

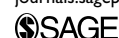
# Unmet Needs in Pediatric Functional Constipation

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## Introduction

Pediatric functional constipation (PFC) is one of the most common functional gastrointestinal complaints in pediatric patients, accounting for 3% of visits to a general pediatrician and up to 25% of visits to a pediatric gastroenterologist in the United States.<sup>1</sup> Across epidemiologic studies, global prevalence of PFC has been reported as being between 0.3% and 29.6%, with similar rates for both genders.<sup>2-5</sup> PFC has a significant impact on patient and family quality of life, and in the United States alone, the estimated economic burden of childhood constipation in 2011 was US\$3.9 billion.<sup>6-8</sup> Disease severity may vary from mild and short-lived to severe and chronic, with approximately 25% of patients continuing to have symptoms into adulthood.<sup>2</sup> Despite currently available treatment options, quality of care in PFC is limited by lack of guidance for disease management, a poorly defined disease state, and insufficient data on drug therapies.<sup>9,10</sup>

PFC is defined in the Rome IV diagnostic criteria for childhood functional gastrointestinal disorders (FGIDs) as the patient (1) having 2 or more of the following symptoms at least once each week for 1 month prior to diagnosis:  $\leq 2$  defecations per week, at least 1 episode of fecal incontinence per week, history of retentive posturing or excessive volitional stool retention, history of painful or hard bowel movements, presence of a large fecal mass in the rectum, and history of large diameter stools that may obstruct defecation; and (2) having insufficient criteria for a diagnosis of irritable bowel syndrome.<sup>11,12</sup> Although the Rome IV diagnostic criteria for childhood FGIDs provide a classification system, the criteria do not overlap well with physician diagnosis or daily symptoms reported in patient diaries.<sup>9</sup> Similarly, issues also exist with treatment options used in PFC such as lack of data to support long-term use, lack of placebo-controlled trials, high levels of heterogeneity in eligibility criteria, lack of generally accepted endpoints for clinical data, and lack of established safety profiles in the pediatric population. Given the dearth of consistent guiding information, we conducted a systematic

literature review to identify gaps and unmet medical and educational needs in PFC.

## Methods

### Search Strategies

A comprehensive literature search was performed using targeted PubMed queries for articles published between January 1, 2010, and August 1, 2017, on current treatments, clinical trial outcomes, clinical practice, and PFC education/awareness among health care professionals and patients. Publications included systematic reviews (SRs), randomized controlled trials (RCTs), evidence-based treatment guidelines, cohort studies, outcomes research, descriptive studies (eg, case series/reports, questionnaires/surveys), and expert opinions.

A total of 23 search terms were applied, 18 of which were a combination of “pediatric functional constipation” and another search term (“adolescent,” “bowel function,” “bowel habit,” “bowel movement,” “bowel symptoms,” “childhood,” “clinical severity,” “clinical severity rating,” “cost-effectiveness,” “guidelines,” “nonpharmacological treatment,” “Patient Global Impression of Change,” “PedsQL,” “pharmacological treatment,” “randomized controlled trials,” “treatment effectiveness,” and “quality of life”). The remaining 5 search queries were the following: “management of functional constipation” [AND] children,” “pediatric constipation by general pediatrician [AND] specialist,” “treatment [AND] functional constipation [AND] children,” “evidence-based recommendations [AND] functional constipation [AND] children,” and “fecal impaction [AND] pediatrics.”

