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Review Article

Pediatric Functional Gastrointestinal Disorders: Pathophysiology, Diagnosis and Management

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Abstract

Functional Gastrointestinal Disorders (FGIDs), also recently referred to as disorders of gut-brain interaction, are common in the pediatric population and vary according to age groups, i.e., neonatal/toddler and child/adolescent FGIDs. Pediatric FGIDs tend to evolve and persist into adulthood, contributing to financial burdens and psychological problems. Despite several decades of progress and advancements in molecular biology and medical sciences, the exact pathophysiology remains unknown, although genetic, psychosocial, gut dysbiosis, visceral hypersensitivity, and neuroimmune causes have been implicated. The ROME IV criteria facilitate easier and earlier diagnosis of FGIDs, excluding organic causes while minimizing unnecessary investigations. Dietary, psychosocial, neuro-stimulatory, and pharmacological management methods exist, although fewer trials have focused on pediatric drug-based management. Early identification and appropriate treatment hold the potential for cure and improvement in quality of life.

Introduction

Functional Gastrointestinal Disorders (FGIDs), recently referred to as disorders of gut-brain interaction, are conditions that cannot be easily attributed to any structural, biochemical, or organic abnormalities.[1] A child is not a miniature adult, and similarly, the FGID spectrum varies from infancy to adulthood. The ROME criteria, established in the late 20th century, have been updated periodically based on clinical experience and scientific evidence. The latest version, ROME IV, has been in use since 2016. Even within the pediatric age group, FGIDs are classified for both neonates/toddlers (< four years) and children/adolescents (four to 18 years).[1,2] Infant regurgitation, infant rumination syndrome, cyclic vomiting syndrome, infant colic, functional diarrhea, infant dyschezia, and functional constipation constitute the neonate/toddler age group. Meanwhile, functional nausea and vomiting disorders (cyclic vomiting syndrome, functional nausea, functional vomiting, rumination syndrome, aerophagia), functional abdominal pain disorders (functional dyspepsia, irritable bowel syndrome, abdominal migraine, functional abdominal pain not otherwise specified), and functional defecation disorders (functional constipation, non-retentive fecal incontinence) constitute the children/adolescent age group.[1,2] The inability of children to express the exact nature of their problem and the changing developmental factors make it challenging to diagnose, study, and treat pediatric FGIDs.[3]

Most pediatric FGIDs may evolve and continue into adulthood, contributing to significant morbidity, absenteeism, expenditure, and reduced quality of life.[4–6] FGIDs significantly burden the healthcare system, contributing to both inpatient and emergency visits.[7,8] They are also associated with various psychological problems such as low self-esteem, childhood trauma, anxiety, and depression.[9–11] Health-related quality of life in pediatric FGID patients was lower in all domains compared to healthy children.[12,13] A recent systematic review of 20 studies, including a total of 18,935 children, showed the median prevalence of FGID in children under four years to be up to 22.2%, and in those aged four to 18 years, up to 21.8%. Infant regurgitation dominated in the under 12 months age group, functional constipation, and cyclic vomiting dominated in the 13–48 month age group and functional constipation, functional dyspepsia and irritable bowel syndrome dominated in the over four years age group.[13] Moreover, older children are more likely to qualify for FGIDs, especially functional dyspepsia, if their parents also qualify for the same.[14] In this review, we discuss the latest advances in our understanding of the mechanisms and management of common pediatric FGIDs.

Keywords: Functional gastrointestinal disorders; ROME criteria; Functional abdominal pain; Functional constipation; Gut-brain axis; Irritable bowel syndrome.
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Diagnosis

Diagnosing FGIDs can be challenging, with physicians often going the extra mile to investigate for organic causes, leading to costly expenditures. The ROME IV criteria are predominantly symptom-based with less emphasis on investigations. Nonetheless, a detailed history and thorough clinical examination are essential, including an assessment of stressors, psychosocial factors, and past medical or drug history.[15] It is crucial to be aware of red flag signs such as declining weight and height, delayed puberty, painful swallowing, bile-stained or persistent vomiting, bleeding, localized pain away from the umbilicus, fever, arthritis, perianal disease, and a family history of inflammatory bowel disease, or celiac disease, etc.[16] Among the various lab tests available, fecal calprotectin and celiac markers are the most cost-effective investigations for a child presenting with an irritable bowel syndrome (IBS) phenotype, with the role of endoscopy being limited.[17–19] Providing reassurance, acknowledging the symptoms, educating the parents, and guiding them to appropriate therapy forms the cornerstone of successful management. An earlier diagnosis, especially during the first visit, can significantly improve recovery outcomes for children (hazard ratio 2.1, 95% confidence interval 1.0 to 4.5).[20]

Neonate/Toddler FGID

Infant regurgitation

Involuntary movement of gastric contents into the mouth, nose, or esophagus is common in infants between three weeks and 12 months of age. It should occur at least twice per day for at least three weeks without any retching, failure to thrive, apnea, feeding difficulty, or posturing. The estimated prevalence is 41–67%.[2]

Infant rumination syndrome

This condition is rare compared to regurgitation. It involves effortless regurgitation of food, which is chewed and re-swallowed, accompanied by repetitive contractions of abdominal muscles, lasting for at least two months. Its estimated prevalence is 1.9%.[2] The onset is between three to eight months of age, without any distress, and usually does not occur during sleep. It has been considered a self-stimulatory mechanism in a child with maternal emotional and sensory deprivation or neglect.[21]

Cyclic vomiting syndrome

This condition involves stereotypical and repetitive episodes of vomiting lasting hours to days, with episodes separated by weeks to months of return to baseline. For diagnosis, it must occur at least twice within six months. The estimated prevalence is 3.4%.[2] Although it has a wide range of onset ages, an onset before two years of age might warrant metabolic, neurological, or anatomical testing for more serious conditions.[22]

Infant colic

This condition has an onset before five months of age and is characterized by recurrent and prolonged irritability, fussing, and crying without any obvious cause and no evidence of failure to thrive. These episodes should last for at least 3 h a day, three days a week, or in a 24-hour behavior diary record of 3 h of crying with fussing. About 5–19% of infants are thought to have infant colic.[2]

