Epidemiological and pathophysiological aspects of abdominal pain predominant functional gastrointestinal disorders in children and adolescents: a Sri Lankan perspective
Devanarayana, N.M.

Citation for published version (APA):
Chapter 2

Childhood functional abdominal pain: mechanisms and management

This chapter of the thesis was published as

Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA.
Nature Reviews Gastroenterology and Hepatology; 2015; 12: 159-71

ABSTRACT

Chronic abdominal pain is one of the most common clinical syndromes encountered in day to day clinical pediatric practice. Although common, its definition is confusing, predisposing factors are poorly understood and the pathophysiological mechanisms are not clear. The prevailing viewpoint in the pathogenesis involves the inter-relationship between changes in hypersensitivity and altered motility, to which several risk factors have been linked. Making a diagnosis of functional abdominal pain can be a challenge, as it is unclear which further diagnostic tests are necessary to exclude an organic cause. Moreover, large, well-performed, high-quality clinical trials for effective agents are lacking, which undermines evidence-based treatment. This Review summarizes current knowledge regarding the epidemiology, pathophysiology, risk factors and diagnostic work-up of functional abdominal pain. Finally, management options for children with functional abdominal pain are discussed including medications, dietary interventions, probiotics and psychological and complementary therapies, to improve understanding and to maximize the quality of care for children with this condition.
INTRODUCTION
At the beginning of the 1900s Still, a British pediatrician, wrote “I know of no symptom which can be more obscure in its causation than colicky abdominal pain in childhood”. Today, more than a century later, both clinicians and researchers are still struggling to understand this enigmatic clinical issue. This lack of understanding often leads to extensive investigations, non-effective therapeutic modalities, poor patient satisfaction, reduced health-related quality of life, staggering health-care costs and an insurmountable amount of suffering in the patients' themselves. However, the landscape has changed, especially during the past two decades. Definitions are being refined from the previously labelled and vague ‘chronic or recurrent abdominal pain’ to the more-specific symptom-based Rome III criteria. Pathophysiological mechanisms are being explored and knowledge is expanding. New noninvasive investigational techniques are emerging to elaborate underlying abnormalities. Although the traditional pharmacological treatment modalities are failing, some novel pharmacological agents and non-pharmacological therapeutic components are showing promising results. In this Review, we concentrate on the scientifically valid and clinically relevant entity of pain-predominant functional gastrointestinal disorders (FGIDs) rather than simply recurrent abdominal pain.

DEFINITIONS
In 1958, John Apley, a British pediatrician who pioneered research in children with abdominal pain, named the condition as “recurrent abdominal pain syndrome of childhood” and defined it as “at least three episodes of abdominal pain, severe enough to affect their activities over a period longer than 3 months”. Since then, for nearly four decades, this definition has been the standard definition used to diagnose chronic abdominal pain in both research and clinical practice. In 1996, Hyams et al observed that 51% of children with recurrent abdominal pain could be classified as having IBS utilizing the criteria designed for adults. In 1999, the Rome II criteria for children were published and were appropriate to be used as diagnostic tools and to advance empirical research. Using these criteria, it was noted that 73–89% of children with recurrent abdominal pain (RAP) could be classified as having a pain-predominant FGID. Since then, the term RAP has been replaced by abdominal-pain-predominant FGIDs (AP-FGIDs); namely, functional dyspepsia, IBS, functional abdominal pain (FAP) and abdominal migraine. Although the Rome II criteria laid a firm foundation to study pain-predominant FGIDs, they were found to have several limitations. The Rome II criteria demanded persistence of symptoms for over 3 months before the diagnosis. In addition, Saps and Di Lorenzo noted that the diagnostic agreement between pediatric gastroenterologists and gastroenterology fellows when adhering to the Rome II criteria was low. Another study assessing the Rome II criteria reported only limited agreement between physician diagnosis and parent-reported symptoms. These
limitations led to the development of the new Rome III criteria, introduced in 2006. The Rome III criteria have been shown to be more inclusive than the Rome II criteria, and the majority of children with RAP can be classified as having one or more of the FGIDs. Unfortunately, the renewed Rome III criteria failed to improve the diagnostic agreement between pediatric gastroenterologists and gastroenterology fellows compared with the Rome II criteria. Another limitation of the current Rome III criteria is the substantial overlap among FGIDs in children with nausea. The Rome III classification and the definitions for AP-FGIDs are given in Box 2.1.

A range of studies have noted that the majority of children with RAP have no organic pathology that can account for their symptoms. As epidemiology, pathophysiology and treatment options might be different in these distinct disease entities, it could be helpful for both clinicians and researchers to use up-to-date and accepted criteria to diagnose different types of AP-FGIDs to optimize and tailor individual treatment.

**Epidemiology**

The first epidemiological study on RAP was conducted in the UK by Apley and Naish in 1958. This landmark study found that 10.8% of British school children had RAP. Studies published in the 2000s conducted in Western and Asian countries have reported more or less similar prevalence rates of RAP (between 10% and 12%).

