Abdominal Pain in Children

From the Eternal City to the Examination Room

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KEYWORDS

• Abdominal pain • Functional gastrointestinal disorders • Rome IV
• Visceral hypersensitivity

KEY POINTS

- Abdominal pain in children is a common entity.
- A majority of abdominal pain in children is classified as functional.
- The Rome Foundation and the Rome IV play a critical role in setting diagnostic criteria for research and practice as well as in educating the public and practitioners about functional gastrointestinal disorders (FGIDs).
- FGIDs are best understood using the biopsychosocial model of disease. Pain is a result of early life events, psychosocial factors, and physiologic factors.
- Physiologic factors leading to FGIDs include motility disturbance, visceral hypersensitivity, altered central nervous system (CNS) processing, altered mucosal and immune function, and altered gut microbiome.

Chronic abdominal pain continues to be one of the most common problems seen by pediatricians and pediatric gastroenterologists. Globally, irritable bowel syndrome (IBS) seems to affect 11% of the population, with 30% of these individuals presenting for medical care.[1] In a community-based study from 1996, 13% of middle school students and 17% of high school students experienced pain on a weekly basis.[2] A more recent study used online questionnaires and the ROME III criteria. In this study, parents of children living in the United States between the ages of 4 years and 18 years were asked to report on gastrointestinal symptoms[3]; 23.1% of children qualified for at least 1 FGID.[3] FGIDs account for approximately 50% of pediatric gastroenterology consultations.[4]

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Abdominal pain continues to be a frustrating presenting symptom, putting strain on the current fast-paced health care environment. Diagnosis and treatment of a child with abdominal pain take time—time for listening, counseling, and education; time that is difficult to find in current practice settings. A vast majority of patients who present for evaluation of abdominal pain do not have organic disease in the classic sense and fall into a functional category.

Many providers still believe that children with chronic abdominal pain are anxious or stressed. According a survey by the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 16% of the 300 pediatricians surveyed thought that functional abdominal pain was a wastebasket diagnosis. Only 11% of these pediatricians thought that functional abdominal pain was a specific diagnosis based on clear criteria.[5] Any of these preconceptions has an impact on the physician-patient relationship and potentially affects future therapeutic interaction.

FGIDs have a significant impact on those effected. FGIDs lead to significant difficulties with long-term comorbidities, including depression anxiety, lifetime psychiatric disorders, social phobia, and somatic complaints.[4] The distinction between *organic disease* and *nonorganic disease* (FGIDs) is a spurious one. Research continues to support the understanding that these disorders are related to alterations in the enteric nervous system (ENS) and in the modulation between the ENS and the CNS, alterations that have an organic etiology through the modulation of neurotransmitters, receptors, and cellular processing pathways involved in the nervous system.

Abdominal pain is best understood within the framework of the biopsychosocial model of disease. The biopsychosocial model emphasizes the multifactorial nature of abdominal pain, including genetic, environmental, social, and psychological components. Treatment plans need to develop and adapt over time and be extremely individualized. As understanding of the pathophysiology of FGIDs increases, there will be a larger repertoire of therapies from which to select. This article reviews current understanding of pain-related FGIDS and the etiology, pathophysiology, and treatment modalities available.

ETIOLOGY

The possible causes of abdominal pain in children are numerous, ranging from benign disorders to life-threatening surgical emergencies. Abdominal pain may arise from disorders in multiple organ systems, including the pulmonary, gastrointestinal, urologic, and gynecologic systems. Infectious, neoplastic, metabolic, and anatomic mechanisms may all lead to the presenting symptom of abdominal pain (**Table 1**) Patients and families are left anxious. Providers are concerned that they may be missing a diagnosis. These concerns often lead to numerous referrals and ongoing potentially invasive testing. Fortunately, there are a several alarm symptoms that help practitioners differentiate those children with organic disease, who requiring further investigation from those with FGIDs (**Box 1**).[5] Without these symptoms, extensive testing is unlikely to uncover other disorders.

EVALUATION

The evaluation of a patient with abdominal pain begins with a detailed history and physical examination. Patients often describe their symptoms using “diagnoses,” such as “I have been having problems with reflux.” Providers must focus specifically on each symptom. How long has the pain been occurring? Has the pain gotten better or worse or remained stable? What is the pain’s location? Is the pain associated with meals or sleep? Are there any specific triggers that worsen or alleviate the pain?

Table 1
Potential causes of abdominal pain in the pediatric patient

Functional	IBS FD Functional abdominal pain Functional constipation Cyclic vomiting syndrome Abdominal migraine
Gynecologic	Ovarian cyst Ovarian torsion Testicular torsion
Pulmonology	Pneumonia
Infectious	Viral Enterovirus, adenovirus Bacterial *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E coli* Parasites *Giardia*, *Entamoeba histolytica*
Intestinal	Gastroesophageal reflux (esophagitis) Gastritis Ulcer (duodenal/peptic) Cholelithiasis, cholecystitis, choledochal cyst Pancreatitis (acute, chronic), pancreatic pseudocyst Hepatitis Inflammatory bowel disease (Crohn/ulcerative colitis) Eosinophilic disease (esophagitis, gastroenteritis) Carbohydrate malabsorption (lactose intolerance)
Metabolic	Diabetes mellitis
Neoplastic	Porphyria tumors
Structural/surgical	Malrotation Intussusception Polyp Foreign body Meckel diverticulum Volvulus Trauma
Urologic	Urinary tract infection Nephrolithiasis Urinary pelvic junction obstruction

History and physical examination should always include review of alarm symptoms, which may guide a provider to more specific testing (see **Box 1**). Clinical judgment should be used, however, in this evaluation and these alarm symptoms should be seen in the context of the entire history.[6] Finally, evaluation of the patient's functioning, although it often does not indicate the ultimate diagnosis, provides clues as to child and parent coping strategies.

