

Pediatric Functional Constipation in Clinical Practice: The Continuous Search for the Light at the End of the Tunnel

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Abstract

Functional constipation (FC) has a pooled world prevalence of 9.5%, a clear definition by Rome IV Criteria, and the NAPGHAN/ESPGHAN guidelines recommendation for management. With well-defined parameters, this commentary discusses the paths followed by the literature to implement different therapeutic modalities over time. The text will prioritize information based on systematic reviews, meta-analyses, or reviews. Recently, an Editorial exploring gastrointestinal diseases across the Lifespan linked constipation as a “vexing issue that, unfortunately, has the potential to impair Health-Related Quality of Life (HRQOL).” Indeed, The Rome Foundation recommended that HRQOL scores may assist in diagnosis, management, prognosis, and therapeutic decisions. Therefore, it can be helpful for clinicians, psychologists, and researchers and could be used to support health services that want to implement an HRQOL program. The final idea is to propose HRQOL as a secondary outcome for Pediatric FC monitoring this disorder.

Keywords: Functional constipation, Health-related quality of life, Outcomes, Rome criteria, Functional constipation management, Behavioral approach, Stressful life events

Introduction

The remarkable text by Read & Timms [1] asked, “Is there light at the end of the tunnel?” to patients who complained of hard stool, strain to defecate, pain, and incomplete evacuation. Accordingly, searching the path taken for the best way to manage Functional constipation (FC) in pediatric patients is the main objective of this text. From the evolution of definition criteria to the development of specific health-related quality-of-life assessment questionnaires in FC and the possibility of using them as an outcome of management response in daily clinical practice. The text will prioritize information based on systematic reviews, meta-analyses, or reviews.

Definitions of FC in Pediatric Ages

FC definitions were continually becoming more appropriate.

Table 1 presents the criteria for definitions of FC. In 1999, Rome II Criteria [2] was released. In 2005, the PACCT Group (Paris Consensus on Childhood Constipation Terminology) [3] brought an excellent qualification to the definition of FC, which was incorporated into the Rome III criteria [4,5]. In 2014, a guideline summarized the best treatment recommendations with the co-participation of the North American and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) was published. They defined *Intractable Constipation* as not responding to optimal conventional treatment for at least three months [6].

Finally, in 2016, The Rome IV Criteria was launched incorporating an incredible burden of knowledge regarding FC [7,8]. Furthermore, Functional Faecal Incontinence was

Table 1. Rome II, III, IV, and Paris Criteria for Functional Constipation in children/adolescents.

	Rome II Criteria (1999)		Paris Criteria PACCT (2005)	Rome III Criteria (2006)		Rome IV Criteria (2016)	
Age of interest	Infants and preschool	Infants to 16 years	Children	Infants up to ≤ 4 years	Developmental age ≥ 4 years	Infants up to ≤ 4 years	Developmental age ≥ 4 years
Symptom Duration	≥ 2 weeks	≥ 12 weeks	The last 8 weeks of ≥ 2 of the following	≥ 1 month of ≥ 2 of the following	≥ 1x/week for ≥ 2 months of ≥ 2 of the following	≥ 1 month of ≥ 2 of the following	≥ 1x/week for ≥ 1 month of ≥ 2 of the following
Defecation frequency	≤ 2x/week	<2x/week	≤ 2x/week	≤ 2x/week	≤ 2x/week in the toilet	≤ 2x/week	≤ 2x/week in the toilet
Fecal characteristics	Firm stools		<i>Painful defecation</i>	Painful or hard bowel movements	Painful or hard bowel movements	Painful or hard bowel movements	Painful or hard bowel movements
	Scybalous, pebble-like, hard stools	<i>Passage of large-diameter stools</i>	Large-diameter stools that obstruct the toilet	Large-diameter stools that obstruct the toilet	Large-diameter stools that obstruct the toilet	Large-diameter stools that obstruct the toilet	Large-diameter stools that obstruct the toilet
			≥ 1x/week of fecal incontinence	≥ 1x/week of fecal incontinence after toileting training	≥ 1x/week of fecal incontinence	≥ 1x/week of fecal incontinence after toileting training	≥ 1x/week of fecal incontinence
		<i>Retentive posturing</i>	<i>Retentive posturing and withholding behavior</i>	Excessive stool retention	Retentive posturing or excessive volitional stool retention	Excessive stool retention	Retentive posturing or excessive volitional stool retention
	No evidence of structural, endocrine or metabolic disease		<i>Large stools in the rectum or palpable on examination</i>	Large fecal mass in the rectum	Large fecal mass in the rectum	Large fecal mass in the rectum	Large fecal mass in the rectum

divided into Constipation-Associated Fecal Incontinence and Nonretentive Fecal Incontinence (FNRFI). So, the clinical practice was provided with adequate definitions.