Using the Rome III criteria, a school-based study among 1,850 Sri Lankan school children showed that FGIDs related to abdominal pain were highly prevalent. According to this study, FAP, IBS, functional dyspepsia and abdominal migraine were found in 9.7%, 4.9%, 0.6% and 1.9% of children, respectively. Similar to this finding, a study from Colombia reported a prevalence of pain-predominant FGIDs in 27.9% of children (FAP 2.4%, IBS 5.1%, functional dyspepsia 2.4%, abdominal migraine 1.6%). An observational prospective multicenter study showed that among pediatric patients with IBS, constipation-predominant IBS was the prevalent subtype (45%), with a prevalence of 62% in girls ($P<0.005$); diarrhea-predominant IBS was reported in 26% of children, with a prevalence in boys of 69% ($P<0.005$); and alternating-type IBS was described in 29% of children, without a difference between the sexes. By contrast, other studies have reported a female preponderance for IBS, with diarrhea-predominant IBS and mixed-type IBS as the most common forms. The prevalence of functional dyspepsia is reported to vary from 0.3–2.5%, and that of abdominal migraine from 1.0–4.1% in children.
Box 2.1 - ROME III criteria for AP-FGIDs

**Functional dyspepsia***
- Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
- Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e. not IBS)
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the individual’s symptoms

**IBS***
- Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time: improved with defecation; onset associated with a change in frequency of stool; onset associated with a change in form (appearance) of stool
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the individual’s symptoms

**Abdominal migraine‡**
- Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 h or more
- Intervening periods of usual health lasting weeks to months
- The pain interferes with normal activities
- The pain is associated with 2 or more of the following: anorexia; nausea; vomiting; headache; photophobia; pallor
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the individual’s symptoms

**Functional abdominal pain***
- Episodic or continuous abdominal pain
- Insufficient criteria for other FGIDs
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms

**Functional abdominal pain syndrome***
- Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following: some loss of daily functioning; additional somatic symptoms such as headache, limb pain, or difficulty sleeping

*Criteria fulfilled at least once per week for at least 2 months before diagnosis. ‡Criteria fulfilled 2 or more times in the preceding 12 months.

Abbreviation: AP-FGID, abdominal-pain-related functional gastrointestinal disorder.
RISK FACTORS AND PATHOPHYSIOLOGY

The prevailing viewpoint is that the pathogenesis of functional pain syndromes involves the inter-relationship between changes in visceral sensation, so-called visceral hyperalgesia or hypersensitivity, and altered gastrointestinal motility. The symptoms of hypersensitivity are pain and discomfort, whereas the symptoms of altered motility can be diarrhea, constipation, nausea, bloating and distension. Several factors have been linked to this hypersensitivity and altered motility and discussed herein (Figure 2.1).

Figure 2.1 - Pathogenesis of childhood abdominal pain. Several risk factors are associated with changes in visceral hypersensitivity and motility and contribute to the development of functional abdominal pain. Abbreviation: 5-HT, 5-hydroxytryptamine; FGID, functional gastrointestinal disorder.
**Visceral hypersensitivity**

Several investigators have studied visceral sensitivity in children with FAP and IBS.\(^{20-31}\) These studies clearly demonstrate that children with FAP or IBS as a group have a lower sensory threshold for gastric or rectal balloon distension than healthy controls. However, the clinical utility value of this invasive test is debatable as not all patients have abnormal test results.\(^{30}\) Imaging studies of adults with IBS have shown that rectal hypersensitivity is associated with greater activation of the rostral anterior cingulate cortex than in healthy individuals.\(^{32,33}\) To date, it is unknown whether children with IBS have similar reduced sensory thresholds (centrally mediated) that lead to visceral hypersensitivity.

**Gastrointestinal motility abnormalities**

A series of studies have shown an association between abnormalities in physiological function in the stomach and the gastric antrum and AP-FGIDs and RAP. Using a non-invasive ultrasonographical method, delayed liquid gastric emptying and impaired antral motility was found in children with RAP, FAP, IBS or functional dyspepsia.\(^{34-36}\) The gastric emptying rate had a statistically significant negative correlation with symptom severity in children with FAP and functional dyspepsia.\(^{35,36}\) Furthermore, among children with IBS, patients who had been exposed to stressful events had markedly lower gastric emptying rates than patients who had no history of exposure to stress.\(^{34}\) Similarly, several other studies have described that children with functional dyspepsia have abnormal gastric emptying to both solids and liquids.\(^{37,38}\) In addition, using the octanoic acid breath test, Hoffman and Tack\(^{39}\) demonstrated abnormalities in solid emptying in children with functional dyspepsia.

One important physiological function of the proximal stomach is meal accommodation. Abnormalities in meal accommodation are suggested as a possible pathophysiological mechanism for functional dyspepsia in adults.\(^{40,41}\) Two small studies have demonstrated abnormal gastric accommodation to a solid meal in children with functional dyspepsia.\(^{38,42}\)

Muscular activity of the stomach is preceded by gastric electrical activity; therefore, it is possible that children with RAP and FGIDs have abnormal gastric myoelectrical activity. Several studies have demonstrated abnormal electrical rhythms (such as tachygastria and bradygastria) in children with functional dyspepsia.\(^{43,44}\) However, the relationship between abnormal gastric motility and clinical symptoms in children with FGIDs is not completely elucidated: not all children with symptoms have disturbed motility and vice versa.
Early life events