At minimum, basic laboratory studies should include a complete blood cell count and urinalysis. Depending on the history, a complete metabolic panel, amylase, lipase, erythrocyte sedimentation rate, C-reactive protein, or thyroid function testing may be indicated.

In the appropriate clinical setting, the practitioner needs to evaluate for Infectious causes, such as *Giardia* and other parasitic, bacterial, and viral diseases.

Many patients with IBS present with diarrhea. In children, this may raise concerns for inflammatory bowel disease. Fecal calprotectin has become a more common

Box 1
Warning signs that suggest a higher risk of organic disease in children with chronic abdominal pain

- Involuntary weight loss
- Deceleration of linear growth
- Gastrointestinal blood loss
- Significant vomiting (bilious emesis, protracted vomiting)
- Dysphagia
- Odynophagia
- Chronic severe diarrhea
- Nighttime stooling
- Pain awakening the child at night
- Persistent right upper or right lower quadrant pain
- Unexplained fever
- Abnormal physical findings (clubbing, localized tenderness, mass, hepatomegaly, splenomegaly, perianal abnormalities, erythema nodosum)
- Abnormal laboratory testing (elevated C-reactive protein/erythrocyte sedimentation rate, occult blood in stool)
- Family history of inflammatory bowel disease

screening test for mucosal inflammation with values of less than 50 mg/g stool, suggesting that inflammation is unlikely.[7]

Although controversial, screening for celiac disease is recommended in the current Rome IV. In a prospective cohort study, the prevalence of celiac disease was 4 times higher in patients with IBS compared with the general population.[8]

Carbohydrate malabsorption may lead to abdominal pain, bloating, and diarrhea, symptoms that mimic IBS. The most common disaccharidase deficiency is primary lactase deficiency. Before more formal testing, a brief period of a lactose elimination diet should be considered in patients with compatible symptoms. Endoscopic biopsies may be sent for measured disaccharidase activity. Breath testing is a more functional test and is helpful in determining malabsorption of the tested disaccharide. Patients may be enzyme deficient or malabsorb carbohydrate; however, these abnormalities do not necessarily correlate with intolerance and symptoms.

Routine radiographic studies have minimal yield in patients with abdominal pain and no alarm symptoms. Abdominal radiographs may help define a pneumonia, demonstrate free air, and help evaluate intestinal air or access stool burden. Studies have indicated that without alarm symptoms, ultrasound has little utility in differentiating a patient with organic disease from functional causes. One study demonstrated that abdominal/pelvic ultrasound in patients with abdominal pain and no alarm symptoms only detected abnormalities in 1%.[9] Recent studies on cancer risks in children receiving CT have led to a move to limit its use as an investigational tool for abdominal pain.[10]

More invasive testing, such as endoscopy, remains controversial. Endoscopy in patients with chronic abdominal pain may find abnormalities 25% to 56% of the time; however, the presence of inflammation may not predict successful resolution of the problem.[11] There is little evidence that a normal endoscopy in patients without alarm

symptoms provides benefit in the management of children with abdominal pain.[11] A recent study demonstrated that a negative endoscopy did not affect the persistence, frequency, or intensity of abdominal pain.[12] A negative endoscopy did not lead to improvement in school absenteeism or disruption of daily functioning.[12]

Fortunately, classification systems, such as ROME IV, exist to help physicians make a diagnosis of FGIDs in a proactive manner and not by exclusion.

ROME IV

Approximately 25 years ago, an international group of clinical practitioners and researchers met to establish a classification system for FGIDs, which would help in the diagnosis, the standardization of research, and dissemination of information on these common but poorly understood disorders. The symptoms-based classification was selected because it was thought the most relevant to clinical practice and less tied to a single pathophysiologic mechanism (ie, motility).[13] The process of consensus was used to revise these criteria in 1999, 2006, and most recently 2016 with the publication of *Rome IV*.[14] Rome IV now divides pediatric FGIDs into 3 forms[6]:

Nausea and vomiting disorders
Abdominal pain disorders
Defecation disorders

Pediatric FGIDs are outlined in chapters 15 and 16 of *Rome IV*.[6,15] **Boxes 2** and **3** outline those disorders. These criteria include all symptoms of FGIDs, not just the complaint of abdominal pain.

For the purposes of this article, however, functional abdominal pain, IBS, and functional dyspepsia (FD) are reviewed.

FUNCTIONAL ABDOMINAL PAIN DISORDERS (FAPDs) IN CHILDREN AND ADOLESCENTS

In Rome IV, the committee reevaluated the terminology used in describing pain-based FGIDs.

The term, *functional abdominal pain*, was not specific enough a descriptor for either clinical or research purposes. The terminology has been changed to FAPDs, which is inclusive of FD, IBS, functional abdominal pain–not otherwise specified (FAP-NOS), and abdominal migraine.[6] Each of these disorders has been carefully defined

Box 2
Childhood FGIDs, Neonate/toddler[10]

- Infant regurgitation
- Rumination syndrome
- Cyclic vomiting syndrome
- Infant colic
- Functional diarrhea
- Infant dyschezia
- Functional constipation

Data from Nurko S, Benninga M, Faure C, et al. Childhood functional gastrointestinal disorders, neonate/toddler. In: Drossman D, Chang L, Chey W, et al, editors. ROME IV, functional gastrointestinal disorders, disorders of gut-brain interaction. Raleigh (NC): The Rome Foundation; 2016. p. 1237–96.