Functional diarrhea

Painless and recurrent passage of four or more well-formed stools, lasting for a minimum of four weeks without any failure to thrive in a child aged six months to 60 months, constitutes functional diarrhea. About 6–7% of infants have functional diarrhea.[2]

Infant dyschezia

This condition has an onset before nine months of age, without any other red flag signs, and involves at least 10 m of crying and straining before the passage of soft stools. The estimated prevalence is about 2.4%.[2]

Functional constipation

A child who is afraid of the unpleasant evacuation of the rectum voluntarily withholds feces, leading to overabsorption of water and hard stools that further cause painful defecation. This condition is called functional constipation.[23] For children up to four years of age, it should include at least two of the following features: history of stool retention, hard painful bowel movements, larger diameter stools, fecal mass in the rectum, with two or fewer defecations per week. For a toilet-trained child, it can involve at least one episode of incontinence or large stools clogging the toilet. About 3–27% of children are found to have functional constipation.[2]

Child/Adolescent FGID

Cyclical vomiting

Diagnosing cyclical vomiting in older children is similar to that in younger children, with an emphasis on ruling out other medical conditions. The estimated prevalence is 0.2–1.0%.[1]

Rumination syndrome

One significant change for older children is that it can occur secretly without the parents' knowledge. It does not occur during sleep and involves no retching, but begins as soon as food is taken. Eating disorders and other medical conditions need to be ruled out.[1]

Functional nausea and vomiting

Pediatric data is rare. It is characterized by bothersome nausea at least twice a week or one episode of non-self-induced vomiting per week, not explainable by any other medical condition.[1]

Aerophagia

Excessive air swallowing leading to belching, flatus, and abdominal distension lasting for at least two months and not explainable by another medical condition constitutes a diagnosis of aerophagia. It occurs in about 4.2–7.5% of children.[1]

Functional dyspepsia

Postprandial fullness, early satiety, or epigastric pain, all not explainable by other medical conditions, must be present for at least four days a month for two months. This can be further subclassified as postprandial distress syndrome or epigastric pain syndrome based on predominant symptoms. The estimated prevalence is about 1.4% in children and ranges from 5 to 10% in adolescents.[1]

IBS

IBS is classified as IBS with diarrhea, IBS with constipation, or IBS unspecified. Symptoms must include abdominal pain related to defecation, a change in stool frequency, or stool consistency, lasting for at least four days a month for a minimum of two months, and not explained by other medical conditions. About 1.2–5.4% of children are thought to have IBS.[1] The presence of red flag signs like blood in stools or failure to thrive should prompt a thorough

search for organic causes like celiac disease and inflammatory bowel disease.

Abdominal migraine

It is characterized by paroxysmal episodes of severe and diffuse abdominal pain that last for a minimum of 1 h, interfering with normal daily activities, and presenting a stereotypical pattern with at least two of the following six features: anorexia, nausea, vomiting, headache, photophobia, and pallor. there must be a minimum of two episodes separated by weeks or months within a 6-month period and possible medical conditions must be ruled out. The estimated prevalence is up to 23%.[1] Cyclical vomiting, abdominal migraine, and migraine headache are all episodic, stereotypical conditions with symptom-free periods in between, often triggered by stress, fatigue, or travel, and likely share a common pathophysiology. These abdominal conditions can develop into migraine headaches in adulthood.

Functional abdominal pain not otherwise specified

This group includes conditions that involve abdominal pain for four days a month for at least two months without the classic features of IBS, dyspepsia, or abdominal migraine, and not explained by other medical conditions. An estimated 1.2–4% of children have this disorder.[1]

Functional constipation

As discussed in the toilet-trained children category above, the only change for older children is that constipation should last for at least one month, should not fulfill IBS criteria, and should not be explained by other medical conditions. The estimated prevalence is about 14%.[1] In the absence of any red flag signs, routine testing for celiac disease, hypothyroidism, cow milk allergy, or radiography is not recommended. An X-ray can be considered if fecal impaction is suspected.

Non retentive fecal incontinence

A child older than four years should have at least a one-month history of defecation in inappropriate places with no evidence of fecal retention or other medical conditions. Around 0.8–4.1% of the children may have this disorder.[1] It has been postulated to occur as a result of emotional disturbance and even sexual abuse in childhood.[24]

Mechanisms

The exact pathophysiology behind FGIDs is still poorly understood. Traditionally, early life factors (genetic and environmental), psychosocial factors, physiological factors (abnormal motility, visceral hypersensitivity, immune dysregulation, diet), and the gut-brain axis are known to play a role in FGIDs.[15]

Genetic and environment

An early life stressful event like physical injury or infection can cause persistent structural and functional disruption of the neural and enteral neural circuitry during a vulnerable developmental period.[25,26] A meta-analysis showed girls have a higher risk (Odds ratio 1.5, 95% confidence interval 1.3–1.7) of developing functional abdominal pain compared to boys.[27] The same study did not show any difference in the prevalence of functional abdominal pain disorders between those under 12 years and those older.[27] Earlier studies on IBS have shown monozygotic twins to be at a higher risk than dizygotic twins (17.2% vs 8.4%) with subsequent studies estimating the heritability of FGIDs to be between 22% to 57%.[28,29] A polygenic mode of inheritance influenced by environmental factors leading to epigenetic changes is widely accepted.[29,30]

Psychosocial factors

Psychosocial factors like somatization and ineffective coping mechanisms, alongside anxiety and depression, can lead to FGIDs. These maladaptations and negative emotions can increase colonic transit time. They are postulated to alter the gut mucosal barrier, affecting the gut-brain axis and creating a vicious bidirectional cycle.[31]

Altered gut physiology and immune dysregulation

Changes in visceral afferent processing mediated by infection, inflammation, or stress can lead to a state of hyperalgesia with changes in mucosal permeability, impaired barrier function, immune dysregulation, serotonin, and histamine release, activating nociceptors, leading to reduced thresholds for pain and distention response, with children being more susceptible.[32,33] Central sensitization in the form of secondary hyperalgesia and altered cortical nociceptive processing has been shown in functional abdominal pain.[34,35] Moreover, an increase in mast cells and eosinophils suggests a role of immune dysregulation in FGIDs.[36] Both upper and lower gastric dysmotility, such as delayed gastric emptying, reduced gastric accommodation, delayed or accelerated colonic transit, and pelvic floor dyssynergia, have been postulated to be associated with FGIDs along with an increased inter-digestive migrating contraction, which has a housekeeping role in the gastrointestinal tract.[37] The gut-brain axis has come under the scanner as of late as a popular theory for FGID causation.