Early life events, such as hypersensitivity to cow’s milk protein, pyloric stenosis, umbilical hernia repair and Henoch-Schönlein purpura, are known to be associated with the development of visceral hyperalgesia and abdominal pain in children.\textsuperscript{45-47} The putative mechanisms include sensitization of spinal neurons, impaired stress response, and/or altered descending limb inhibitory control.\textsuperscript{29} In a rat model, Miranda \textit{et al.}\textsuperscript{48} found that exposure to nociceptive somatic stimuli in the early neonatal period resulted in chronic somatic and visceral hyperalgesia. In addition, the same group of researchers found that neonatal gastric suction also led to visceral hyperalgesia through corticotrophin-releasing factor.\textsuperscript{49} These observations suggest a possibility of the existence of a critical vulnerable period in early development of the nervous system that can be associated with prolonged structural and/or functional alterations that affect pain perception. Stress is a known trigger for symptoms of FAP and IBS.\textsuperscript{50} Therefore, adverse events in early life might give rise to long-lasting or permanent alterations in central nervous system responses to stress and bowel sensitivity, thereby inducing an increased susceptibility to the development of FGIDs.\textsuperscript{49}

Psychological factors

Psychological stress has long been recognized as a risk factor for the development of FGIDs in children. Several patient studies have shown an association between RAP and exposure to stressful events.\textsuperscript{51-55} In children this stress can be, for example, separation from the best friend at school, failure in an examination, loss of a parent’s job and hospitalization.\textsuperscript{19,25,56} In addition, exposure to abuse is also an important risk factor for abdominal pain in children.\textsuperscript{57} Studies among adults have shown an association between abuse as a child and development of IBS in later life.\textsuperscript{58} Also, in children, an association was found between all three types of child abuse (physical, emotional and sexual) and AP-FGIDs.\textsuperscript{15,27} Furthermore, anxiety and depression were reported to be substantially more frequent among children with FGIDs than in healthy children.\textsuperscript{59-63}

How these psychological factors lead to the development of FGIDs is still debated. Depression and anxiety can be the result of ineffective mechanisms of coping with stress, as limited coping strategies are demonstrated in children with chronic abdominal pain.\textsuperscript{64} This finding might also account for the association with traumatic life events. In addition, stressors have been shown to be associated with enhanced visceral perception.\textsuperscript{65} Several functional MRI studies have shown that abuse and related stresses lead to activation of the anterior mid cingulate and posterior cingulate cortices.\textsuperscript{66} Furthermore, a simultaneous deactivation of the anterior cingulate cortex supragenual region, an area associated with the down regulation of pain signals, was noted in
adults with FGIDs. Animal studies have shown that exposure to stress predisposes them to develop stress-induced visceral hypersensitivity, altered defecation, intestinal mucosal dysfunction, alterations in the hypothalamo–pituitary–adrenal (HPA) axis and disruption of the intestinal microbiota. Similarly, studies conducted in adults with IBS have revealed stress-induced alterations in gastrointestinal motility, visceral sensitivity, autonomic dysfunction and HPA axis dysfunction. Therefore, it is possible that, through the same mechanisms, abuse and stress lead to the alteration of both the HPA and brain–gut neural axes, predisposing individuals to develop FGIDs.

**Inflammation of the intestinal mucosa**

Faure and colleagues have analyzed the inflammatory cells in the colonic and gastric mucosa of children with functional dyspepsia or IBS. Of 12 patients with IBS, 11 had minimal inflammation of the intestinal mucosa, whereas 9 of 17 patients with functional dyspepsia had variable degrees of inflammation; however, the place of inflammation was not specified, which is a drawback of this important study. Another study noted that 71% of children evaluated for suspected functional dyspepsia had duodenal eosinophilia (>10 eosinophils per high-power field of view). However, the real clinical utility of such findings is still not clear.

**Mast cell dysfunction and 5-hydroxytryptamine**

5-hydroxytryptamine (5-HT, serotonin) is considered to be an important regulatory chemical compound in the brain–gut axis. 5-HT is released by the enterochromaffin cells of the intestinal mucosa and its action is regulated by the 5-HT selective reuptake transporter (also known as sodium-dependent serotonin transporter, SERT) and organic cation transporter-1 (OCT-1). Studies have shown variable results of 5-HT signaling in colonic mucosa in adults with IBS. One study conducted in children with either IBS or functional dyspepsia was unable to demonstrate increased numbers of enterochromaffin cells in the gastric mucosa of children with functional dyspepsia or the colonic mucosa of children with IBS. However, the 5-HT content in the colonic mucosa was increased in the IBS group and normal in the gastric mucosa of individuals with functional dyspepsia. No difference of TPH1 (tryptophan 5-hydroxylase 1, the rate-limiting enzyme in the synthesis of 5-HT) mRNA expression was observed in the gastrointestinal biopsy samples of both those with IBS or functional dyspepsia compared with controls. Children with IBS had lower expression of SERT mRNA in the rectal mucosa than healthy controls. These findings indicate that children with IBS have an increased availability of 5-HT in their rectal mucosa. Possibly, 5-HT interacts with peripheral nerves in the submucosa and contributes to the development of abdominal pain through heightening visceral sensitivity and stimulating pain pathways in children with FGIDs.
**Human gut microbiota**

Alteration of the gut microbiota has long been considered as a potential mechanism for the development of pain-predominant FGIDs. In an elegant study, Saulnier *et al.*\(^7^8\) noted that children with IBS had a greater proportion of the phylum Proteobacteria, and genera such as *Dorea* (a member of Firmicutes) and *Haemophilus* (a member of Proteobacteria); in addition, it was also noted that species such as *H. parainfluenzae* and *Ruminococcus* were more abundant and Bacteroides were markedly less abundant in children with IBS than healthy individuals as controls.\(^7^8\) Another study comparing the fecal microbiota of healthy children and pediatric patients with diarrhea-predominant IBS noted that levels of *Veillonella*, *Prevotella*, *Lactobacillus* and *Parasporobacterium* were increased in patients with IBS, whereas a reduction in levels of *Bifidobacterium* and *Verrucomicrobium* was reported.\(^7^9\) Although further studies are needed to clarify and clearly identify the exact changes in the gut microbiota of children with FGIDs, these research efforts provide some insight to the possibility of alteration of the microbiota leading to symptom generation. These microbes might alter visceral perception, gut motility, intestinal gas production and gut permeability with their metabolites leading to pain-predominant FGIDs.\(^8^0,8^1\)