Box 3
Childhood functional gastrointestinal disorders: child/adolescent

- Functional nausea and vomiting disorders
  - Cyclic vomiting syndrome
  - Functional nausea and functional vomiting
    - Functional nausea
    - Functional vomiting
  - Ruminations syndrome
  - Aerophagia
- FAPDs
  - FD
    - Postprandial distress syndrome
    - Epigastric pain syndrome
  - IBS
  - Abdominal migraine
  - FAP-NOS
- Functional defecation disorders
  - Functional constipation
  - Nonretentive fecal incontinence

Data from DiLorenzo C, Hyams J, Saps M, et al. Childhood functional gastrointestinal disorders, child/adolescent. In: Drossman D, Chang L, Chey W, et al, editors. ROME IV, functional gastrointestinal disorders, disorders of gut-brain interaction. Raleigh (NC): The Rome Foundation; 2016. p. 1297–371.

by the committee. The last phrase of each definition was altered to ensure that FAPD did not become a diagnosis of exclusion and mandates an appropriate, selective evaluation.

FD is defined as

- Bothersome symptoms at least 4 times a month for at least 2 months, which include
- Postprandial fullness
- Early satiation
- Epigastric pain or burning not associated with stooling
- After appropriate evaluation, symptoms that cannot be fully explained by another medical condition

IBS is defined as

Abdominal pain at least 4 days per month over at least 2 months associated with
1 or more of the following:
Related to defecation
A change in stool frequency
A change in stool form

In children with abdominal pain and constipation, the pain does not resolve with resolution of the constipation and, after appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

IBS has been divided into 4 subtypes based on the Bristol Stool Form Scale[6]:

IBS-C — constipation predominate
IBS-D — diarrhea predominate
IBS-M — mixed stool types
IBS-U — unsubtyped

Subtyping of IBS has been important in directing therapy. Many current therapies are being targeted to treat and approved for use with specific subtypes.[6]

FAP-NOS is defined as abdominal pain occurring at least 4 times a month and all of the following:

- Episodic or continuous abdominal pain that does not occur solely during physiologic events
- Insufficient criteria for IBS, functional dyspepsia, or abdominal migraine—after appropriate evaluation, the symptoms cannot be fully explained by another medical condition.[6]

PATHOPHYSIOLOGY

FGIDs are the result of a complex interplay of factors that affect the individual and combine to produce disease. This paradigm is the biopsychosocial conceptual model. This model defines FGIDs as gastrointestinal symptoms resulting from a combination of

- Early life events, which may include
  - Genetics
  - Environmental factors (trauma, infections, parental behaviors)
- Psychosocial factors
  - Life stress
  - Personality traits
  - Psychological state
  - Coping
  - Social support
- Physiologic factors
  - Motility disturbance
  - Visceral hypersensitivity
  - Altered CNS processing
  - Altered mucosal and immune function
  - Altered gut microbiota[13]

Early Life Events

Early life pain or stress seems able to lead to chronic abdominal pain later in life through the development of visceral hypersensitivity. The abdominal pain may be the result of

- Increased sensitization of central neurons
- Sensitization of primary sensory neurons
- Impaired stress response through alterations in the hypothalamic-pituitary-adrenal axis (HPA) axis altered descending inhibition of sensory stimulation[16]

The development of CNS changes has been studied in neonatal rats[16] as well as human infants. Exposure to colonic irritation in neonatal rats results in permanent alteration in spinal neurons, which leads to visceral hypersensitivity, a decreased pain threshold, when they become adults.[16] Also in rats, somatic pain experienced in the neonatal period can increase sensitization of spinal neurons and lead to visceral hypersensitivity in adult rats.[16] Infants with prior surgical history have been shown to have increased need for anesthesia during procedures as well as higher pain control postoperatively.[17]

The sensory neurons of the ENS also seem to have a lower sensory threshold and increased signaling to the CNS in individuals with FAPD. Animal studies have shown

that colonic irritation sensitizes the sensory neuron in the lumbosacral region, leading to increased signaling in response to colorectal distension.[18]

Stress seems to be 1 trigger for FGIDs in children. Animal studies have demonstrated the development of visceral hypersensitivity after stress events.[16] Stress events have also been shown to increase corticotropin-releasing factor (CRF) expression in the periventricular nucleus, locus coeruleus, and amygdala of adult rats.[19] This action alters the set point of the CRF system and may affect an organism's response to stress and pain later in life.

Pain signals sent by the ENS undergo processing in the spinal cord by inhibitory or excitatory neurons from the CNS. Studies evaluating the effect of fentanyl in response to rectal stimulation demonstrate an improved response in patients with IBS compared with controls. This suggests an alteration in the pain modulatory opioid system.[16]

Genetics

The clustering of FGIDs in families suggest a possible genetic cause of chronic abdominal pain, although this finding could be explained by common environmental factors. Twin studies have not been consistent; however, several studies from the United States, Australia, and Norway have shown increasing concordance for IBS in twins.[20]

Evidence supporting the role of early life events in the etiology of FGIDs has led to research into candidate genes. Studies have identified numerous genes and gene products, which may lead to altered visceral sensitivity and pain processing, including; α_2-adrenergic receptors, serotonin receptors, serotonin and norepinephrine transporters, interleukin (IL)-10, tumor necrosis factor (TNF)-α, TNF superfamily member 15, G proteins (involved in intracellular signaling and ion channels [SCN5A]).[21]