Gut-brain axis

There is increasing evidence of gut microbiota dysbiosis, with a decrease in species with anti-inflammatory effects, such as Bifidobacterium and Faecalibacterium in FGIDs, especially IBS.[38–40] A recent review showed stress, early life events, diet, and antibiotic therapy might alter the gut microbiota, and some probiotic strains can improve gastric emptying with potential improvement in FGIDs.[41] However, there are marked heterogeneities among studies, and limited evidence exists regarding gut microbiota dysbiosis leading to FGIDs.[42] To summarize, there may be a complex interplay between the viscera, central nervous system, and gut microbiota mediated via the vagus nerve, hypothalamus-pituitary axis, endocrine, and immune systems. Factors such as interleukins 1 and 6, neurotransmitters like gamma-aminobutyric acid, serotonin, acetylcholine, and metabolites such as short-chain fatty acids, contribute to visceral and central hypersensitivity involving cortical structures like the amygdala, prefrontal cortex, somatosensory cortex, insula, periaqueductal gray matter, anterior cingulate cortex, and thalamus.[43] The simplified mechanism is shown in Figure 1.

Management

Most children with FGIDs require a multifaceted approach, combining medical, behavioral, and dietary methods. It is best if all these modalities are available under one roof, as a single modality rarely resolves FGIDs satisfactorily. Given the heterogeneity of FGIDs, one treatment algorithm cannot fit all patients. A biopsychosocial approach that identifies and addresses triggers educates parents with information sheets, and integrates multidisciplinary care forms the backbone of successful therapy.[44] Up to 60–70%

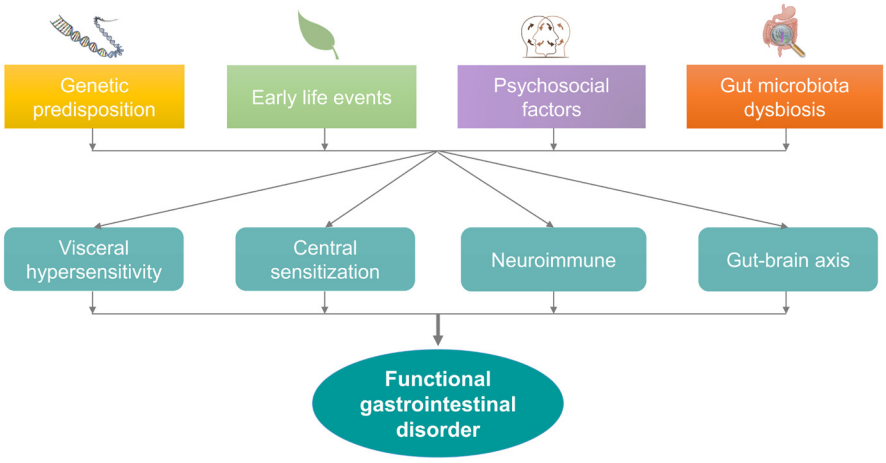

Fig. 1. Pathophysiology of FGID.

of children are known to recover from FGIDs over time but are at risk of developing migraine headaches, anxiety, and other disorders later in adulthood, necessitating proper transition of care and collaboration between pediatric and adult healthcare providers.[4,45]

Dietary methods

Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet (FODMAP)

High FODMAPs such as wheat, lentils, barley, rye, and asparagus can alter the gut microbiome and enhance visceral nociception.[46] Although few studies showed a trend toward improvement in abdominal pain symptoms in children with a low FODMAP diet, overall results are conflicting.[47,48]

Lactose and gluten-free diet

Lactose intolerance and non-celiac gluten sensitivity symptoms might mimic those of IBS. The role of lactose elimination in FGID is controversial. Several randomized controlled trials (RCTs) have not shown promising results with lactose-restricted diets.[49,50] Pediatric studies are lacking in the prevalence of non-celiac gluten sensitivity. Although a recent RCT showed promising results in reducing abdominal pain symptoms, the overall evidence is still not concrete.[51,52]

Fiber supplementation

Soluble dietary fibers that are viscous and moderately fermented improve IBS symptoms via laxative effect, increasing stool bulk and forming a gel-like covering. They also promote a beneficial gut microenvironment via short-chain fatty acids like butyrate and help regulate the gut-brain axis.[53] Meta-analyses on predominantly adult populations have shown a proven role of soluble dietary fibers in IBS.[54] Pediatric RCTs have also shown a greater reduction in pain and IBS severity scores with the use of psyllium.[55,56]

Probiotics

Probiotics, beneficial organisms that inhabit the gut, have a proven role in antibiotic-associated diarrhea, ulcerative colitis, and celiac.[57–59] A systematic review in 2018 showed *Lactobacillus rhamnosus GG* reduces the intensity and frequency of IBS-related abdominal pain in children though evidence is unsatisfactory for functional constipation and functional abdominal pain disorder.[60] An RCT on infants showed a 50% reduction in infant colic with *L. reutreri*.[61]

Nutraceuticals

Peppermint oil has shown some efficacy in relieving abdominal pain symptoms, though quality studies are lacking.[62] Fennel, a medicinal herb with potential antioxidant, antispasmodic, and anti-inflammatory properties, seemed to reduce crying episodes in infants with colic.[63] A meta-analysis on the role of vitamin D in IBS showed poor quality evidence for improvement in IBS severity scores but not in quality of life.[64]

Psychosocial methods

Cognitive behavioral therapy (CBT)

A Cochrane review done in 2017 of 18 RCTs, has shown CBT to be effective in addressing the anxiety and stress related to somatic sensations found in these patients.[65] CBT can be delivered both via in person as well as telephonic means. Patient motivation and engagement are necessary.