**Genetic and environmental factors**

Genetic and environmental factors have long been considered as risk factors for the development of pain-predominant FGIDs. In a genome-wide association study in adults, a locus on chromosome 7p22.1 has consistently been shown to be associated with a genetic risk of developing IBS, although it still did not reach genome-wide significance in the meta-analysis of combined index and replication findings.\(^8^2\) The most convincing genetic association is with the *TNFSF15* polymorphism, which has been observed in three independent cohorts in Sweden, the USA and England.\(^8^3,8^4\) The *TNFSF15* polymorphism has been associated with constipation-predominant IBS, diarrhea-predominant IBS and postinfectious IBS phenotypes. TL1A, the protein encoded by *TNFSF15*, modulates inflammatory responses, which supports the role of immune activation in IBS.\(^8^3,8^4\) A twin study, performed by Levy *et al.*,\(^8^5\) showed a 17% concordance for IBS in monozygotic twin patients, with only 8% concordance in dizygotic twins, supporting a genetic contribution to IBS. This study, however, also showed that a parental history of IBS was a stronger predictor of developing IBS than having a twin with IBS, suggesting that social learning is much more important than genetic factors. Furthermore, Buonavolonta *et al.*\(^8^6\) noted that parents of children with FGIDs have a higher prevalence of similar diseases than parents of children without FGIDs. Another study found that children of parents with IBS tend to use health care substantially more for gastrointestinal problems than children of parents who do not have IBS.\(^8^5\)
In addition, parental response to a child’s pain behaviors seems to be a key factor in the development and recurrence of FAP, and interventions that target changes in parental responses can decrease complaints of pain and other illness behaviors in children.\textsuperscript{87} In addition, high somatization scores in mothers and fathers are associated with high somatization scores in children with RAP.\textsuperscript{88} Parents’ over-reactive behavior during pain episodes probably influences not only the frequency and intensity of the abdominal pain but also the cognition of pain and extraintestinal somatic symptoms, which are an integral part of FAP. These findings suggest the possibility of genetic predisposition and social and environmental susceptibility to developing pain-predominant FGIDs.

Postinfectious causes

Studies in adults have established the possibility of developing IBS after an episode of acute gastroenteritis.\textsuperscript{89} The possible mechanisms are genetic predisposition, psychological status during infection, acute inflammation leading to alteration of 5-HT metabolism, sensitivity of enteric neurons, ongoing immune cell activation in the gastrointestinal tract and an altered gut microbiota.\textsuperscript{90} In one study, children developed IBS after exposure to an outbreak of \textit{Escherichia coli} gastroenteritis. Female sex, increased duration of symptoms, use of antibiotics and weight loss were statistically significant risk factors for developing IBS in this group of children.\textsuperscript{91} On the other hand, it has been shown that rotavirus gastroenteritis does not seem to be a risk factor for FGIDs in children.\textsuperscript{92}

CLINICAL EVALUATION

A comprehensive history-taking and physical examination of children with AP-FGIDs are essential to rule out most organic causes. Alarm symptoms that might be related to organic causes of AP-FGIDs are summarized in Box 2.2.\textsuperscript{93} Several studies evaluating the medical history of children with chronic abdominal pain have provided some evidence that frequency, severity, location and timing (postprandial or waking during night) of abdominal pain do not help distinguish between organic abdominal pain and FAP.\textsuperscript{93,94}

Abdominal pain diaries can be helpful in clarifying details of the abdominal pain and possible triggering factors, such as specific foods or stressors. An assessment of the stool pattern can differentiate between different subtypes of AP-FGIDs. Furthermore, dietary history and the history of previous treatment strategies for AP-FGIDs should be investigated. Owing to the high degree of association of AP-FGID with a range of psychological problems, particular attention
must be paid to this part of the history. Children suspicious for any psychological disorder should be referred to a mental health professional.

The physical examination should consist of a basic abdominal examination to identify any obvious abnormalities rather than to confirm a diagnosis of an AP-FIGDs. A lack of physical findings might be reassuring to both physician and patient.

**Box 2.2 - Warning symptoms in childhood AP-FIGIDs**

**Historical findings**
- Persistent right upper or right lower quadrant pain
- Persistent vomiting
- Gastrointestinal blood loss
- Chronic severe diarrhea
- Involuntary weight loss
- Unexplained fever
- Family history of IBD, coeliac disease or familial Mediterranean fever

**Examination findings**
- Deceleration of linear growth
- Uveitis
- Oral lesions
- Skin rashes
- Icterus
- Anaemia
- Hepatomegaly
- Splenomegaly
- Arthritis
- Costovertebral angle tenderness
- Tenderness over the spine
- Perianal abnormalities

Abbreviation: AP-FID, abdominal-pain-related functional gastrointestinal disorder.