Using genome-wide association studies and data from the Screening Across the Lifespan Twin Study, a locus on 7p22.1 consistently showed increase genetic risk for IBS.[22] This area maps to 2 genes, KDEL receptor 2 gene (*KDELR2*) expressed in all tissues and glutamate receptor-ionotropic-delta 2 interacting protein (*GRID2IP*) localized expression in the brain. KELR2 seems to play a role in vesicle trafficking and transport to the endoplasmic reticulum. The gene seems more highly expressed in the rectum of patients with IBS. GRID2IP encodes a protein, delphilin, which plays a role in glutamatergic neurotransmission.[22]

Psychosocial Factors

Studies have demonstrated an increase rate of stress, anxiety, and depression in patients with FGIDs.[6] There do not seem to be any differences in psychosocial profiles among patients with different abdominal pain–based FGIDs.[23] Children with FAP have a decreased quality of life, frequent school avoidance, school absences, and social difficulties.[24] These pain syndromes are not short lived. In 25% to 45% of patients, these pain symptoms persist for 5 years.[24] Children with extraintestinal somatic symptoms, such as dizziness, back pain, headache, and depression, are more likely to have FGIDs, which extend into young adulthood.[25] It is important to know, however, that 50% of children with FGIDs have no emotional, behavioral, or social functioning problems.[26]

Each individual approaches stress differently. This approach depends on how a child perceives an event and the available coping strategies. Children who feel threatened by a pain event and use passive coping strategies do not have as good an outcome. Children who are more accepting of the pain and have accommodating coping strategies tend to have better function.[27]

In addition to individual strategies, a child's social network provides potential support for coping with chronic abdominal pain, in both positive and negative ways. Families and friends can facilitate wellness or promote disability.

Physiologic Factors

The network of communication between the gut and the brain includes the CNS (brain and spinal cord), the autonomic nervous system, the ENS, and the HPA axis.[28]

Sensations from the gastrointestinal tract are the result of signaling from mechanoreceptors located in the afferent terminal of spinal afferent nerves. These nerves have cell bodies in the vagal nodose ganglia and dorsal root spinal ganglia. The signals are then sent via vagal sensory afferents to the brainstem via the nodose ganglia and nucleus tractus solitarius. Serotonin is an important neurotransmitter in pain signaling, mainly through the 5-HT3 receptor.[29] Increased secretion of serotonin or decreased uptake of serotonin leads to increased pain signaling.[29]

In patients with visceral hypersensitivity, afferent sensory receptors seem to have a lower threshold for stimulation. These receptors continue to send pain signals after the stimulus has already passed.[30] This increased sensitivity may be triggered by intestinal inflammation related to inflammatory bowel disease, allergy, or infection.

The role of pain signal processing in the cerebral cortex has been investigated in humans using both functional MRI and PET. These imaging studies have demonstrated that pain signaling from the secondary somatosensory cortex projects to the limbic and paralimbic regions. These are areas of the brain that are important in an individual's mood, motivation, and cognition, all important components in the experience of visceral pain.[29] Functional MRI has demonstrated that patients with IBS have increased activation of the midcingulate cortex in response to rectal distention.[31] The cingulate cortex is believed an integrative center for emotional experience and pain information.[29]

The HPA axis is vital in coordinating the organism's response to stress. The HPA is part of the limbic system of the brain that is involved with memory and emotional response. Stress activates release of CRF from the hypothalamus, which then stimulates secretion of corticotropin from the pituitary. Corticotropin then stimulates the secretion of cortisol from the adrenal glands.

Both neural and hormonal mechanisms allow the brain to influence many cell functions in the intestine, including immune cells, epithelial cells, neurons, smooth muscle cells, interstitial cells of Cajal, and enterochromaffin cells.[28]

INFLAMMATION

There is evidence to suggest that an imbalance in proinflammatory and anti-inflammatory cytokines may play a role in the development of IBS.[6] Children with IBS seem to have a lower secretion of an anti-inflammatory cytokine (IL-10), which suggests altered immune regulation in this disease process. These changes are subtle and may be induced by prior infections.[6]

MICROBIOME

Studies have demonstrated differences in the microbiome of children with IBS. These children have a higher proportion of Proteobacteria than healthy children.[32] There seems to be bidirectional influence between the gut microbiome and the gut-brain axis via neural, endocrine, immune, and humoral mechanisms.[28]

In the CNS, studies using germ-free mice have demonstrated that the microbiome can effect stress reactivity as well as modulate the serotonergic system.[28,33] In these same germ-free mice, addition of probiotics has led to changes in gut-brain axis

mRNA expression in the brain, reduced stress-induced release of cortisol, and reduced anxiety and depression behaviors.[28]

Peripherally, the microbiome may interact with the GBA by modulating afferent sensory nerves, producing molecules that act as local neurotransmitters, and through the production of short chain fatty acids, which can stimulate the sympathetic nervous system.[28]

The CNS also interacts in direct ways with the gut microbiome. For reasons not fully understood, bacteria in the colon contain binding sites for enteric neurotransmitters, the same neurotransmitters used in signaling by the ENS and CNS. The CNS directly controls the environment in which the microbiome resides by modulating intestinal motility; the secretion of acid, bicarbonate, and mucus; intestinal fluid handling and the mucosal immune system. These studies point to the microbiome as a compelling area of research and possible therapeutic target in the treatment of FGIDs.