Hypnotherapy

By inducing a deep state of relaxation, hypnotherapy helps in reducing pain outcomes in pediatric FGIDs.[65] A recent RCT showed superior efficacy of hypnotherapy compared to medical treatment for functional nausea.[66]

Yoga therapy

Yoga improved physical and mental well-being, and multiple studies have shown the downregulation of the sympathetic and hypothalamic-pituitary axis.[67] However the Cochrane review did not show any proven role of yoga therapy in IBS and it is not recommended as a routine treatment.[65]

Neuro-electrical stimulation

Gastric electrical stimulation and percutaneous electrical nerve field stimulation are examples of electrical neurostimulation therapies investigated in pediatric FGIDs. Gastric electrical stimulation significantly improved gastroparesis and chronic nausea, while percutaneous electrical nerve field stimulation reduced pain symptoms of IBS.[68,69] More studies are needed to make a

Table 1. Brief summary of FGIDs diagnosis, mechanism, and management

S. No.	Topics	Summary
1.	Diagnostic criteria	ROME IV
2.	Neonatal/ toddler FGIDs	Infant regurgitation, Infant rumination syndrome, Cyclic vomiting syndrome, Infant colic, Functional diarrhea, Infant dyschezia, Functional constipation
3.	Child/Adolescent FGIDs	Cyclical vomiting, Rumination Syndrome, Functional nausea and vomiting, Aerophagia, Functional Dyspepsia, Irritable bowel syndrome, Abdominal migraine, Functional abdominal pain not otherwise specified, Functional constipation, Non-retentive fecal incontinence
4.	Red flag signs	Declining weight and height, delayed puberty, painful swallowing, bile-stained vomiting or persistent vomiting, bleeding, localized pain away from the umbilicus, fever, arthritis, perianal disease, and family history of inflammatory bowel disease or celiac disease
5.	Pathophysiology	Genetic and environmental, psychosocial factors, abnormal motility, visceral hypersensitivity, mucosal permeability, central sensitization, immune dysregulation, diet, and gut-brain axis
6.	Management	
	1. Dietary	Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet (FODMAP), lactose-gluten free diet, fiber supplementation, probiotics, nutraceuticals
	2. Psychosocial	Cognitive behavioral therapy, hypnotherapy, yoga therapy, neuro-electrical stimulation, fecal microbiota transplantation
	3. Pharmacological	Antispasmodics, antibiotics, antidepressants, laxatives, prokinetics, antidiarrheals
7.	Knowledge gained and application in clinical practice	FGIDs contribute to significant morbidity and reduced quality of life for both children and their caregivers; Different age groups can have their own unique manifestations; Despite several advancements the exact pathophysiology is poorly understood; Diagnosis does not need investigations and red flag signs should be watched out for; Early identification, parent education, and a combined multi-integrated biopsychosocial treatment modality can help in better outcomes.

FGIDs, Functional Gastrointestinal Disorders.

routine recommendation.

Fecal microbiota transplantation

This procedure involves manipulating the gut microbiota by administering an oral solution of fecal matter from a donor to confer a health benefit, such as treating *Clostridium difficile*.[70] A recent study on 12 pediatric patients showed good responses in bloating, pain, and diarrheal symptoms, with evidence of positive manipulation of the recipient gut microbiota.[71]

Pharmacological methods

Being a functional disorder, the placebo response is much higher, making it difficult to assess whether there is an actual response to a drug.[72] Antispasmodics, antibiotics, laxatives, antihistamines, antireflux drugs, analgesics, and antidepressants have all been tried in pediatric FGIDs. A systematic review done in 2015 with six studies on children above 4.5 years of age showed some evidence for peppermint oil polyethylene glycol, with tegaserod and cyproheptadine reducing pain intensity, while famotidine and amitriptyline improved the quality of life.[73]

Antispasmodics

Antispasmodics act on gastric smooth muscles leading to relaxation. Trimebutine, mebeverine, and drotaverine are the only drugs used in three RCTs in children. All three drugs improved abdominal pain and discomfort compared to the placebo.[74–76]

Antibiotics

Rifaximin, a poorly absorbed oral antibiotic, is known to control small intestinal bacterial overgrowth and regulate gut microbial dysbiosis. Rifaximin is even approved for adults with IBS.[77] Pediatric studies are fewer and the results are conflicting, so it is not routinely recommended.[78,79]

Antidepressants

Antidepressants like amitriptyline can have anticholinergic side effects, QT prolongation, and increased suicidal thoughts.[80] Nonetheless, they have been tried in those refractory cases.

RCTs have shown improvement in quality of life, anxiety, pain, and depression with the usage of amitriptyline and citalopram.[81–83]

Laxatives, prokinetics and antidiarrheals

Polyethylene glycol with tegaserod improved pain and stooling in IBS with constipation.[84] Linaclotide, lubiprostone, and prucalopride have shown efficacy in adult studies, but quality pediatric studies are lacking, so they are not recommended for IBS.[85] For functional constipation, disimpaction and maintenance regimens may be necessary. Osmotic laxatives like PEG, lactulose, sorbitol, and milk of magnesia, as well as stimulant laxatives like senna and bisacodyl, glycerin suppositories, rectal enemas, such as sodium phosphate and saline enema, and lubricants like mineral oil, are used to produce soft painless stools, and prevent re-impaction.[86] Prokinetics like domperidone, a dopamine antagonist, have a beneficial role in adult dyspepsia. An RCT of 89 children using domperidone versus placebo showed it may be a safe and effective drug for reducing pain and overall feeling of improvement.[87] Loperamide, though a first-line anti-diarrheal drug for the IBS-diarrhea type, has no RCT in children and is not recommended.[88,89]

The summary of the diagnosis, pathophysiology, and treatment is provided in Table 1.