**LABORATORY INVESTIGATIONS**

Although no evidence is available to evaluate the predictive value of laboratory tests, in general, urinalysis, blood analysis and stool analysis are often ordered by clinicians to distinguish between organic and FAP.95 Notably, performing multiple tests might provide nonspecific results that are unrelated to the presenting symptom or have no clinical relevance, which might cause confusion and lead to further invasive testing and procedures.96 A limited and reasonable screening protocol could include a complete blood cell count, levels of C-reactive protein and screening for coeliac disease. If a child has diarrhea alongside abdominal pain, one might
consider stool analysis for infection with *Giardia lamblia*. Several studies have investigated the prevalence of lactose intolerance in children with abdominal pain, but elimination of lactose often does not result in resolution of abdominal pain.\textsuperscript{97,98} Also, *Helicobacter pylori* infection can be found in children with RAP.\textsuperscript{99} This finding does not, however, necessarily indicate a causal relationship between the two, as children with *H. pylori* infection are not more likely to have abdominal pain than children without *H. pylori* infection.\textsuperscript{100} In the past few years, elevated concentrations of fecal calprotectin has been shown to be a valuable biomarker in diagnosing IBD in children.\textsuperscript{101} A study in 126 children with an FGID showed fecal calprotectin concentrations within the normal limit; therefore, this approach seems to be a useful and noninvasive test for distinguishing between FAP and IBD in these children.\textsuperscript{102} A proposed diagnostic flowchart is shown in Figure 2.2.

![Figure 2.2 - Diagnostic algorithm for childhood functional abdominal pain. Abbreviations: CBC, complete blood count; CRP, C-reactive protein; FGID, functional gastrointestinal disorder.](image-url)
Radiological and endoscopic investigations

A retrospective study in 644 children with RAP showed that abdominal abnormalities were detected by ultrasonographical examination in just 2% of patients. When atypical symptoms were present, such as jaundice, vomiting, back or flank pain, urinary symptoms or abnormal findings on physical examination, abnormalities observed by ultrasonography increased to 11%. Ultrasonography should therefore only be used in children with RAP and atypical clinical features. A prospective study of 290 children with chronic abdominal pain demonstrated a diagnostic value of esophagogastroduodenoscopy in 38% of the children. At least two alarm symptoms were predictive of diagnostic yield, but without alarm symptoms the diagnostic yield was still 34%, including reflux esophagitis ($n = 16$), eosinophilic esophagitis or gastroenteritis ($n = 6$), erosive esophagitis ($n = 1$), coeliac disease ($n = 1$) and $H. pylori$ infection ($n = 1$). However, medical therapy started after identification of the disorders was effective in only 67% of children during the year after diagnosis, questioning the relationship between the abnormalities found during endoscopy and the clinical symptoms. When presenting with functional dyspepsia, abnormalities have been shown in only 6.3% of children. The use of esophagogastroduodenoscopy in the presence of alarm symptoms might be considered in the diagnostic work-up of chronic abdominal pain in children.

MANAGEMENT STRATEGIES

Treatment of children with an AP-FGIDs starts with explaining the diagnosis to the parent(s) and child. The Rome III criteria encourage physicians to make a positive diagnosis of an AP-FGID rather than using exhaustive investigations to exclude an underlying organic cause. A multidisciplinary approach to management of childhood AP-FGIDs might be needed in case of social and psychological comorbidities. The primary goal of therapy might not always be complete eradication of pain, but resumption of a normal lifestyle with regular school attendance, normal sleep pattern and participation in extracurricular activities. An active listening approach of the physician and an encouraging attitude towards treatment helps improve the patient’s responses to therapeutic attempts. Furthermore, parents should be informed that a solicitous response (specifically showing concern or anxiety) by parents might negatively influence the treatment outcomes in children. In instances of persisting symptoms and serious disruption of a child’s well-being, pharmacological therapy or non-pharmacological treatment can be considered. If possible, treatment should be individualized, taking into account risk factors, comorbidities and personal preferences of each patient and their parents. A therapeutic flowchart for AP-FGIDs is shown in Figure 2.3.
**Pharmacological treatment**

Evidence for pharmacological treatment in children with AP-FGIDs is very low, only a few placebo-controlled randomized controlled trials (RCTs) are available, as detailed in a systematic review. Pharmacotherapeutic agents used to treat AP-FGIDs encompass antispasmodic agents, antidepressants, antireflux agents, antihistamine agents and laxatives. The role of placebo in functional disease in general is substantial and will therefore be discussed separately before addressing the efficacy of the different drugs used in children with AP-FGIDs.

![Flowchart](image-url)  

*Figure 2.3 - Therapeutic algorithm for childhood functional abdominal pain. Abbreviations: CBT, cognitive behavioral therapy; FGID, functional gastrointestinal disorder.*
The role of placebo

Owing to a strong placebo response, several studies\textsuperscript{109,110} have failed to demonstrate a statistically significant benefit of an intervention, although an absolute improvement was seen in the trial by Saps \textit{et al.}\textsuperscript{110} that evaluated the effect of amitriptyline compared to placebo. These researchers hypothesized that the placebo effect was due to a high level of expectancy of the children and the parents, and the frequent contact between the doctors and the patients.\textsuperscript{110} Furthermore, it is known that an active listening approach and encouraging attitude towards treatment help improve patient responses to both therapeutic attempts and placebo.\textsuperscript{111,112} On the other hand, a strong placebo response might point towards variation in the natural course of disease or fluctuations in symptoms.\textsuperscript{113} A physician should keep in mind that all these components can result in a 50\% chance of improvement, no matter which medication is prescribed.\textsuperscript{109,110}