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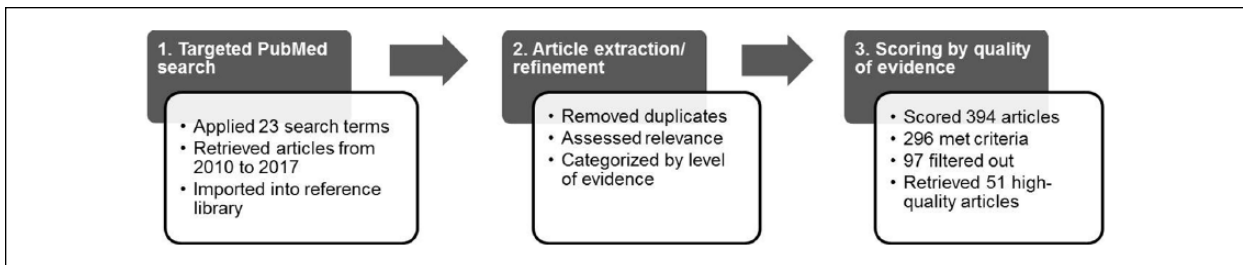
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**Figure 1.** Search methodology for evaluating published literature on pediatric functional constipation treatment and management.

The articles retrieved from these searches were combined into a single repository, and any duplicate records were removed. We assessed the abstract contents for relevance based on key topics related to epidemiology, pathophysiology, treatment paradigm, and clinical outcomes (Figure 1).

### Critical Appraisal of Published Literature on PFC

Articles retrieved from the PubMed search were imported into a reference library (Endnote, Thomson Reuters) for sorting and analysis. Publications were categorized into 1 of 4 tiers based on the level of evidence (high/moderate/low/very low) using criteria adapted from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system<sup>13</sup> as outlined in Table 1. Articles not meeting these criteria were discarded or reclassified into a lower tier where applicable. Findings from RCTs, SRs, and cohort studies were used to inform gaps in PFC research and unmet medical needs, whereas descriptive studies and expert opinion-based articles were used to identify gaps in education, disease awareness, and clinical practice.

## Results

### Literature Search and General Description of Included Studies

A total of 394 publications were retrieved from the literature search, 296 of which were included for further analysis (Figure 2). Ninety-eight articles were filtered out based on scope (eg, nonclinical studies), products tested (eg, common food items, off-label use of existing drugs), and study population (eg, limited geographical areas). Among the 296 articles that were scored by level and quality of evidence, we retrieved 51 high-quality publications (SRs, RCTs, and evidence-based treatment guidelines) that were most influential in describing the PFC treatment landscape (Table 2).

### Current Treatment Options

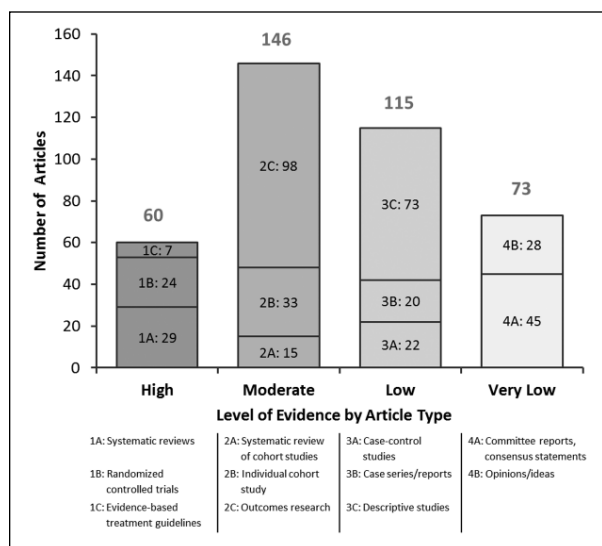
Oral laxatives are the most commonly prescribed treatments for fecal disimpaction and maintenance therapy, but their long-term use has not been adequately evaluated.<sup>14-17</sup> The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines recommend polyethylene glycol (PEG) with or without electrolytes, dosed orally (1-1.5 g/kg/d) for 3 to 6 days as the first-line treatment for children presenting with fecal impaction.<sup>16</sup> If PEG is unavailable, lactulose is recommended as the first-line maintenance treatment, whereas milk of magnesia, mineral oil, and stimulant laxatives may be considered as additional or second-line treatment.<sup>16</sup> While significant improvements in constipation symptoms have been reported with both osmotic (eg, PEG) and stimulant (eg, senna) laxatives in RCTs, approximately 40% to 50% of children with functional constipation experience at least 1 episode of relapse within the first 5 years after initial recovery.<sup>14,16,18</sup> Dietary fibers, traditional medicine, and probiotics are commonly used; however, the clinical evidence supporting their use is not clear.<sup>16,19-22</sup> Prebiotics and probiotics may be effective at improving clinical symptoms, but data from RCTs are limited.<sup>19,21</sup>