THERAPY IN PAIN-RELATED FUNCTIONAL GASTROINTESTINAL DISORDERS

The development of a treatment plan for the patient with FGIDs is an individualized process. Therapeutic outcomes depend on a plan that directs treatment to many aspects of the disorder. The arms of therapy include

Dietary therapy
Pharmacologic therapy
Psychosocial support
Complementary/alternative interventions[34]

Simple reassurance in the setting of a strong clinical therapeutic relationship can be helpful in enabling children with FD to resume normal activity. Placebo response rates in patients with FGIDs range from 20% to 60%.[35]

Dietary Therapy

If FGIDs are understood as the result of visceral hypersensitivity, foods that increase abdominal distention, and therefore pain signaling, may complicate symptoms. Recently, studies have evaluated food triggers and have suggested a role of nonabsorbable carbohydrates, nonceliac gluten sensitivity, and food chemical sensitivity.[36]

More specifically, fermentable oligosaccharides, disaccharides and monosaccharides, and polyols (FODMAPs) are a group of poorly digestible carbohydrates that seem to participate in causing symptoms.[36] These carbohydrates include fructose, lactose, sorbitol, fructo-oligosaccharides, gluco- oligosaccharides, and mannitol. FODMAPs are believed to lead to symptoms through several mechanisms, including increase osmotic load and intestinal distention, altered intestinal motility, direct injury to colonic epithelium with increased permeability, and interaction with the intestinal microbiome and the varied metabolism of those organisms.[36]

There are few current tables of FODMAPs in foods and no validated FODMAP cutoff levels to help determine whether a food is truly high FODMAP. Recommendations are to attempt to keep FODMAPs below 3 g a day, however, to benefit IBS patients.[36] On a strict restriction, studies out of Australia have demonstrated a 74% response rate with durability linked directly to dietary compliance.[37]

Probiotics

Intestinal bacteria play a complex role in multiple processes, including effects on bowel motility, pain signaling, immune response, nutrient processing. Manipulation of this microbiome is a potential therapeutic target.

In a recent meta-analysis of placebo-controlled randomized studies,[38] *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri* DSM 17938, and VSL#3 were all shown to increase treatment success with abdominal pain type FGIDs, especially in those patients with IBS. LGG and *L reuteri* DSM 17938 significantly decreases the intensity of the pain. The data for VSL#3 demonstrated that the intensity of pain and bloating was significantly lower than placebo; however, pain frequency was unchanged.[38] More research is needed to determine the exact strain, dosage, or combination that is the most effective.

Pharmacotherapy

Medications for the treatment of FGIDs target multiple points along the pain transmission pathway — from the peripheral receptor, the spinal cord, and also the cortex. Controlled trials in pediatrics continue to be rare.

Antibiotics

With the understanding that the microbiome plays an important role in the etiology of FGIDs, the use of antibiotics in therapy seems a logical step. TARGET-1 and TARGET-2 were 2 double-blind, placebo-controlled studies comparing rifaximin to placebo in the treatment of IBS without constipation.[39] These 2 large-scale trials, enrolling 1260 patients, demonstrated that a 14-day course of rifaximin, at a dose of 550 mg 3 times a day for 14 days, was superior to placebo in improving IBS symptoms with no increased risk of side effects.[39] The Food and Drug Administration–approved rifaximin for treatment of IBS-D in May 2015.

Antispasmodics

Although commonly used in treating patients with pain FGIDs, the anticholinergic hyoscyamine (Levsin) has not been studied in a controlled fashion.[40] Dicyclomine (Bentyl) has been studied in IBS-C and was found to improve overall IBS symptoms.[40]

Antidepressants

Antidepressants affect both the central and peripheral nervous system through multiple pathways, including anticholinergic effects, leading to decreased gastrointestinal transit, improved sleep, treatment of comorbid depression, and analgesia through receptor binding throughout the pain transmission pathway.[41] In a pediatric study, citalopram improved function and decreased pain in 84% of patients with FGIDs.[42]

Serotonin

Serotonin is a critical neurotransmitter in the pain pathway and is an attractive target for potential therapy. Two serotonin type 3 compounds have been developed and studied in adults, alosetron and cilansetron. Complications with these medications, including severe constipation and ischemic colitis, have restricted their use.[41]

Tegaserod, a serotonin type 4 antagonist, is used in constipation predominate IBS.

Psychosocial Support

One of the most important aspects of therapy in these patients is the development of a supportive doctor-patient relationship in which the patient is an active participant in developing to plan of care. Drossman,[13] in *Rome IV*, outlines 12 steps to enhance this relationship.

These steps include:

- Learning to engage the patient in the visit
- Being nonjudgmental and patient centered while taking the history

- Determining the immediate need for the patient visit
- Conducting a careful physical examination and cost-efficient investigation
- Determining patients' understanding of their illness and focus on their concerns
- Eliciting patient understanding of symptoms and provide education
- Responding to patient expectations
- Associating stress and symptoms in a way that is consistent with patient beliefs
- Setting limits
- Involving the patient in treatment
- Making recommendations consistent with patient interests
- Establishing an ongoing relationship[13]

Cognitive Behavioral Therapy

Psychological therapies are effective in the treatment of FGIDs and include parent training, family support, psychotherapy/cognitive behavioral therapy (CBT), relaxation, distraction, hypnotherapy, and biofeedback.[43]

Multiple studies have demonstrated that psychological therapy, such as hypnotherapy and CBT, are effective in the treatment of FGIDs.[44,45]

Family therapy and parent training help address acceptance of a rehabilitation approach to therapy. These interventions are also helpful in changing behaviors in the family that may promote disability or catastrophizing; ongoing behavioral plans should promote independence and functioning.