Antispasmodics

Antispasmodic agents are thought to be helpful in the treatment of AP-FGIDs through their effects on decreasing smooth muscle spasms in the gastrointestinal tract, resulting in a reduction of abdominal pain.\textsuperscript{114} These agents are effective in adults with IBS.\textsuperscript{115} Two pediatric trials have evaluated the effect of antispasmodic agents compared with placebo.\textsuperscript{116,117} Kline \textit{et al.}\textsuperscript{116} compared peppermint oil to placebo in 50 children with IBS—the menthol component of peppermint oil is known to block Ca\textsuperscript{2+} channels,\textsuperscript{118,119} which might lead to reduction of colonic spasms.\textsuperscript{120} After 2 weeks, 76\% of children receiving peppermint oil reported improvement in severity of symptoms versus 19\% of children receiving placebo (\(P<0.001\)). Unfortunately, no follow-up data were available. Another trial investigated the efficacy of mebeverine in 115 children with FAP.\textsuperscript{117} Mebeverine is considered an antispasmodic owing to its anticholinergic effects on smooth muscles.\textsuperscript{121} After 4 weeks of treatment and 12 weeks of follow-up, no statistically significant effect on abdominal pain was shown compared to placebo. Both studies were affected by a high drop-out rate, 16\% and 24\% for the peppermint oil and mebeverine trial, respectively. Notably, peppermint oil and mebeverine were well tolerated.

Antidepressants

Antidepressants, such as tricyclic antidepressants and selective 5-HT-reuptake inhibitors, are used as a therapy for AP-FGIDs.\textsuperscript{122} Amitriptyline (a tricyclic antidepressant) works primarily by inducing pain tolerance through peripheral or central antinociceptive properties and anticholinergic effects when administered in low doses.\textsuperscript{123} Beneficial effects have been shown in the treatment of adults with IBS\textsuperscript{124} and functional dyspepsia.\textsuperscript{125} However, these effects were not confirmed in pediatric AP-FGIDs, when comparing amitriptyline to placebo.\textsuperscript{110,126} Saps \textit{et al.}\textsuperscript{110}
included 90 children with AP-FGIDs; 59% of children receiving amitriptyline compared to 53% receiving placebo reported feeling better after 4 weeks treatment, a difference that was not statistically significant. Bahar et al.\textsuperscript{126} investigated the efficacy of amitriptyline for 8 weeks in 33 adolescents with IBS. An inconsistent improvement of pain and no statistically significant improvement in any IBS-related symptoms were found. However, children receiving amitriptyline reported significantly greater improvements in overall quality of life scores at week 6, 10 and 13 ($P = 0.019$, $P = 0.004$ and $P = 0.013$, respectively).\textsuperscript{126} Adverse events were only reported in the study by Saps and colleagues;\textsuperscript{110} two children in the amitriptyline group dropped out due to fatigue, rash and headaches. An association between dose-response of tricyclic antidepressants with prolongation of corrected QT interval has been demonstrated;\textsuperscript{127} therefore, a screening echocardiogram should always be performed before initiating amitriptyline therapy.\textsuperscript{128} In addition, preliminary results of a small study suggest that low doses of amitriptyline can be considered as a safe drug in children with AP-FGIDs.\textsuperscript{129}

Two trials describe the effectiveness of selective 5-HT-reuptake inhibitors in the pediatric AP-FGID population, both investigating citalopram. In a small open-label trial, Campo et al.\textsuperscript{130} included 25 children (aged 7–18 years) with RAP who were treated for 12 weeks. Abdominal pain, anxiety, depression, other somatic symptoms and functional impairment all improved markedly compared with baseline. However, these promising results were not confirmed by a second placebo-controlled randomized trial in 115 children (aged 6–18 years) with FAP receiving citalopram for 4 weeks.\textsuperscript{131} No statistically significant difference was observed in treatment response rate between citalopram and placebo at week 4 (40.6% versus 30.3%, $P = 0.169$) and at 12 weeks follow-up (52.5% versus 41.0%, $P = 0.148$). The study was, however, conducted in a tertiary-care setting and the results might not be generalized to other pediatric-care settings. The quality of the study was limited due to a drop-out rate >20% and important differences in baseline characteristics of the study participants.

**Antireflux agents**

One placebo-controlled RCT evaluated the efficacy of a H2 receptor antagonist, famotidine. See et al.\textsuperscript{132} included 25 children with RAP and dyspeptic symptoms who received famotidine twice daily for 3 weeks. In cases of persisting symptoms, after crossing over, treatment continued for another 3 weeks. A notable benefit of famotidine compared with placebo was found when assessing global symptom improvement (67% versus 15%, $P = 0.015$). However, no substantial decrease in abdominal pain was demonstrated. Famotidine inhibits gastric acid secretion\textsuperscript{133} and is therefore promising in patients with dyspeptic symptoms. No controlled studies on the use of
PPIs in children with FAP are available. Among adults with nonulcer dyspepsia, PPIs were markedly more effective than placebo in the reduction of dyspeptic symptoms.\textsuperscript{134}

\textit{Antihistaminic agents}
Cyproheptadine is an antihistaminic agent with possible Ca\textsuperscript{2+} channel blocking and anti-5-HT effects.\textsuperscript{135–137} Because of its anti-5-HT effect, cyproheptadine was hypothesized to be effective in pediatric AP-FGIDs. In a double-blind placebo-controlled trial, a beneficial effect of cyproheptadine was demonstrated in 29 children with FAP.\textsuperscript{138} After 2 weeks of treatment a significant improvement in abdominal pain frequency ($P = 0.002$), pain intensity ($P = 0.001$) and global improvement ($P = 0.005$) was demonstrated. Nevertheless, results should be interpreted cautiously because of the small sample size and limited follow-up of only 2 weeks. Furthermore, a small retrospective trial evaluated the effect of cyproheptadine in children with abdominal migraine. After treatment, 83\% of the children reported an excellent or fair response and 17\% reported no response.\textsuperscript{139} Duration of treatment varied between 10 months and 3 years. Large clinical trials with longer follow-up periods are needed to confirm these results.