Conclusion

This review highlights the prevalence, economic and psychosocial burden, age-stratified ROME IV classification, pathophysiology, diagnosis, red flag signs, and pharmacological and non-pharmacological treatment modalities for pediatric FGIDs. Compared to adult studies, well-controlled RCTs are lacking in the pediatric age group, especially with respect to pharmacological treatment. There is a trend towards greater emphasis on the gut-brain axis and the role of prebiotics and probiotics in maintaining favorable gut microbiota in FGIDs. Having a multi-integrated, biopsychosocial approach with enriched parental knowledge is the current recommended modality of treatment. Early recognition and treatment initiation can prevent long-term morbidity and improve the quality of life for both parents and their children.

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Conflict of interest

None.

Author contributions

Study concept and design (AM, GK and SG), acquisition of data (AM, GK and SG), analysis and interpretation of data (AM, GK and SG), drafting of the manuscript (AM, GK and SG), critical revision of the manuscript for important intellectual content (AM, GK and SG), administrative, technical, or material support (SG), and study supervision (SG). All authors have made a significant contribution to this study and have approved the final manuscript.

References

[1] Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. Gastroenterology 2016;150(6):1456–1468.E2. doi:10.1053/j.gastro.2016.02.015, PMID:27144632.

[2] Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. Gastroenterology 2016;150(6):1443–1455.E2. doi:10.1053/j.gastro.2016.02.016, PMID:27144631.

[3] Van Tilburg MAL. Pediatric functional gastrointestinal disorders. Clinical and Basic Neurogastroenterology and Motility. Cambridge, MA: Academic Press; 2020:557–563.

[4] Horst S, Shelby G, Anderson J, Acra S, Polk DB, Saville BR, *et al*. Predicting persistence of functional abdominal pain from childhood into young adulthood. Clin Gastroenterol Hepatol 2014;12(12):2026–2032. doi:10.1016/j.cgh.2014.03.034, PMID:24732284.

[5] Caplan A, Walker L, Rasquin A. Development and preliminary validation of the questionnaire on pediatric gastrointestinal symptoms to assess functional gastrointestinal disorders in children and adolescents. J Pediatr Gastroenterol Nutr 2005;41(3):296–304. doi:10.1097/01.mpg.0000172748.64103.33, PMID:16131984.

[6] Mahon J, Lifschitz C, Ludwig T, Thapar N, Glanville J, Miqdady M, *et al*. The costs of functional gastrointestinal disorders and related signs and symptoms in infants: a systematic literature review and cost calculation for England. BMJ Open 2017;7(11):e015594. doi:10.1136/bmjopen-2016-015594, PMID:29138194.

[7] Park R, Mikami S, LeClair J, Bollom A, Lembo C, Sethi S, *et al*. Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009. Neurogastroenterol Motil 2015;27(5):684–692. doi:10.1111/nmo.12542, PMID:25809794.

[8] Yousaf A, Mutalib M. Burden of Pediatric Functional Gastrointestinal Disorder in an Emergency Department-A Single-Center Experience. Pediatr Emerg Care 2022;38(9):e1512–e1516. doi:10.1097/PEC.0000000000002807, PMID:35969269.

[9] Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, *et al*. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology 2006;130(5):1447–1458. doi:10.1053/j.gastro.2005.11.057, PMID:16678558.

[10] Lee SY, Ryu HS, Choi SC, Jang SH. A Study of Psychological Factors Associated with Functional Gastrointestinal Disorders and Use of Health Care. Clin Psychopharmacol Neurosci 2020;18(4):580–586. doi:10.9758/cpn.2020.18.4.580, PMID:33124590.

[11] Zanchi C, Pintaldi S, Di Leo G, Ronfani L, Zamagni G, Viel M, *et al*. Fifteen-Years Follow-Up in a Cohort of Children with Functional Gastrointestinal Disorders: Prevalence and Risk Factors to Develop Neuropsychiatric Disorders and Other Comorbidities. Children (Basel) 2021;8(10):838. doi:10.3390/children8100838, PMID:34682103.

[12] Chang L. Review article: epidemiology and quality of life in functional gastrointestinal disorders. Aliment Pharmacol Ther 2004;20(Suppl 7):31–39. doi:10.1111/j.1365-2036.2004.02183.x, PMID:15521853.

[13] Varni JW, Bendo CB, Nurko S, Shulman RJ, Self MM, Franciosi JP, *et al*. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. J Pediatr 2015;166(1):85–90. doi:10.1016/j.jpeds.2014.08.022, PMID:25241177.

[14] Vernon-Roberts A, Alexander I, Day AS. Systematic Review of Pediatric Functional Gastrointestinal Disorders (Rome IV Criteria). J Clin Med 2021;10(21):5087. doi:10.3390/jcm10215087, PMID:34768604.

[15] Robin SG, Keller C, Zwiener R, Hyman PE, Nurko S, Saps M, *et al*. Prevalence of Pediatric Functional Gastrointestinal Disorders Utilizing the Rome IV Criteria. J Pediatr 2018;195:134–139. doi:10.1016/j.jpeds.2017.12.012, PMID:29398057.

[16] Thapar N, Benninga MA, Crowell MD, Di Lorenzo C, Mack I, Nurko S, *et al*. Paediatric functional abdominal pain disorders. Nat Rev Dis Primers 2020;6(1):89. doi:10.1038/s41572-020-00222-5, PMID:33154368.

[17] Nightingale S, Sharma A. Functional gastrointestinal disorders in children: What is new? J Paediatr Child Health 2020;56(11):1724–1730. doi:10.1111/jpc.14857, PMID:32468619.

[18] Cristofori F, Fontana C, Magistà A, Capriati T, Indrio F, Castellaneta S, *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):555–560. doi:10.1001/jamapediatrics.2013.4984, PMID:24756157.

[19] Fiori Nastro F, Serra MR, Cenni S, Pacella D, Martinelli M, Miele E, *et al*. Prevalence of functional gastrointestinal disorders in children with celiac disease on different types of gluten-free diets. World J Gastroenterol 2022;28(46):6589–6598. doi:10.3748/wjg.v28.i46.6589, PMID:36569268.

[20] Jeong SJ. The role of fecal calprotectin in pediatric disease. Korean J Pediatr 2019;62(8):287–291. doi:10.3345/kjp.2019.00059, PMID:30999729.

