergic reactions. To date, there has only been one pediatric study of antispasmodic medication for FGIDs. Kline *et al.* performed a small, randomized, placebo-controlled trial of peppermint oil in 42 children with IBS [111]. At the end of the 2-week trial, 76% of the children receiving peppermint oil reported improvement on an IBS symptom severity scale compared with 19% in the placebo group ($p < 0.001$). However, there was no difference between groups in terms of heartburn, belching, stool pattern or stool consistency [111].

Hyoscyamine and dicyclomine are both considered antispasmodics due to their anticholinergic effects on smooth muscle. Hyoscyamine has been used occasionally in children on a short-term basis for GI symptoms of pain, but long-term use has been associated with anticholinergic

side effects such as dry mouth, urine retention, blurred vision, tachycardia, drowsiness and constipation. There have been no studies of either medication for pediatric FAP or IBS, but hyoscyamine was found to have consistent evidence of efficacy in an adult meta-analysis [80].

Cyproheptadine

Cyproheptadine is a medication with multiple mechanisms, including antihistaminic, anticholinergic and antiserotinergic properties as well as possible calcium channel blockade effects. It has been used in appetite stimulation and prevention of pain and vomiting in abdominal migraine and cyclic vomiting syndrome. In a small trial of 29 children and adolescents with FAP, Sadeghian *et al.* reported that 86% of patients in the cyproheptadine group had improvement or resolution of abdominal pain compared with 35.7% in the placebo group ($p = 0.003$) [112]. These results need to be confirmed with larger, additional trials.

Prokinetics

Prokinetic agents that stimulate GI motility have been employed for patients with FGIDs, especially for conditions involving constipation or delayed gastric emptying, such as IBS and functional dyspepsia [113]. Tegaserod is a serotonin agonist that induces acceleration of small bowel and colonic transit through activation of 5-HT4 receptors in the enteric nervous system. When combined with polyethylene glycol (PEG) 3350, tegaserod was found to be more effective in alleviating abdominal pain and increasing the number of bowel movements in adolescents with constipation-predominant IBS compared with PEG 3350 alone [114]. However, due to an increased rate of cardiovascular events in adults taking the medication, tegaserod was removed from the market in March 2007. Alosetron and cilansetron, two other serotonin-based agents with actions upon the 5HT-3 receptor, were also shown to be effective for adults with diarrhea-predominant IBS, but complications of severe constipation, ischemic colitis and perforations prompted withdrawal of these medications from the market in 2000 [115]. Dopamine (D2) receptor antagonists, such as metoclopramide and domperidone, improve gastric motility, but their use in pediatric FAP and IBS is limited by concerns of side effects, including extrapyramidal reactions, drowsiness, agitation, irritability and fatigue [116]. Erythromycin, an antibiotic with motilin receptor agonist properties in the stomach at doses of 1–2 mg/kg/dose may also be helpful for symptoms of pain or dyspepsia, but there are no pediatric data to support its routine use in FAP or IBS [117].

Other agents

Several agents have been studied for the treatment of conditions such as dyspepsia, constipation, diarrhea, abdominal migraine or small bowel bacterial overgrowth in conjunction with FAP or IBS. Lubiprostone is a member of a new class of bicyclic fatty acid derivatives known as prostones. Lubiprostone acts on type-2 chloride channels located on the apical side of GI epithelial cells to promote electrolyte and fluid secretion into the small intestine and may also stimulate colonic motility. In a combined analysis of two clinical trials of adults with constipation-predominant IBS, 17.9% of patients treated with lubiprostone reported improvement in IBS symptoms compared with 10.1% of those treated with placebo ($p = 0.001$) [118]. A pediatric trial of lubiprostone for functional constipation has been completed and preliminary data suggest it was efficacious in the treatment of children with constipation.

Loperamide is an opioid-receptor agonist that slows colonic transit by acting on myenteric plexus receptors of the large intestine. Although loperamide is commonly used for treating diarrhea and urgency in patients with diarrhea-predominant IBS, adult studies have shown efficacy only against symptoms of diarrhea and not abdominal pain [119]. For patients with FAP or IBS associated with constipation, stool softeners and laxatives are commonly employed. Finally, small bowel bacterial overgrowth has been suggested as a potential cause of IBS symptoms, such as abnormal gas production and bloating. Treatment of bacterial overgrowth with antibiotics, such as neomycin and rifaxamin, has been found to be beneficial in adults with IBS [120,121]. Similar studies in children and adolescents are currently lacking.

Despite the wide range of potential pharmacologic options, the lack of good quality, well-controlled, pediatric trials prompted a recent Cochrane review to conclude that the "true efficacy of drugs for FGIDs in children remains to be elucidated" [122]. A technical review endorsed by the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition similarly found limited evidence to justify the use of drugs or herbal preparations for chronic abdominal pain in children [71]. The use

of low-dose antidepressants may be beneficial for a select group of patients, especially those with anxiety or other psychological comorbidities.

Complementary & alternative therapies

Approximately 36–41% of children with GI complaints use complementary and alternative medicine (CAM) each year [123–125]. By definition, complementary medicine is used alongside conventional medicine, while alternative medicine is used in place of conventional medicine. CAM includes techniques such as acupuncture, chiropractics, homeopathy, herbal medicine and spiritual healing. It is important for clinicians to be aware of some of the more common forms of CAM, especially since some therapies can have adverse effects and may interfere with conventional, allopathic medications. Not surprisingly, evidence to support the use of CAM modalities in children is lacking and there is a serious need for further research in this area.