CBT is a psychotherapeutic approach focused on changing unhelpful cognitions, assumptions, beliefs, and behaviors.[43] During this therapy, patients learn a more biopsychosocial framework of disease. They may keep a diary of symptoms and events to help identify triggers or outcomes that can be targeted for intervention. Patients learn to question their thoughts, assumptions and beliefs that may not be helpful and formulate a new approach.[43]

Hypnotherapy helps patients focus away from the pain, alter sensory experience, decrease stress, promote relaxation, and provide a way to reconsider painful stimuli. In patients with FGIDs, there are gut-specific techniques that may be used.[43]

Complementary Medicine

Complementary medicine techniques may include acupuncture, Ayurveda medicine, chiropractic, homeopathy, and mind-body medicine. Modalities include herbal supplementation, massage therapy, acupuncture, and hypnotherapy.[46]

Peppermint oil is a common and studied herbal often used in patients with FGIDs. In 1 study in children, there was a 76% improvement in symptoms compared with a 19% placebo response.[47] Ginger has been shown helpful in patients with nausea and seems to have a prokinetic function.[46]

The use of massage therapy remains controversial. The underlying theory is that massage may reduce visceral hypersensitivity and alter gastrointestinal tone and motility. Although promising, more studies are needed to confirm its efficacy.

Acupuncture has been shown to effect acid secretion, gastrointestinal motility, and visceral pain in animals. Studies at this time, however, have not demonstrated efficacy for FGIDs.

Gut-directed hypnotherapy has been shown effective in both adults and children in the management of FGIDs. One study demonstrated that hypnotherapy was superior to standard medical therapy. Most interestingly, at 1-year follow-up, symptoms were successfully treated in 85% of the cases.

FUNCTIONAL DYSPEPSIA

Although FAP-NOS and IBS refer to more generalized abdominal pain, functional dyspepsia (FD) refers to symptoms that seem to refer to the gastroduodenal region. These symptoms may include abdominal bloating, epigastric pain, early satiety, belching, epigastric burning, nausea, and vomiting. In Rome IV, FD in children has been divided into 2 subtypes, postprandial distress syndrome and epigastric pain syndrome.[6,48] There is some controversy around this separation. A recent study demonstrated that in a significant number of patients, no clinical distinction was possible and 43% of children switched subtypes, suggesting a common pathophysiology.[49] In another study, however, 29% of patients fit into the postprandial distress syndrome, 24% met criteria for epigastric pain syndrome, 26% met criteria for both, and 21% did not fulfill either diagnosis.[50] The clinical distinction, when present, may provide an alternative to overuse of empiric acid-blocking therapy as well as alternatives to immediate endoscopy or subspecialty referral.[51]

FD is defined as symptoms occurring at least 4 times a month for at least 2 months, including

1. Postprandial fullness
2. Early satiety
3. Epigastric pain or burning not associated with stooling
4. After appropriate evaluation, symptoms that cannot be fully explained by another medical condition[6]

Postprandial distress syndrome is defined as bothersome postprandial fullness or early satiation that prevents finishing a meal. These sensations may include upper abdominal bloating, postprandial nausea, or excessive belching.[6]

Epigastric pain syndrome includes pain or burning located in epigastrium, a burning quality pain that may be induced or relieved by ingestion of a meal.[6]

The major pathophysiologic mechanisms of other FGIDs are also thought to lead to FD, including motility abnormalities, abnormalities of accommodation, and visceral hypersensitivity.[51]

A direct link between motor abnormalities and resultant symptoms is not firmly established.[52] Changes in gastric motor patterns may be the result of abnormalities of the vasovagal reflex, the intrinsic inhibitory innervation, or altered smooth muscle.[51] Approximately two-thirds of adults with FD have abnormal gastroduodenal motility, leading to postprandial fullness, nausea, and vomiting.[51]

Gastric accommodation is a motor event in which the gastric fundus seems to relax in an attempt to accept an incoming meal, without increasing gastric pressure. In patients with abnormal gastric accommodation, the food bolus seems to localize to the distal stomach. Abnormal gastric accommodation has been demonstrated in 40% of adult patient with FD, leading to early satiety or postprandial pain.[51]

Visceral hypersensitivity may occur at many levels in the upper gastrointestinal tract. Adults with FD have increased sensitivity to acid within the duodenum, leading to nausea in a subset of patients. Adults with FD have also been found more sensitive to gastric balloon distention, with increased brain signaling.[52]

Recent studies in adults have also demonstrated a link between prior infections, such as *Salmonella*, *Eshcherichia coli* 0157, *Campylobacter jejuni*, *Giardia lamblia*, and norovirus, and the development of FD.[53]

Work-up of Functional Dyspepsia

In the upper tract, alarm symptoms include vomiting, dysphagia, odynophagia, weight loss, hematemesis, and abnormal laboratory studies, such as anemia. In

the setting of alarm symptoms, endoscopy is the most sensitive and specific test for the evaluation of other inflammatory causes of upper gastrointestinal symptoms. Gastric emptying scans may also be helpful in demonstrating motor dysfunction and delayed gastric emptying. Anatomic studies, such as an upper gastrointestinal radiograph, help define normal anatomy and evaluate for malrotation, hiatal hernia, rings, or webs. Upper gastrointestinal radiography does not establish the diagnosis of gastroesophageal reflux disease in any meaningful way.

Endoscopy continues to be controversial in pediatric FD. Adult Rome criteria have required an esophagogastroduodenoscopy; in pediatrics, esophagogastroduodenoscopy is not a requirement in the diagnosis of FD.[6] In a study from Hong Kong, 80 consecutive children with FD were evaluated.[54] Alarm symptoms included gastrointestinal blood loss, dysphagia, vomiting and right upper quadrant pain, nocturnal pain, family history of peptic ulcer disease, and weight loss. Endoscopic mucosal abnormalities were noted in 3 of 9 patients with alarm symptoms and 2 of 71 children without alarm symptoms.[54] If no alarm symptoms are present, a therapeutic trial of acid blockade, prokinetic agents, or other motility agents, such as cyproheptadine, may lead to symptomatic improvement.