[21] Trivić I, Hojsak I. Initial Diagnosis of Functional Gastrointestinal Disorders in Children Increases a Chance for Resolution of Symptoms. Pediatr Gastroenterol Hepatol Nutr 2018;21(4):264–270. doi:10.5223/pghn.2018.21.4.264, PMID:30345239.

[22] Fleisher DR. Infant rumination syndrome: report of a case and review of the literature. Am J Dis Child 1979;133(3):266–269. PMID:425942.

[23] Raucci U, Borrelli O, Di Nardo G, Tambucci R, Pavone P, Salvatore S, *et al*. Cyclic Vomiting Syndrome in Children. Front Neurol 2020;11:583425. doi:10.3389/fneur.2020.583425, PMID:33224097.

[24] Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, *et al*. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014;58(2):258–274. doi:10.1097/MPG.0000000000000266, PMID:24345831.

[25] Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. Gastroenterology

2016;150(ISSUE 6):12621279.E2. doi:10.1053/j.gastro.2016.02.032, PMID:27144617.
[26] Bonilla S, Saps M. Early life events predispose the onset of childhood functional gastrointestinal disorders. Rev Gastroenterol Mex 2013;78(2):82–91. doi:10.1016/j.rgmx.2013.02.001, PMID:23578567.
[27] Collins J, Borojevic R, Verdu EF, Huizinga JD, Ratcliffe EM. Intestinal microbiota influence the early postnatal development of the enteric nervous system. Neurogastroenterol Motil 2014;26(1):98–107. doi:10.1111/nmo.12236, PMID:24329946.
[28] Saito YA, Mitra N, Mayer EA. Genetic approaches to functional gastrointestinal disorders. Gastroenterology 2010;138(4):1276–1285. doi:10.1053/j.gastro.2010.02.037, PMID:20176021.
[29] Korterink JJ, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. PLoS One 2015;10(5):e0126982. doi:10.1371/journal.pone.0126982, PMID:25992621.
[30] Newton E, Schosheim A, Patel S, Chitkara DK, van Tilburg MAL. The role of psychological factors in pediatric functional abdominal pain disorders. Neurogastroenterol Motil 2019;31(6):e13538. doi:10.1111/nmo.13538, PMID:30729663.
[31] Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology 2001;121(4):799–804. doi:10.1053/gast.2001.27995, PMID:11606493.
[32] Tran L, Chaloner A, Sawalha AH, Greenwood Van-Meerveld B. Importance of epigenetic mechanisms in visceral pain induced by chronic water avoidance stress. Psychoneuroendocrinology 2013;38(6):898–906. doi:10.1016/j.psyneuen.2012.09.016, PMID:23084728.
[33] Faure C, Thapar N, Di Lorenzo C. Pediatric Neurogastroenterology. Cham: Springer International Publishing; 2017.
[34] Halac U, Noble A, Faure C. Rectal sensory threshold for pain is a diagnostic marker of irritable bowel syndrome and functional abdominal pain in children. J Pediatr 2010;156(1):60–65.e1. doi:10.1016/j.jpeds.2009.06.062, PMID:19800076.
[35] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152(3 Suppl):S2–S15. doi:10.1016/j.pain.2010.09.030, PMID:20961685.
[36] Pas R, Ickmans K, Van Oosterwijck S, Van der Cruyssen K, Foubert A, Leysen L, *et al*. Hyperexcitability of the Central Nervous System in Children with Chronic Pain: A Systematic Review. Pain Med 2018;19(12):2504–2514. doi:10.1093/pm/pnx320, PMID:29304243.
[37] Wauters L, Nightingale S, Talley NJ, Sulaiman B, Walker MM. Functional dyspepsia is associated with duodenal eosinophilia in an Australian paediatric cohort. Aliment Pharmacol Ther 2017;45(10):1358–1364. doi:10.1111/apt.14045, PMID:28326599.
[38] Kusano M, Hosaka H, Kawada A, Kuribayashi S, Shimoyama Y, Zai H, *et al*. Gastrointestinal motility and functional gastrointestinal diseases. Curr Pharm Des 2014;20(16):2775–2782. doi:10.2174/13816128113199990572, PMID:23886379.
[39] Wei L, Singh R, Ro S, Ghoshal UC. Gut microbiota dysbiosis in functional gastrointestinal disorders: Underpinning the symptoms and pathophysiology. JGH Open 2021;5(9):976–987. doi:10.1002/jgh3.12528, PMID:34584964.
[40] Chong PP, Chin VK, Looi CY, Wong WF, Madhavan P, Yong VC. The Microbiome and Irritable Bowel Syndrome - A Review on the Pathophysiology, Current Research and Future Therapy. Front Microbiol 2019;10:1136. doi:10.3389/fmicb.2019.01136, PMID:31244784.
[41] Miquel S, Martín R, Rossi O, Bermúdez-Humarán LG, Chatel JM, Sokol H, *et al*. Faecalibacterium prausnitzii and human intestinal health. Curr Opin Microbiol 2013;16(3):255–261. doi:10.1016/j.mib.2013.06.003, PMID:23831042.
[42] Capozza M, Laforgia N, Rizzo V, Salvatore S, Guandalini S, Baldassarre M. Probiotics and Functional Gastrointestinal Disorders in Pediatric Age: A Narrative Review. Front Pediatr 2022;10:805466. doi:10.3389/fped.2022.805466, PMID:35252059.