\textit{Laxatives}
No RCTs evaluating the effect of laxatives in the treatment of children with AP-FGIDs are available. In the past decade, new laxatives such as lubiprostone and linaclootide have been shown to be effective in treating adults with constipation-predominant IBS, without serious adverse effects.\textsuperscript{140} Still, these drugs have not yet been evaluated in children with the same condition.

\textit{Nonpharmacological treatment}

\textbf{Dietary interventions}
Food might trigger symptoms in AP-FGIDs;\textsuperscript{141} however, recognition of specific food components triggering symptoms is difficult. Malabsorption and intolerance to carbohydrates are commonly indicated as an underlying cause. Fermentation of malabsorbed carbohydrates by the colonic microbiota could result in symptoms of carbohydrate intolerance, including abdominal pain, bloating, borborygmi, flatulence and diarrhea.\textsuperscript{142} Therefore, carbohydrates such as lactose have been the major target of dietary modification for functional gut symptoms.\textsuperscript{143} Restriction of lactose, however, did not result in symptom improvement in children with RAP.\textsuperscript{144,145} In addition, in a study published in 2012, neither lactose intolerance nor fructose intolerance could be established as a cause of RAP in 220 children.\textsuperscript{98} Attention has been drawn to diets low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP). Avoiding poorly absorbed short-chain carbohydrates could result in improvement of gastrointestinal...
symptoms, and has already shown promising results in adults with IBS. A randomized, double-blind, crossover trial in 33 children with IBS showed a decrease in frequency of abdominal pain after 48 h of a low FODMAP diet compared with a high FODMAP diet. Low FODMAP diets seem to be effective, but more (long-term) studies are needed to further assess their efficacy and safety. In addition, intake of numerous regular food products had to be eliminated or markedly reduced, very strictly, which can make maintenance of this diet problematic for children and their parents.

Dietary fibres are carbohydrates that are not hydrolyzed or absorbed in the upper part of the gastrointestinal tract. Fibre is thought to improve bowel function by softening stools and enhancing colonic transit, though there is the unwanted adverse effect of increasing gas production. Historically, increasing dietary fibre intake has been a standard recommendation for patients with IBS, but the efficacy of this approach is controversial. Four pediatric trials evaluating fibre supplementation did not show a favorable effect in children with chronic abdominal pain. Horvath et al. performed a meta-analysis of three RCTs including data from 182 children using psyllium fibre or glucomannan. After pooling, there was no significant difference in experiencing ‘no pain’ and/or ‘satisfactory improvement’ between the fibre group (52.4%) and placebo group (43.5%); (relative risk [RR] 1.17, 95% CI 0.75–1.81). Only partially hydrolyzed guar gum resulted in a significant improvement in frequency of IBS symptoms compared with placebo (43% versus 5%, P = 0.025), but no effect on pain intensity was seen. No serious adverse events were reported in any of the trials.

**Probiotics**

The gut microbiota can directly influence intestinal homeostasis by affecting bowel motility and modulation of intestinal pain, immune responses and nutrient processing, whereas alterations of these bacteria can distort the homeostasis. As differences have been found in the gut microbiota of children and adults with IBS compared with healthy controls, it seems prudent to try to improve AP-FGID-related symptoms with probiotics.

A meta-analysis of five pediatric RCTs reported a significantly higher treatment success of *Lactobacillus rhamnosus GG, Lactobacillus reuteri DSM 17938 and VSL#3* compared with placebo (pooled RR 1.50; 95% CI 1.22–1.84). Subgroup analysis showed results being mainly applicable for IBS (pooled RR 1.62; 95% CI 1.27–2.06). Future research needs to determine which species, specific strains and combinations of strains of probiotics are most efficacious in AP-FGIDs, or whether probiotic treatment should be adapted to the disturbances in the gut microbiota of the individual patient.
Cognitive behavioural therapy

Acceptance of the biopsychosocial model of FGIDs has provided the basis for the use of psychosocial interventions, including family therapy, cognitive behavioral techniques (CBT), relaxation, hypnotherapy, guided imagery and biofeedback. CBT aims to change attitudes, cognitions and behavior from children and parents that might have a role in generating or maintaining symptoms. Eight RCTs have been conducted in children with RAP. Four trials evaluated the efficacy of family-orientated CBT (CBT-family) compared with standard care, all of which showed beneficial effects in favor of CBT-family. Levy et al. included 200 children and adolescents in their trial and the results are therefore of particular interest owing to the large size of the cohort. A greater decrease in gastrointestinal symptom severity (estimated mean difference [MD], −0.36; 95% CI, −0.63 to −0.01) and greater improvements in pain coping responses (estimated MD 0.61; 95% CI 0.26−1.02) were still reported 12 months after CBT-family. However, two studies that corrected for patient-therapist time, by comparing it with physiotherapy or with supportive sessions with the pediatric gastroenterologist did not find compelling evidence for CBT, suggesting that the time spent with child and parents is one of the most important components of therapy. This notion was also suggested by the results of Humphreys et al, who divided 64 patients (4–18 years) into four groups comparing CBT, dietary fibre supplementation, biofeedback and parental support in different combinations. Results were only statistically significant when data from individual CBT, biofeedback and parental support were combined and compared with fibre. In conclusion, CBT has shown efficacy, especially when patients’ families are involved, although its working mechanism seems highly influenced by patient-therapist time.