Among the nonpharmacological interventions, sacral neuromodulation provides a suitable option for refractory PFC, but it is not frequently used, and data on its clinical benefits in children are limited. In a prospective cohort study (n = 30), sacral neuromodulation improved the mean defecation frequency, which was sustained over a prolonged period; however, the quality of life of the patients continued to be lower than that of the normal population.<sup>23</sup> Enemas are effective for severe PFC, but their long-term use in children is often impractical and may be perceived as uncomfortable.<sup>24</sup> Several surgical approaches, including antegrade enemas, are associated with improved clinical outcomes in severe and intractable constipation. Surgical implantation of conduits for antegrade enema may cause complications such as stoma-related and other perioperative complications;

**Table 1.** Evaluation Criteria for Assessment of Quality of Evidence.

Quality	Tier	Articles	Inclusion Scoring Criteria (One or More of These Criteria Must Be Met)	Number of Articles	
				By Level	Total
High	1A	SRs	Review of high-quality RCTs; homogeneous population; good methodology; includes Cochrane reviews/meta-analyses	24	51
	1B	RCTs	≥1 large, well-designed (DB, PBO-controlled) study; strong effect size; low bias, peer-reviewed	22	
	1C	Evidence-based treatment guidelines	Based on SRs; ≥3 good-quality RCTs	5	
Moderate	2A	SR of cohort studies	Same criteria as 1A; includes low-quality RCTs	13	95
	2B	Individual cohort study	Nonrandomized study population	23	
	2C	Outcomes research	Prospective/retrospective studies; chart reviews	59	
Low	3A	Case-control studies	Homogeneity of case-control studies for SRs; well-designed, nonrandomized	7	84
	3B	Case series/reports	Includes poor-quality cohort studies and case-control studies	11	
	3C	Descriptive studies	Individual case studies; nonclinical studies; observational findings from surveys/questionnaires	66	
Very low	4A	Committee reports, consensus statements	Explicit critical appraisal; evidence-based recommendations; includes review articles	38	66
	4B	Opinions/ideas	Lacking evidence-based support; commentaries	28	
					296

Abbreviations: SRs, systematic reviews; RCTs, randomized controlled trials; DB, double-blind; PBO, placebo.



**Figure 2.** Number of articles by publication type and level of evidence.

Articles retrieved from PubMed search (N = 394) were evaluated for publication type and level of evidence based on the GRADE system.<sup>13</sup> Article types within each level of evidence (high, moderate, low, and very low) are listed below the corresponding category.

however, long-term use of antegrade enemas does yield successful results in nearly 70% of cases.<sup>25,26</sup>

### Clinical Research

Among pharmacological treatment options, the oral laxatives PEG and lactulose are the preferred choices for maintenance therapy and are used extensively in clinical practice based on physician experience, but the level and quality of supporting evidence from clinical research studies are not robust.<sup>27-29</sup> Data from placebo-controlled trials in PFC are lacking, and no RCT conducted to date has compared the efficacy of lactulose with that of placebo.<sup>29</sup> In multiple studies conducted in pediatric patients, lactulose was compared with liquid paraffin, lactitol, milk of magnesia, dietary fiber, guar gum, and senna. Despite the multitude of agents that lactulose was compared with, no study found clinical superiority of lactulose in terms of efficacy.<sup>28,29</sup>