Epidemiology of FC

FC reputable epidemiological studies were developed along this path. In 2006, a systematic review, including eighteen studies, showed that the prevalence of FC in children from 0 to 18 years ranged from 0.7% to 29.6% (median 8.9%), considered a worldwide common problem [9]. In 2011, the same authors, now including adults, evaluated the epidemiology of FC in 19 articles, and the prevalence rate was between 0.7% and 29.6% (median 12%). Females, increasing age, socioeconomic status, and educational level affected the prevalence of constipation [10].

In 2018, a systematic review and meta-analysis including 35 countries defined a pooled prevalence of 9.5%, with a similar prevalence in boys (8.6%) and girls (8.9%) but with a higher prevalence of 17.5% in children under four years [11]. A systematic review of pediatric functional gastrointestinal disorders, based on Rome IV Criteria, recently included 20 papers in the final analysis. FC was the most common pediatric functional gastrointestinal disorder for children aged 13-48 months and for those over four years [12]. Accordingly, there is a tendency for the median to stabilize around 10% over time.

The Pathway of Investigation

The NASPGHAN/ESPGHAN guidelines do not recommend routine laboratory testing for hypothyroidism, coeliac disease, and hypercalcemia in children with FC. Indeed,

in a retrospective cohort study, children were screened and showed a low prevalence of these diseases [13]. Also, guidelines illustrate that invasive tests, such as barium studies, anorectal manometry, and anorectal biopsy, serve no purpose in clinical practice [6]. Additionally, a systematic review of abdominal radiography detecting fecal impaction showed insufficient evidence for an association between fecal loading and clinical symptoms [14]. So, with a history and physical examination without alarm signs, a diagnosis of FC based on the Rome IV Criteria and NASPGHAN/ ESPGHAN guidelines can be supported only on a clinical basis. Subsequently, improvements in diagnostic criteria led to a reduction in the need for diagnostic exams over the years.

The Pathway to Management

Certainly, FC is challenging to treat. The remarkable publication of NASPGHAN/ESPGHAN on the treatment of FC recommended that the first step consists of education, demystification, change in lifestyle, and a combination of pharmacological and nonpharmacological interventions [6]. Four years later, in 2018, a review combining biomedical, nutritional, and psychological approaches to Pediatric FC defined that the treatment plan must establish an influential relationship between the pediatrician, the patient, and the

family. Supporting successful outcomes implies remaining involved and engaging the parents and children in educational activities about FC during treatment [15]. Next, synthesis and the best evidence for treating FC were sectioned into pharmacological and nonpharmacological management [16].

Pharmacological management

The main studies on FC pharmacological management [17-23] are presented in **Table 2**. The conclusion was that polyethylene glycol (PEG) increased the frequency of stools relative to placebo, lactulose, and milk of magnesia. PEG laxatives are effective and safe and associated with more successful disimpaction than those with non-PEG laxatives. Children's acceptance and adverse events were better than non-PEG laxatives, and the adverse events were acceptable and well tolerated. New pharmacological therapeutic agents were proposed for managing FC. Lubiprostone, with minor side effects, is efficacious and safe [21]. Among the Serotonergic agents, Prucalopride was no more effective than a placebo [23]. Thus, the pediatric population needs more experience with these therapeutic agents. Additionally, pharmacological treatment adherence studies in children with FC are limited. A cross-sectional survey including 115 children, according to the Rome IV criteria, showed that PEG treatment was adherent to

Table 2. Pharmacological management on Functional constipation.