Several herbal preparations have been employed for the treatment of FGIDs in adults. Randomized, placebo-controlled trials of Chinese herbal medications for treatment of IBS in adults have so far had conflicting results [126,127]. Another recent study showed St. John's Wort, which is typically used to treat mild-to-moderate depression, to be inferior to placebo for IBS symptoms in adults [128]. Acupuncture, also adapted from traditional Chinese medicine, is postulated to have effects on acid secretion, GI motility and sensation of visceral pain, possibly mediated through the release of opioid peptides in the central and enteric nervous systems. However, two recent adult trials did not find evidence to support the superiority of acupuncture compared with sham acupuncture in the treatment of IBS [129,130]. There have been no studies using acupuncture to treat children with FAP or IBS. A small, noncontrolled study of 17 children with chronic constipation reported increased frequency of bowel movements with true acupuncture compared with placebo acupuncture [131].

Conclusion

Although most children with functional GI disorders such as FAP and IBS will improve with time and reassurance, a subset of patients may present to the primary care physician or gastroenterologist with more complex, severe or persistent problems. Much of the challenge in managing patients with functional disorders is linked to our incomplete understanding of the responsible pathologic mechanisms. Genetic predisposition, environmental exposures, early childhood stress, social learning and GI factors are all being studied as potential causative factors. The revised Rome III diagnostic criteria hold promise in further enhancing research efforts through better categorization of patients by age and symptoms into separate disorders that may differ in etiology and responsiveness to treatment.

As it stands, there is insufficient data to support the routine use of any dietary interventions or pharmacological agent as first-line therapy for FAP or IBS. Until larger studies with adequate power are conducted and are able to demonstrate efficacy, these therapeutic options should be carefully considered and tailored to each patient's specific symptoms and associated complaints. The largest numbers of studies in children have focused on CBT and psychosocial interventions. Small sample sizes, clinical heterogeneity, differences in specific therapeutic strategies and a lack of detailed descriptions somewhat hinder the ability to apply these therapies in clinical practice or make a strong conclusion about their efficacy. Nevertheless, consistent results supporting the benefit of CBT suggest that it may be a useful intervention in children. Indeed, the importance of psychological factors in patients with FAP and IBS is highlighted by large placebo responses seen in the control groups of several studies that we reviewed, across all types of intervention. For now, effective management of FAP and IBS in children and adolescents will require a multifaceted approach, customized to address each patient's specific symptoms and underlying triggers. It is crucial that physicians develop a positive therapeutic alliance with patients and their families with the goal of helping them understand the concept of the brain–gut axis as well as establish reasonable expectations for symptom improvement.

Future perspective

While the development of the Rome diagnostic criteria has greatly facilitated our understanding of FGIDs, there is still a need for further refinement and improvement of these criteria in order to better identify differences in etiology and pathogenic mechanisms, as well as predict response to therapeutic interventions. Future studies seeking to identify causal genetic loci will likely use a combination of approaches, such as genome-wide assays, whole genome sequencing and expression profiling. The impact of serotoninergic receptors, immune mediators and inflammatory cytokines on GI functions,

such as motility, absorption, secretion and sensation, will need to be further explored in both functional and organic disease on the biomolecular level. Finally, advances in understanding disruptions and homeostasis of the GI microbiome will undoubtedly help shed light on cases of post-infectious IBS and small intestinal bacterial overgrowth, as well as the role of probiotic supplementation and antibiotics as preventative and/or therapeutic strategies. Pharmacologic interventions hold the greatest potential for growth and development, with several candidate medications already in the pipeline based on recent advances in our understanding of neurotransmitters in the brain–gut axis. Continued national and international collaboration will be needed to perform well-designed studies and add to the limited armamentarium of therapeutic strategies currently available for children and adolescents with FAP and IBS.

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Executive summary

Epidemiology

- Functional abdominal pain (FAP) and irritable bowel syndrome (IBS) are common causes of recurrent abdominal pain in childhood and adolescence, which can have a significant impact on overall quality of life.
- Although the majority of patients with FAP or IBS have improvement of abdominal pain with reassurance and time, a significant proportion continue to have symptoms into adulthood.
- FAP and IBS have been associated with genetic, environmental, gastrointestinal and psychosocial factors.

Diagnostic approach

- The Rome III criteria allow the clinician to make a symptom-based, positive diagnosis of FAP or IBS.
- Basic laboratory screening tests may be considered. Extensive testing or radiographic studies are usually unnecessary to rule out other causes of abdominal pain.
- It is important to screen for psychiatric comorbidities, especially anxiety and depressive disorders, which may impact the overall management of abdominal pain symptoms.

Treatment

- The overall approach should be multifaceted and customized to address the patient's specific symptoms and underlying triggers.
- Cognitive behavioral therapy has been shown to be effective in reducing complaints of abdominal pain and helping patients cope with symptoms.
- There is insufficient evidence to support the routine use of dietary interventions, such as lactose restriction, fiber supplementation or probiotics, but these strategies may be considered on a case-by-case basis.
- There is also limited evidence to justify the use of drugs or herbal medications, but antidepressant medications should be considered, especially if there are concurrent psychiatric or emotional disorders.

Future perspective

- Further refinement of the Rome criteria for FAP and IBS should continue.
- Advances in understanding the role of serotonin, immune mediators and the gastrointestinal microbiome in functional and organic disorders will ultimately lead to better diagnostic methods and treatment strategies.

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