PEG was compared with placebo in 2 studies in which PEG showed statistically significant improvement in frequency of defecation (primary efficacy outcome; mean difference was 2.61 stools per week, 95%

**Table 2.** Summary of Key Findings and Unmet Needs Identified in PFC.

	Current Treatments	Clinical Research	Education/Clinical Practice
Number of articles and key findings	<p>Pharmacological: 38</p> <ul style="list-style-type: none"> <li>Oral laxatives most commonly prescribed, but 40% of patients have frequent relapses or may not respond<sup>8-10</sup></li> <li>Growing use of probiotics/fiber.<sup>10,12-15</sup></li> </ul> <p>Nonpharmacological: 61</p> <ul style="list-style-type: none"> <li>Short-term improvements with enemas and surgery<sup>17,18</sup></li> <li>Sacral nerve modulation benefits sustained; data limited<sup>16</sup></li> </ul>	<p>Randomized controlled trials: 22</p> <ul style="list-style-type: none"> <li>Laxatives more efficacious than placebo short-term<sup>8,11</sup></li> <li>Limited data on prescription drug therapies<sup>6,7,19</sup></li> <li>Prucalopride safe and tolerated; efficacy similar to that of placebo<sup>7</sup></li> </ul> <p>Long-term outcomes: 26</p> <ul style="list-style-type: none"> <li>Limited data; few studies with pharmacological therapies reporting quality of life improvements<sup>11,20,21</sup></li> </ul>	<p>Education: 28</p> <ul style="list-style-type: none"> <li>Currently limited or no public health attention to PFC in pediatric residency programs<sup>22,23</sup></li> <li>Limited knowledge/understanding of idiopathic PFC pathophysiology, secondary causes, comorbidities, and treatment/management<sup>22,24-26</sup></li> </ul> <p>Clinical practice: 37</p> <ul style="list-style-type: none"> <li>Inconsistent use of Rome criteria and treatment guidelines for diagnosis/treatment of PFC<sup>3,4</sup></li> <li>Bowel diaries used more frequently than rectal examinations, X-rays, and laboratory tests for diagnosis<sup>6</sup></li> </ul>
Gaps/unmet needs	<ul style="list-style-type: none"> <li>Complete, sustainable relief in a subset of patients</li> <li>More options for maintenance therapy</li> </ul>	<ul style="list-style-type: none"> <li>Well-designed trials and adequate clinical research</li> <li>Long-term (<math>\geq 6</math> months) and real-world data</li> </ul>	<ul style="list-style-type: none"> <li>Improved education and awareness among clinicians</li> <li>Standard assessment criteria for clinical outcomes</li> <li>Implementation of multimodal treatment approaches</li> </ul>

Abbreviation: PFC, pediatric functional constipation.

confidence interval = 1.15-4.08), but the quality of the evidence for the primary outcome was low because of sparse data (101 patients) and inconsistency in the pooled analysis.<sup>29</sup> In a pooled analysis of 3 studies, PEG was found to be superior to milk of magnesia, but the effect size was modest (mean difference in frequency of defecation was 0.69 stools per week, 95% confidence interval = 0.48-0.89).<sup>28,29</sup> Furthermore, a recent pooled analysis of 6 studies in the pediatric population (n = 465 patients) comparing the effects of PEG versus lactulose in improving frequency of defecation reported a statistically significant difference in favor of PEG, but the risk of bias was high due to several confounding factors between studies that included heterogeneity (eg, different PEG compositions used and variability in study durations [ranging from 2 to 12 weeks]) and inconsistency (eg, definitions of constipation and outcome measures used).<sup>29</sup> Other studies comparing the efficacy of PEG with that of other treatments (eg, liquid paraffin, rectal enema, dietary fibers, and flaxseed [*Descurainia sophia*]) did not demonstrate any significant treatment benefit with PEG on the endpoints assessed (eg, fecal impaction).<sup>28,29</sup>

In a recent RCT conducted in constipated children with anorectal malformations, senna demonstrated greater efficacy than PEG on the endpoints assessed, including presence of daily bowel movements, absence of fecal soiling, and a clean abdominal X-ray obtained

after passing stool.<sup>14</sup> However, in previous studies senna was less effective than lactulose or mineral oil, and was associated with worsened fecal incontinence.<sup>28</sup> Taken together, existing studies do not provide conclusive evidence favoring any particular treatment option for PFC.