[43] Pittayanon R, Lau JT, Yuan Y, Leontiadis GI, Tse F, Surette M, *et al*. Gut Microbiota in Patients With Irritable Bowel Syndrome-A Systematic Review. Gastroenterology 2019;157(1):97–108. doi:10.1053/j.gastro.2019.03.049, PMID:30940523.
[44] Mellon MW, Whiteside SP, Friedrich WN. The relevance of fecal soiling as an indicator of child sexual abuse: a preliminary analysis. J Dev Behav Pediatr 2006;27(1):25–32. doi:10.1097/00004703-200602000-00004, PMID:16511365.
[45] Fikree A, Byrne P. Management of functional gastrointestinal disorders. Clin Med (Lond) 2021;21(1):44–52. doi:10.7861/clinmed.2020-0980, PMID:33479067.
[46] Shelby GD, Shirkey KC, Sherman AL, Beck JE, Haman K, Shears AR, *et al*. Functional abdominal pain in childhood and long-term vulnerability to anxiety disorders. Pediatrics 2013;132(3):475–482. doi:10.1542/peds.2012-2191, PMID:23940244.
[47] Zhou SY, Gillilland M 3rd, Wu X, Leelasinjaroen P, Zhang G, Zhou H, *et al*. FODMAP diet modulates visceral nociception by lipopolysaccharide-mediated intestinal inflammation and barrier dysfunction. J Clin Invest 2018;128(1):267–280. doi:10.1172/JCI92390, PMID:29202473.
[48] Chumpitazi BP, Cope JL, Hollister EB, Tsai CM, McMeans AR, Luna RA, *et al*. Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. Aliment Pharmacol Ther 2015;42(4):418–427. doi:10.1111/apt.13286, PMID:26104013.
[49] Boradyn KM, Przybyłowicz KE, Jarocka-Cyrta E. Low FODMAP Diet Is Not Effective in Children with Functional Abdominal Pain: A Randomized Controlled Trial. Ann Nutr Metab 2020;76(5):334–344. doi:10.1159/000510795, PMID:33075788.
[50] Gijsbers CF, Kneepkens CM, Büller HA. Lactose and fructose malabsorption in children with recurrent abdominal pain: results of double-blinded testing. Acta Paediatr 2012;101(9):e411–e415. doi:10.1111/j.1651-2227.2012.02721.x, PMID:22578243.
[51] Lebenthal E, Rossi TM, Nord KS, Branski D. Recurrent abdominal pain and lactose absorption in children. Pediatrics 1981;67(6):828–832. PMID:7195004.
[52] Llanos-Chea A, Fasano A. Gluten and Functional Abdominal Pain Disorders in Children. Nutrients 2018;10(10):1491. doi:10.3390/nu10101491, PMID:30322070.
[53] Gholizadeh A, Mehrabani S, Esmaeili Dooki M, Haji Ahmadi M. Effect of a synbiotic on functional abdominal pain in childhood. Caspian J Intern Med 2021;12(2):194–199. doi:10.22088/cjim.12.2.194, PMID:34012538.
[54] El-Salhy M, Ystad SO, Mazzawi T, Gundersen D. Dietary fiber in irritable bowel syndrome (Review). Int J Mol Med 2017;40(3):607–613. doi:10.3892/ijmm.2017.3072, PMID:28731144.
[55] Nagarajan N, Morden A, Bischof D, King EA, Kosztowski M, Wick EC, *et al*. The role of fiber supplementation in the treatment of irritable bowel syndrome: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2015;27(9):1002–1010. doi:10.1097/MEG.0000000000000425, PMID:26148247.
[56] Shulman RJ, Hollister EB, Cain K, Czyzewski DI, Self MM, Weidler EM, *et al*. Psyllium Fiber Reduces Abdominal Pain in Children With Irritable Bowel Syndrome in a Randomized, Double-Blind Trial. Clin Gastroenterol Hepatol 2017;15(5):712–719.e4. doi:10.1016/j.cgh.2016.03.045, PMID:27080737.
[57] Menon J, Thapa BR, Kumari R, Puttaiah Kadyada S, Rana S, Lal SB. Efficacy of Oral Psyllium in Pediatric Irritable Bowel Syndrome: A Double-Blind Randomized Control Trial. J Pediatr Gastroenterol Nutr 2023;76(1):14–19. doi:10.1097/MPG.0000000000003622, PMID:36136861.
[58] Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev 2019;4(4):CD004827. doi:10.1002/14651858.CD004827.pub5, PMID:31039287.
[59] Shen ZH, Zhu CX, Quan YS, Yang ZY, Wu S, Luo WW, *et al*. Relationship between intestinal microbiota and ulcerative colitis: Mechanisms and clinical application of probiotics and fecal microbiota transplantation. World J Gastroenterol 2018;24(1):5–14. doi:10.3748/wjg.v24.i1.5, PMID:29358877.
[60] Ali B, Khan AR. Efficacy of Probiotics in Management of Celiac Disease. Cureus 2022;14(2):e22031. doi:10.7759/cureus.22031, PMID:35340497.
[61] Wegh CAM, Benninga MA, Tabbers MM. Effectiveness of Probiotics in Children With Functional Abdominal Pain Disorders and Functional Constipation: A Systematic Review. J Clin Gastroenterol 2018;52:S10–S26. doi:10.1097/MCG.0000000000001054, PMID:29782469.
[62] Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, *et*