Review/systematic review/metanalysis	Year of publication	Number of studies	Number of patients	Drug	Main conclusion
The Canadian Agency for Drugs and Technologies in Health [17]	2014	12 systematic reviews	Adults and children	Polyethylene glycol (PEG) osmotic laxative	Increased the frequency of stools relative to placebo, lactulose, and milk of magnesia.
Chen et al. [18] Meta-analysis	2014	10 suitable studies	1052 children	PEG Osmotic laxative	Effective and safe. Adverse events are better than non-PEG laxatives. Successful disimpaction
Hyman et al. [21]	2014	Prospective, multicenter, open-label study	127 children	Lubiprostone Prosecretory agent	It is well tolerated in children, with minor side effects, suggesting it is efficacious and safe.
Mugie et al. [23]	2014	Double-blind, placebo-controlled study	213 children	Prucalopride	No more effective than a placebo
Gordon et al. [19] Cochrane Database Systematic Review	2016	25 randomized, controlled trials	2316 children	PEG Osmotic laxative	Superior to placebo, lactulose, and milk of magnesia
Sajid et al. [22] Systematic review and meta-analysis	2016	16 randomized, controlled trials	3943 adults	Prucalopride Serotonin 5-HT4 receptor agonist	Effectiveness, increased frequency of spontaneous bowel movements
De Geus et al. [20]	2023	Review		PEG Osmotic laxative	First choice for disimpaction and maintenance

only 37% of all children [24]. Thus, pharmacological treatment involves often-forgotten disimpaction, poor adherent maintenance, and precocious weaning.

Nonpharmacological management

Nonpharmacological interventions involve education – actively involving the child in the conversation is essential. Toilet Training is an integral part of constipation management. Physical activity should be encouraged. Dietary counseling, such as dietary fiber (DF) and fluid intake, will be discussed below.

Dietary fibre

Although a low-DF diet is recognized as a risk factor for FC in children, the NASPGHAN/ESPGHAN guidelines and the Rome IV criteria recommend a regular DF intake for children and do not support using additional DF to treat Pediatric FC [6]. In 2018, a meta-analysis (9 randomized control studies [RCTs], n=680) of DF in patients with FC observed no statistical significance for stool consistency, movement frequency, and fecal incontinence [25]. Nevertheless, in 2018, another excellent review demonstrated some beneficial effects of DF in children with FC and concluded that adequate DF intake should be recommended but did not allow strong recommendations [26]. However, additional supplementation should not be given, agreeing with what was previously defined by NASPGHAN/ESPGHAN recommendations [6].

Recently, in 2022, a meta-analysis of 10 RCT (randomized control studies) (690 children) with FC evaluated the effect of seven different DF mixtures. The authors highlighted that the type of fiber used in the studies may not reflect those most likely to benefit from constipation [27]. Despite this, in general practice, healthcare professionals recommend dietary changes as the first step in managing children with FC and commonly recommend increasing DF intake.

Fluid intake

One RCT assessing extra fluid intake in children with FC showed insufficient evidence for a beneficial effect [28]. Therefore, current pediatric guidelines do not recommend increasing fluid intake [6].

Probiotics

In 2017, one systematic review included seven RCTs with 515 participants, demonstrated no significant difference between the probiotic and control groups, and concluded no support for using any currently evaluated probiotics in treating FC in children [29]. Conversely, in the same year, another systematic review and meta-analysis of six RCTs showed significant beneficial effects of probiotics compared with control interventions, suggesting that probiotics may constitute an efficacious option for treating children with FC [30].

In 2018, a systematic review on probiotics in pediatric FC included 6 RCTs (n=411) and concluded that insufficient evidence exists for using probiotics in pediatric FC [31]. Once again, in the same year, a systematic review and meta-analysis evaluated the effect of probiotics and placebo on FC children. Overall, there were no significant differences in spontaneous bowel movements, fecal incontinence episodes, straining at defecation, pain during defecation, flatulence, and use of laxatives [32].

In 2022, a Cochrane review on the use of probiotics in FC children included 14 randomized studies involving 1127 participants under 18 years of age. It showed no difference in health outcomes or adverse effects of probiotics/synbiotics compared with placebo treatments. As such, insufficient evidence exists to link probiotics to improved outcomes for pediatric FC [33].

In 2023, a comprehensive review of nine meta-analyses and systematic reviews evaluated the quality, effectiveness, and bias regarding the relationship between probiotic intake and improved constipation outcomes in children. The study revealed that the intake of probiotics in children with FC significantly improved treatment success. However, no significant association was detected between probiotics intake and frequency of abdominal pain, stool consistency, defecation pain, and fecal incontinence [34]. So, conflicting findings of previous reviews probably resulted from methodologic errors, and the evidence available thus does not support using probiotics as a single or adjuvant therapy for treating FC in children [35].

Neuromodulation

Neuromodulation use for FC and fecal incontinence has increased in popularity over the past few years. Invasive and non-invasive techniques are currently available. A review on sacral nerve stimulation [36] in children reported that 80% of children experienced improvement, including increased defecation frequency. The provocative title was “Is it time to shock the gut?”. Three years later, a systematic review screened 241 papers, with 14 included, showing overall improvement or resolution in constipation and incontinence symptoms. The study highlights neuromodulation’s position in the management of refractory FC [37].