Currently, few data exist about the safety profiles and reported adverse events of laxatives; compounding this issue, the potential side effects of laxatives are gastrointestinal-related, similar to complaints mentioned by constipated children. The common adverse events of laxatives include diarrhea, bloating, flatulence, nausea, and abdominal cramping, many of which are similar to symptoms of PFC. Therefore, well-designed large placebo-controlled trials are needed to establish the tolerability profile of these treatments in the pediatric population.

Because constipation is a chronic problem, treatment outcomes ideally need to be assessed over the long term. However, it is difficult to assess the long-term efficacy of PEG and other laxatives when the great majority of published studies had short durations and lacked follow-up periods. Our research showed that among 25 RCTs conducted for laxatives, only 1 study assessed long-term efficacy ( $>3$  months), and nearly half of the remaining studies measured outcomes at  $\leq 1$  month.<sup>29</sup> These findings highlight the need for well-designed clinical studies of sufficient duration that permit investigation of current treatments on constipation outcomes over an extended period (6-12 months).

Besides oral laxatives, a limited number of pharmacological therapies have been studied in PFC. Our literature review revealed that prucalopride was the only drug therapy tested in phase 3 clinical trials for PFC. Although these studies demonstrated an acceptable safety profile for prucalopride in the pediatric population, they failed to meet their primary efficacy endpoint (percentage of responders, defined as the proportion of children with toileting skills who had a mean of >3 spontaneous bowel movements per week and 1 episode of fecal incontinence per 2 weeks), and response rates with prucalopride versus placebo were 17.0% and 17.8% ( $P = .90$ ), respectively.<sup>30</sup>

### Education and Clinical Practice

Currently, the knowledge and awareness among pediatricians of PFC pathophysiology and diagnosis and treatment strategies are quite limited, creating barriers to disease management.<sup>31,32</sup> While treatment guidelines are a valuable resource providing clarity on disease definition, diagnosis, and overall approaches to treatment,<sup>16</sup> a recent survey found that 84.3% of practicing pediatricians ( $n = 967$  completed responses) considered themselves to be unfamiliar or slightly familiar with the current NASPGHAN treatment guidelines.<sup>31</sup> Regarding common initial interventions for PFC without fecal incontinence, polled physicians opted for increased fluid intake (92.1%), dietary fiber (89.5%), prune/fruit juice (77.7%), behavioral interventions (71.2%), regular follow-up (53.4%), and reducing constipating foods (50.1%). Medication was reserved as the secondary intervention in most cases (55.2%), highlighting its lack of use until after the previous interventions failed. The above-mentioned study also reported that for constipation with fecal incontinence, bowel cleanout was considered crucial because disimpaction needs to occur before maintenance therapy can begin, yet 26.6% of respondents were unaware of this intervention. Regarding the choice of maintenance medication, 90.5% of respondents used osmotic laxatives, 27% used stimulant laxatives, and 28% used a combination of the two. Given that stimulant laxatives may be useful as rescue medication in refractory cases and in children with cecostomies, their use should be encouraged or at least evaluated more often.