Therapy

There are few randomized studies on the treatment of FD, especially in children. Acid suppression was shown helpful in a study comparing cimetidine, ranitidine, famotidine, and omeprazole in the treatment of children with FD. This study demonstrated a 53.8% symptom relief with omeprazole after 4 weeks of therapy, 44.4% for famotidine.[55] The study supported the use of proton pump inhibitors over H_2-receptor antagonists in the treatment of FD.

There are few data in children supporting the use of prokinetics in children for the treatment of FD. Pharmacotherapy has focused on agents that stimulate gastric emptying by targeting serotonin receptors (serotonin type 2 antagonists and serotonin type 4 agonists), dopamine, and motilin receptors.[51] Unfortunately, most of these agents, such as cisapride, domperidone, and reglan, are either ineffective or carry significant cardiac or neurologic risk.

Cyproheptadine, an antagonist of serotonin, histamine H_1, and muscarinic receptors, seems to improve gastric accommodation and has been shown to improve symptoms in children with FD. In a retrospective, open-label study, there was a 55% improvement in dyspeptic symptoms in pediatric patients.[56] There was also a 30% incidence of side effects; however, all were mild and self-limited. Only 2 of 80 children stopped therapy.[56]

As in the treatment of other FGIDs, antidepressant medications, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, may also be helpful in treating FD. These medications may act by improving gut motility or modulations of visceral hypersensitivity.[51]

Abdominal pain continues to be a common and concerning symptom in children. Abdominal pain leads to frequent physician visits and often extensive testing. Rome IV has helped to define FGIDs, and promote education and research into these disorders. A fascinating, intricate web of neurologic signaling, hormonal signaling, commensal organisms, stress, anxiety, social support, and genetics seems involved in the ultimate manifestation of FGIDs. Further research is needed to more specifically define this interplay and effects. Therapeutic interventions need to address these multiple pathophysiologic mechanisms in the setting of individual experience of disease.

REFERENCES

1. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014;6:71–80.
2. Hyams JS, Burke G, Davis P, et al. Abdominal pain and irritable bowel syndrome in adolescents: a community- based study. J Pediatr 1996;129:220–6.
3. Lewis ML, Palsson OS, Whitehead WE, et al. Prevalence of functional gastrointestinal disorders in children and adolescents. J Pediatr 2016;177:39–43.e3.
4. Nurko S, Di Lorenzo C. Functional abdominal pain: time to get together and move forward. J Pediatr Gastroenterol Nutr 2008;47:679–80.
5. Di Lorenzo C, Colletti RB, Lehmann HP, et al. Chronic abdominal pain in children: a clinical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005;40:245–8.
6. DiLorenzo C, Hyams J, Saps M, et al. Childhood functional gastrointestinal disorders, child/adolescent. In: Drossman D, Chang L, Chey W, et al, editors. ROME IV, functional gastrointestinal disorders, disorders of gut-brain interaction. Raleigh (NC): The Rome Foundation; 2016. p. 1297–371.
7. Henderson P, Anderson NH, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2013;109(5): 637–45.
8. Cristofori F, Fontana C, Magistà A, et al. Increased prevalence of celiac disease among pediatric patients with irritable bowel syndrome a 6-year prospective cohort study. JAMA Pediatr 2014;168(6):555–60.
9. Yip W, Ho T, Yip Y, et al. value of abdominal sonography in the assessment of children with abdominal pain. J Clin Ultrasound 1998;26:397–400.
10. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 2012;380:499–505.
11. Di Lorenzo C, Colletti RB, Lehmann HP, et al. Chronic abdominal pain in children: a technical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition: AAP Subcommittee and NASPGHAN Committee on Chronic Abdominal Pain. J Pediatr Gastroenterol Nutr 2005;40:249–61.
12. Bonilla S, Wang D, Saps M. The prognostic value of obtaining a negative endoscopy in children with functional gastrointestinal disorders. Clin Pediatr (Phila) 2011;50:396–401.
13. Drossman D. Functional gastrointestinal disorders and the Rome IV Process. In: Drossman D, Chang L, Chey W, et al, editors. ROME IV, functional gastrointestinal disorders, disorders of gut-brain interaction. Raleigh (NC): The Rome Foundation; 2016. p. 1–32.
14. Drossman D, Chang L, Chey W, et al. ROME IV, functional gastrointestinal disorders, disorders of gut-brain interaction. Fourth. Raleigh (NC): The Rome Foundation; 2016.
15. Nurko S, Benninga M, Faure C, et al. Childhood functional gastrointestinal disorders, neonate/toddler. In: Drossman D, Chang L, Chey W, et al, editors. ROME IV, functional gastrointestinal disorders, disorders of gut-brain interaction. Raleigh (NC): The Rome Foundation; 2016. p. 1237–96.
16. Miranda A. Early life events and the development of visceral hyperalgesia. J Pediatr Gastroenterol Nutr 2008;47:682–4.