In 2020, randomized sham-controlled trials were conducted in adults to differentiate overall treatment responses from placebo, investigating the effect of electrical nerve stimulation on constipation and fecal incontinence. In conclusion, sham stimulation is associated with clinical improvements in symptoms of fecal incontinence, highlighting the importance of sham controls in nerve stimulation trials [38]. Subsequently, in adults in 2021, a systematic overview of the different modalities of neurostimulation and their effect on chronic FC concludes that the beneficial effect of neuromodulation remains questionable [39].

More recently, in 2023, a systematic review of randomized clinical trials based on 164 children and adolescents analyzed the effects of transcutaneous neuromodulation and concluded that transcutaneous neuromodulation is an effective adjuvant treatment modality that improves children's FC and retentive fecal incontinence [40].

Biofeedback

Biofeedback is used to restore a regular defecation pattern using visual and verbal feedback techniques. In 2015, based on high-quality evidence, the position paper and consensus guidelines on biofeedback therapy for anorectal disorders recommended Biofeedback therapy for treating constipation with dyssynergic defecation and for fecal incontinence in adults. However, the evidence does not support the efficacy of biofeedback therapy for treating childhood FC in children. Biofeedback therapy requires specialized training and older cooperative children [41].

In 2021, a network meta-analysis was conducted to evaluate the effectiveness of the efficacy of auxiliary therapies (behavioral therapy, physiotherapy, biofeedback, or anorectal manometry) in children with FC. These complementary therapies were effective but must be used simultaneously with standard medical care [42].

On the Way to Quality of Life: Stressful Life Events

In 2015, a systematic review to determine the prevalence of stressful life events searched 946 articles, of which eight were included (FC= 654, and constipation-associated fecal incontinence=1931 children). Overall, children with functional defecation disorders were more exposed to stressful life events compared with healthy children [43]. In 2022, another systematic review included 15 articles (2954 children) with FC. It defined child maltreatment, divorce/separation of parents, severe illness in the family, and parental job loss as home stressors. In the same way, bullying, change in school, separation from the best friend, and failure on examination as school-related stressors were associated with childhood constipation [44].

A recent good-quality systematic review of eleven studies evaluated the relationship between psychological stress and pediatric FC. Similarly to the previous review, the authors classify psychological stressors into family, school, and related psychological disorders. In conclusion, most studies showed a significant relationship with constipation, suggesting a collaborative effort between parents, children, and healthcare professionals [45]. Specific parental characteristics, for instance, neuroticism, depression, overprotection, and attitudes that foster a high or low degree of autonomy, are reported to be associated with the pathophysiology and prognosis of childhood FC and fecal incontinence [46,47].

Behavioral interventions

Behavioral treatment for fecal incontinence in constipation children aged 4-18 was published as a systematic review in 2014 and supports this modality of treatments [48]. Symptoms of fecal incontinence are often associated with frustration of the child and have a severe impact on the entire family [47,49]. Indeed, a high prevalence of behavioral problems in children with FC affects the HRQOL of the child-parent interaction. The probable conflict between children and their parents can come from confrontation to toilet training, taking medications, enemas, and diets. Children with FC have a higher prevalence of negative psychological maladjustment, resulting in a decreased HRQOL [50].

FC and HRQOL

The etiology of FC implies interactions between physiologic, psychological, social, cultural, and behavioral factors and effects on families concerning worrying, social isolation, and economic limitations. Indeed, all these factors negatively impact the HRQOL of children and their families. Next, studies on HRQOL and defecation disorders in children will be described.

A study in the United States of America observed that the QOL score for FC was significantly reduced compared to healthy controls [51]. A Dutch-specific HRQOL questionnaire to assess constipation, named "Defecation Disorder List" (DDL), was developed [52]. The tool consists of 37 questions covering four domains: emotional functioning, social functioning, and treatment/interventions. The DDL was used to evaluate children with FC, significantly impacting the HRQOL of children and families [53]. In addition, an Australian study using a generic instrument assessed the HRQOL in 51 children (8 to 18 years old). The total HRQOL score in constipated children was significantly lower than in controls [54].