In clinical practice, there are inconsistencies in the use of the Rome criteria for the diagnosis of PFC, as physicians often do not adhere to categories listed in the Rome questionnaires for diagnosing bowel-related FGIDs.<sup>9,10</sup> Approximately 75% of children with a Rome III diagnosis of PFC report abdominal pain, a diagnostic criteria for PFC and functional abdominal pain, both of which are distinct diagnoses per the Rome criteria.<sup>33</sup> Because of the

overlapping symptoms, about 40% of children qualify for 2 diagnoses, and 30% for 3 diagnoses based on the Rome III criteria.<sup>9</sup> This discrepancy between actual and perceived diagnoses may be attributed to physicians ignoring symptoms they regarded as unimportant, or including other symptoms in their diagnosis.<sup>9</sup>

Inconsistencies in diagnostic and outcome measures also occur in the clinical research setting, where various definitions of PFC and measures for assessing treatment outcomes are used in RCTs. A recent study reported that only 17 out of 45 clinical trials in PFC used the internationally accepted Rome III criteria.<sup>34</sup> Furthermore, across these 45 trials, 22 different definitions of PFC and 29 different definitions of treatment success were reported, and 24 of the 30 studies analyzed (80%) reported using patient/parental diaries or questionnaires to measure study outcomes.<sup>34</sup> Additionally, only 8 of 20 (40%) trials that considered stool consistency as an outcome measure used the internationally available Bristol Stool Scale. These findings are consistent with those from the 2015 survey of pediatricians and pediatric residents, in which the majority (61.3%) reported never or rarely performing digital rectal examinations, and nearly half (54.8%) ordered radiographic imaging.<sup>31</sup> Importantly, most of the study respondents were trainee physicians and attending physicians who recently finished their training, indicating that respondents remain unaware of the guidelines despite the existence of the guidelines throughout the duration of their practice.

Collectively, these findings highlight the need for greater public health attention to PFC in the clinical setting and in academic institutions with pediatric residency programs.

### Conclusions

Although several treatments are available, complete and sustainable symptomatic relief remains a major unmet medical need for patients with PFC. PEG and enemas are generally recommended for fecal disimpaction and PEG and lactulose are preferred as maintenance therapy; however, patients are likely to have incomplete symptomatic relief and relapse of constipation during the years following therapy. More options for maintenance therapy may be needed. Ideally, a novel pharmacological therapy could bridge this gap if it provides good-quality symptomatic relief over long periods while demonstrating safety in the pediatric population.

For novel molecules to become established as PFC therapies, and for existing options to increase supporting clinical evidence, well-designed trials and adequate clinical research are required. Currently, there are large discrepancies in disease definitions and choice of

outcome measures and methods. As a result, the existing clinical trials have a high degree of heterogeneity, magnified by the lack of placebo comparisons. Treatment outcomes would need to be studied in clinical trials with standardized long-term ( $\geq 6$  months) follow-up periods. Furthermore, real-world data from current prescribing patterns may offer valuable insight into treatment outcomes when drugs are administered outside the clinical trial setting. Analysis of such real-world data would also be valuable in understanding PFC prognosis in the current PFC patient population.

Improved education and awareness of multimodal treatment strategies can facilitate better diagnosis and management of PFC. Current treatment guidelines (eg, NASPGHAN-European ESPGHAN guidelines, 2014) serve as a valuable resource for disease definition, diagnosis, and overall approaches to treatment, but pediatricians and trainees may not be fully aware of such guidelines. As a result, the knowledge and understanding of idiopathic PFC pathophysiology, secondary causes, comorbidities, and treatment among pediatricians is quite limited. Improving awareness in pediatric residency programs would increase the likelihood of guideline recommendations becoming a part of pediatricians' medical training and clinical practice, thereby improving the outlook for PFC treatment and management.

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### Author Contributions

All authors contributed to conception, design, analysis, and interpretation of data. All authors critically revised and reviewed the final manuscript.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MS served on the Sucampo Advisory Board and his spouse holds stock options in Abbott and AbbVie. PL is an employee of Mallinckrodt Pharmaceuticals (previously Sucampo AG) and held stock options in Sucampo Pharmaceuticals, Inc. MCP is an employee of Takeda Development Center Americas, Inc.

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