17. Peters J, Schouw R, Anand K, et al. Doesneonatal surgery lead to increased pain sensitivity in later childhood? Pain 2005;114:444–54.
18. Lin C, Al-Chaer ED. Long-term sensitization of primary afferents in adult rats exposed to neonatal colon pain. Brain Res 2003;971:73–82.
19. Plotsky PM, Thrivikraman KV, Nemeroff CB, et al. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. Neuropsychopharmacology 2005;30:2192–204.
20. Talley N. Genetics and functional bowel disease. J Pediatr Gastroenterol Nutr 2008;47:680–2.
21. Saito Y, Talley N. Genetics of irritable bowel syndrome. Am J Gastroenterol 2008; 103:2100–4.
22. Ek WE, Reznichenko A, Ripke S, et al. Exploring the genetics of irritable bowel syndrome: a GWA study in the general population and replication in multinational case-control cohorts. Gut 2015;64:1774–82.
23. Rutten JMTM, Benninga MA, Vlieger AM. IBS and faps in children. J Pediatr Gastroenterol Nutr 2014;59:493–9.
24. Cunningham NR, Lynch-Jordan A, Mezoff AG, et al. Importance of addressing anxiety in youth with functional abdominal pain: suggested guidelines for physicians. J Pediatr Gastroenterol Nutr 2013;56(5):469–74.
25. Horst S, Shelby G, Anderson J, et al. Predicting persistence of functional abdominal pain from childhood into young adulthood. Clin Gastroenterol Hepatol 2014; 12(12):2026–32.
26. Schurman JV, Danda CE, Friesen CA, et al. Variations in psychological profile among children with recurrent abdominal pain. J Clin Psychol Med Settings 2008;15:241–51.
27. Walker LS, Smith CA, Garber J, et al. Testing a model of pain appraisal and coping in children with chronic abdominal pain. Health Psychol 2005;24:364–74.
28. Carabotti M, Scirocco A, Maselli MA, et al. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 2015;28:203–9.
29. Wood JD. Functional abdominal pain: the basic science. J Pediatr Gastroenterol Nutr 2008;47:688–93.
30. DiLorenzo C, Youssef N, Sigurdsson L, et al. Visceral hyperalgesia in children with functional abdominal pain. J Pediatr 2001;139:838–43.
31. Naliboff B, Derbyshire S, Munakate J, et al. Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. Psychosom Med 2001;63:365–75.
32. Saulnier DM, Riehle K, Mistretta T-A, et al. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. Gastroenterology 2011;141(5): 1782–91.
33. Heijtz RD, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci U S A 2011;108:3047–52.
34. Giannetti E, Staiano A. Probiotics for irritable bowel syndrome: clinical data in children. J Pediatr Gastroenterol Nutr 2016;63:25–6.
35. Benninga MA, Mayer EA. The power of placebo in pediatric functional gastrointestinal disease. Gastroenterology 2009;137:1207–10.
36. Mansueto P, Seidita A, D'Alcamo A, et al. Role of FODMAPs in patients with irritable bowel syndrome. Nutr Clin Pract 2015;30:665–82.
37. Shepherd S, Gibson P. Fructoe malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. J Am Diet Assoc 2006; 106:1631–9.

38. Korterink JJ, Ockeloen L, Benninga MA, et al. Probiotics for childhood functional gastrointestinal disorders: a systematic review and meta-analysis. Acta Paediatr 2014;103:365–72.
39. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2016;364:22–32.
40. Trinkley KE, Nahata MC. Treatment of irritable bowel syndrome. J Clin Pharm Ther 2011;36:275–82.
41. Lebel A. Pharmacology. J Pediatr Gastroenterol Nutr 2008;47:703–6.
42. Campo J, Perel J, Lucas A, et al. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. J Am Acad Child Adolesc Psychiatry 2004;43:1234–42.
43. Bursch B. Psychological/cognitive behavioral treatment of childhood functional abdominal pain and irritable bowel syndrome. J Pediatr Gastroenterol Nutr 2008;47:706–7.
44. Whitehead W. Hypnosis for irritable bowel syndrome: the empirical evidence of therapeutic effects. Int J Clin Exp Hypn 2006;54:7–20.
45. Duarte MA, Penna FJ, Andrade EMG, et al. Treatment of nonorganic recurrent abdominal pain: cognitive-behavioral family intervention. J Pediatr Gastroenterol Nutr 2006;43:59–64.
46. Vlieger A, Benninga M. Complementary Therapies for pediatric functional gastrointestinal disorders. J Pediatr Gastroenterol Nutr 2008;47:707–9.
47. Kline RM, Kline JJ, Di Palma J, et al. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr 2001;138:125–8.
48. Tilburg M, van, Hyams J, Leiby A. Functional dyspepsia in children: can we distinguish epigastric pain and postprandrial distress? Gastroenterology 2014; 146:S143.
49. Turco R, Russo M, Martinelli M, et al. No Titdo distinct Functional Dyspepsia Subtypes Exist in Children? J Pediatr Gastroenterol Nutr 2016;62:387–92.
50. Schurman JV, Singh M, Singh V, et al. Symptoms and subtypes in pediatric functional dyspepsia: relation to mucosal inflammation and psychological functioning. J Pediatr Gastroenterol Nutr 2010;51:298–303.
51. Romano C, Valenti S, Benninga M. Functional dyspepsia: an enigma in a conundrum. J Pediatr Gastroenterol Nutr 2016;63(6):579–84.
52. Tack J, Talley N, Camilleri M, et al. Functional gastroduodenal disorders. Gastroenterology 2006;130:1466–79.
53. Futagami S, Itoh T, Sakamoto C. Systematic review with meta-analysis: post-infectious functional dyspepsia. Aliment Pharmacol Ther 2015;41:177–88.
54. Tam YH, Chan KW, To KF, et al. Impact of pediatric Rome III criteria of functional dyspepsia on the diagnostic yield of upper endoscopy and predictors for a positive endoscopic finding. J Pediatr Gastroenterol Nutr 2011;52:387–91.
55. Dehghani S, Imanieh M, Haghighat M. The comparative study of the effectiveness of cimetidine, ranitidine, famotidine, and omeprazole in the treatmtne of children with dyspepsia. ISRN Pediatr 2011;2011:219287.
56. Rodriguez L, Diaz J, Nurko S. Safety and efficacy of cyproheptadine for treating dyspeptic symptoms in children. J Pediatr 2013;163:261–7.