An instrument to assess HRQOL in children with constipation, non-retaining pattern fecal incontinence, and irritable bowel syndrome subtype constipation named "Parental Opinions of Pediatric Constipation" (POOPC) was developed [55]. Also, using the Rome III Criteria, another English questionnaire named "The Self-Efficacy for Functional Constipation Questionnaire" (SEFCQ) was developed and validated for children with FC. The questionnaire measures the child's academic, social, and emotional self-efficacy [56].

In Brazil, 100 consecutive children attending a tertiary Pediatric Gastroenterology Clinic were evaluated using the CHQ-PF50 and compared with healthy, non-constipated children. A significant impairment in HRQOL psychological and physical well-being scores was observed [57]. In the same group, in 2021, a specific instrument parent-reported for the Brazilian Portuguese language to assess HRQOL in children and adolescents with FC was developed and validated. The

Pediatric Functional Constipation Questionnaire – Parent Report (PedFCQuest-PR) showed good acceptability, validity, sensitivity, responsiveness, reliability, and general applicability of the instrument for the target group. Cronbach's alpha for internal consistency was 0.88. results confirmed an excellent association between the PedFCQuest-PR total score and the presence/absence of the Rome IV Criteria items [58].

The results of both generic and FC-specific HRQOL questionnaire studies demonstrated a consistent effect on the emotional and physical components of HRQOL, which may affect children's psychosocial development, relationships with parents, friends, siblings, and success at school. In 2019, an outstanding systematic review on HRQOL in children with FC and to identify disease-related factors evaluated 2658 studies, including 20 with a total of 2344 children. Pooled total HRQOL scores were lower than healthy reference values, concluding impaired HRQOL in children with FC [59]. Additionally, two previous reviews included a few pediatric studies that reported impaired HRQOL in children with FC [60,61].

Prognosis and the “Long and Winding” Tunnel

Many studies have applied proposals for treating FC in children and adolescents along this long path. The filter of these actions can be selected in prognostic studies. Thus, the prognostic factors of FC, including 14 prospective studies (n=1752), were investigated in a systematic review. Half of the children recovered and were taken off laxatives after 6–12 months of follow-up. An additional 10% were symptom-free but still being treated with laxatives. After a follow-up of 1–2 years and 5–10 years, the recovery rate was 58% and 56%, respectively. Children treated in a Pediatric Gastroenterology Department had a higher recovery rate than those treated in General Pediatric Departments [62].

So, many improve, but some symptoms may persist into adolescence or adulthood despite medical treatment. Delays between the age of symptoms onset and the first visit are negatively related to recovery [63]. Thus, long-term FC in children and adolescents is a frequent reason for healthcare consultations and increased healthcare expenditure [64,65].

Final Comments

In children with FC, colon sensations, such as pain and distention ascending via afferent pathways from the enteric nervous system to the cerebral cortex might, eventually, affect brain processing and lead to psychological and emotional components that modulate colonic and rectal function via efferent pathways. Compared with healthy individuals, pediatric patients with FC showed different brain processing patterns in response to rectal distention [66]. Reasonably, psychological factors and FC are associated with the gut-brain axis.

Recently, in an Editorial [67] exploring gastrointestinal diseases across the lifespan, constipation was described as a “vexing issue that, unfortunately, has the potential to impair health-related quality of life.” Accordingly, evaluating constipation is challenging, and the HRQOL questionnaires could be beneficial in medical practice to gain a complete overview of the patient [68]. Scores may assist in diagnosis, management, prognosis, and therapeutic decisions. The Rome Foundation recommended HRQOL questionnaires as a secondary outcome for pediatric FC [69]. Therefore, it can be helpful for clinicians, psychologists, and researchers and could be used to support health services that want to implement an HRQOL program.

Finally, and with great optimism, we observed lights that clarified the treatment, a significant advance in understanding the enteric nervous system-central nervous system connection, and advances in the valorization of behavioral aspects. Also, there is a need to seek comprehensive therapeutic response variables such as the assessment of HRQOL. So, the FC-related “long and winding” tunnel will likely give us excellent times.

Abbreviations

FC: Functional Constipation; PACCT: Paris Consensus on Childhood Constipation Terminology; NASPGHAN: North American and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition; ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology, and Nutrition; DF: Dietary Fiber; RCT: Randomized Control Trials; HRQOL: Health-Related Quality of Life; POOPC: Parental Opinions of Pediatric Constipation; SEFCQ: Self-Efficacy for Functional Constipation Questionnaire; CHQ-PF50. Child Health Questionnaire - Parent Form 50; PedFCQuest-PR: Pediatric Functional Constipation Questionnaire – Parent Report

Conflict of Interest

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