Hypnotherapy

Gut-directed hypnotherapy is a trance-based therapy in which a therapist gives the client suggestions aimed at changing intestinal hypersensitivity, ego-strengthening and stress reduction. The mechanisms by which gut-directed hypnotherapy acts in improving abdominal symptoms in FAP and IBS are still not well understood, but beneficial effects are reported in adult and pediatric trials with long-lasting effects. Some evidence exists that gut-directed hypnotherapy affects IBS through a combination of effects on gastrointestinal motility, visceral sensitivity, psychological factors, and/or effects within the central nervous system. After performing a systematic review (including three RCTs), Rutten et al. concluded that the therapeutic effects of hypnotherapy seem superior to standard medical care in children with FAP or IBS. Hypnotherapy was given in individual or group sessions with qualified therapists or by self-exercises on CD. Effects persist up to 5 years after treatment. These results
were supported by a trial comparing hypnotherapy to a waiting list control group in 38 children with FAP and IBS. 55% of children showed a decrease of 80% in abdominal pain after hypnotherapy, compared with 5.6% of waiting list controls (RR 9.90; 95% CI 1.14–69.28; \( P = 0.002 \)). To date, no studies have compared CBT with hypnotherapy in children or adults with FGIDs.

**Complementary and alternative medicine**

The NIH defines complementary and alternative medicine (CAM) as a group of diverse medical and health-care systems, practices and products that are not presently considered to be part of conventional medicine. CAM comprises many different treatment modalities, including acupuncture, yoga, homeopathy, mind–body therapy and musculoskeletal manipulations. Although >40% of children with IBS and FAP use some form of CAM, data on efficacy and safety of almost all forms of CAM in these children and adolescents is lacking. Two RCTs compared yoga to a waiting list in adolescents and young adults with IBS. Beneficial effects in adolescents were seen in functional disability, gastrointestinal symptoms and physical functioning, but no statistically significant improvement of abdominal pain was observed. No other pediatric trials regarding CAM have been formally published.

**PROGNOSIS AND LONG-TERM FOLLOW-UP**

Several longitudinal epidemiological studies have been performed and link pediatric FAP to abdominal pain later in life. A comprehensive systematic review evaluating the prognosis of chronic abdominal pain in 1,331 children demonstrated persisting symptoms in 29.1% of the children after 5 years (median, range 1–29 years) follow-up even when they had received treatment for the pain. In 2014, Horst et al. studied 392 children with AP-FGIDs, of whom 41% still met the criteria for AP-FGIDs after 9 years follow-up. Furthermore, there is evidence from prospective studies that adults with IBS began experiencing recurrent FAP as a child. In particular, females are more likely to meet IBS criteria in adulthood. However, another study demonstrated that persistent abdominal pain in childhood did not predict abdominal pain in adulthood. Instead of persisting abdominal pain symptoms in adulthood, some study authors have concluded that these children are at an increased risk of adult psychiatric disorders, such as anxiety and depressive disorders. This finding was also shown for children with dyspepsia; both children with and without abnormal histological findings were at increased risk of chronic dyspeptic symptoms, anxiety disorder and reduced quality of life in adolescence and young adulthood.
Several factors influence the prognosis of childhood AP-FGIDs. Children with a history of chronic abdominal pain had a four times higher risk of persistent abdominal pain than children who presented for the first time with chronic abdominal pain. The longer the duration of follow-up, the worse was the prognosis, with symptoms persisting in 25.4% of patients at 1–5 years follow-up increasing to 37.4% of patients at ≥10 years follow-up. In addition, the presence of nongastrointestinal symptoms, such as back pain, headaches, dizziness, weakness and low energy, at the initial pediatric evaluation was associated with an increased likelihood of FGIDs in adolescence and young adulthood. Furthermore, a positive family history of anxiety, RAP or IBS and depressive symptoms are important determinants of persistent abdominal pain in adulthood.

CONCLUSIONS
AP-FGIDs in childhood are a common problem worldwide. Enhancements of the terminology and the introduction of the Rome criteria have encouraged health-care providers to make a positive diagnosis and have advanced empirical research in childhood AP-FGIDs. Increased knowledge of the pathophysiology has led to a biopsychosocial model, in which genetic, physiological and psychological factors interplay. Potential targets for pharmacological and non-pharmacological therapy are arising from this model. To date, high-quality efficacy studies of treatment in pediatric AP-FGIDs are scarce. Available evidence indicates beneficial effects of hypnotherapy and CBT-family. Evidence for a low FODMAP diet and probiotics is promising, as well as for drug treatment such as peppermint oil, cyproheptadine or famotidine, but well-designed trials with long-term follow-up are needed to confirm these preliminary results. The use of homogeneous outcome measures, sufficient sample size and a control arm are necessary. Future research should focus on identifying factors predicting response to optimize and tailor individual treatment.

REFERENCES