al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics 2010;126(3):e526–e533. doi:10.1542/peds.2010-0433, PMID:20713478.
[63] Asgarshirazi M, Shariat M, Dalili H. Comparison of the Effects of pH-Dependent Peppermint Oil and Synbiotic Lactol (Bacillus coagulans + Fructooligosaccharides) on Childhood Functional Abdominal Pain: A Randomized Placebo-Controlled Study. Iran Red Crescent Med J 2015;17(4):e23844. doi:10.5812/ircmj.17(4)2015.23844, PMID:26023339.
[64] Anheyer D, Frawley J, Koch AK, Lauche R, Langhorst J, Dobos G, *et al*. Herbal Medicines for Gastrointestinal Disorders in Children and Adolescents: A Systematic Review. Pediatrics 2017;139(6):e20170062. doi:10.1542/peds.2017-0062, PMID:28562281.
[65] Chong RIH, Yaow CYL, Loh CYL, Teoh SE, Masuda Y, Ng WK, *et al*. Vitamin D supplementation for irritable bowel syndrome: A systematic review and meta-analysis. J Gastroenterol Hepatol 2022;37(6):993–1003. doi:10.1111/jgh.15852, PMID:35396764.
[66] Abbott RA, Martin AE, Newlove-Delgado TV, Bethel A, Thompson-Coon J, Whear R, *et al*. Psychosocial interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev 2017;1(1):CD010971. doi:10.1002/14651858.CD010971.pub2, PMID:28072460.
[67] Browne PD, de Bruijn CMA, Speksnijder EM, Hollander BD, van Wering HM, Wessels MMS, *et al*. Skills or Pills: Randomized Trial Comparing Hypnotherapy to Medical Treatment in Children With Functional Nausea. Clin Gastroenterol Hepatol 2022;20(8):1847–1856.e6. doi:10.1016/j.cgh.2021.10.029, PMID:34718171.
[68] Ross A, Thomas S. The health benefits of yoga and exercise: a review of comparison studies. J Altern Complement Med 2010;16(1):3–12. doi:10.1089/acm.2009.0044, PMID:20105062.
[69] Islam S, McLaughlin J, Pierson J, Jolley C, Kedar A, Abell T. Long-term outcomes of gastric electrical stimulation in children with gastroparesis. J Pediatr Surg 2016;51(1):67–71. doi:10.1016/j.jpedsurg.2015.10.015, PMID:26526207.
[70] Krasaelap A, Sood MR, Li BUK, Unteutsch R, Yan K, Nugent M, *et al*. Efficacy of Auricular Neurostimulation in Adolescents With Irritable Bowel Syndrome in a Randomized, Double-Blind Trial. Clin Gastroenterol Hepatol 2020;18(9):1987–1994.e2. doi:10.1016/j.cgh.2019.10.012, PMID:31622740.
[71] Gupta S, Allen-Vercoe E, Petrof EO. Fecal microbiota transplantation: in perspective. Therap Adv Gastroenterol 2016;9(2):229–239. doi:10.1177/1756283X15607414, PMID:26929784.
[72] Wang YZ, Xiao FF, Xiao YM, Li XL, Hu H, Hong K, *et al*. Fecal microbiota transplantation relieves abdominal bloating in children with functional gastrointestinal disorders via modulating the gut microbiome and metabolome. J Dig Dis 2022;23(8-9):482–492. doi:10.1111/1751-2980.13135, PMID:36208299.
[73] Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. Nat Rev Gastroenterol Hepatol 2015;12(8):472–485. doi:10.1038/nrgastro.2015.117, PMID:26194942.
[74] Korterink JJ, Rutten JM, Venmans L, Benninga MA, Tabbers MM. Pharmacologic treatment in pediatric functional abdominal pain disorders: a systematic review. J Pediatr 2015;166(2):424–31.e6. doi:10.1016/j.jpeds.2014.09.067, PMID:25449223.
[75] Karabulut GS, Beşer OF, Erginöz E, Kutlu T, Cokuğraş FÇ, Erkan T. The Incidence of Irritable Bowel Syndrome in Children Using the Rome III Criteria and the Effect of Trimebutine Treatment. J Neurogastroenterol Motil 2013;19(1):90–93. doi:10.5056/jnm.2013.19.1.90, PMID:23350053.
[76] Pourmoghaddas Z, Saneian H, Roohafza H, Gholamrezaei A. Mebeverine for pediatric functional abdominal pain: a randomized, placebo-controlled trial. Biomed Res Int 2014;2014:191026. doi:10.1155/2014/191026, PMID:25089264.
[77] Narang M, Shah D, Akhtar H. Efficacy and Safety of Drotaverine Hydrochloride in Children with Recurrent Abdominal Pain: A Randomized Placebo Controlled Trial. Indian Pediatr 2015;52(10):847–851. doi:10.1007/s13312-015-0730-y, PMID:26499007.
[78] Robertson KD, Nagalli S. Rifaximin. StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
[79] Scarpellini E, Giorgio V, Gabrielli M, Filoni S, Vitale G, Tortora A, *et al*. Rifaximin treatment for small intestinal bacterial overgrowth in children with irritable bowel syndrome. Eur Rev Med Pharmacol Sci 2013;17(10):1314–1320. PMID:23740443.
[80] Collins BS, Lin HC. Double-blind, placebo-controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. J Pediatr Gastroenterol Nutr 2011;52(4):382–386. doi:10.1097/MPG.0b013e3181effa3b, PMID:21240023.
[81] Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63(3):332–339. doi:10.1001/archpsyc.63.3.332, PMID:16520440.
[82] Franks I. Amitriptyline and placebo in children with functional gastrointestinal disorders. Nat Rev Gastroenterol Hepatol 2009;6(12):687–687. doi:10.1038/nrgastro.2009.190.
[83] Saps M, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, *et al*. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. Gastroenterology 2009;137(4):1261–1269. doi:10.1053/j.gastro.2009.06.060, PMID:19596010.
[84] Roohafza H, Pourmoghaddas Z, Saneian H, Gholamrezaei A. Citalopram for pediatric functional abdominal pain: a randomized, placebo-controlled trial. Neurogastroenterol Motil 2014;26(11):1642–1650. doi:10.1111/nmo.12444, PMID:25244442.
[85] Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. Aliment Pharmacol Ther 2006;23(1):191–196. doi:10.1111/j.1365-2036.2006.02705.x, PMID:16393297.
[86] Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, *et al*. Irritable bowel syndrome. Nat Rev Dis Primers 2016;2:16014. doi:10.1038/nrdp.2016.14, PMID:27159638.
[87] Tran DL, Sintusek P. Functional constipation in children: What physicians should know. World J Gastroenterol 2023;29(8):1261–1288. doi:10.3748/wjg.v29.i8.1261, PMID:36925458.
[88] Karunanayake A, Devanarayana NM, de Silva A, Gunawardena S, Rajindrajith S. Randomized Controlled Clinical Trial on Value of Domperidone in Functional Abdominal Pain in Children. J Pediatr Gastroenterol Nutr 2018;66(5):725–731. doi:10.1097/MPG.0000000000001819, PMID:29112086.
[89] Cangemi DJ, Lacy BE. Management of irritable bowel syndrome with diarrhea: a review of nonpharmacological and pharmacological interventions. Therap Adv Gastroenterol 2019;12:1756284819878950. doi:10.1177/1756284819878950, PMID:31632456.