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Constipation in Children: A guide to Prompt Diagnosis and Effective Treatment

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Abstract

Purpose of review Constipation Is a common pediatric symptom that can affect children of all ages. It impacts children both physically and psychosocially while also causing significant emotional and financial stress to their families. Constipation presenting early in life can be secondary to conditions such as anorectal malformations, anal stenosis, Hirschsprung disease, spine abnormalities, cystic fibrosis, or metabolic dysfunction. Yet, the majority of children and adolescents who struggle with constipation do so as a result of a functional disorder. Diagnosis Is primarily based on fulfilling defined clinical criteria. Despite being so prevalent, functional constipation is often misdiagnosed and inappropriately treated. Laxative use Is often avoided due to misconceptions related to their efficacy and safety. This review addresses how to effectively diagnose and treat functional constipation in children of different ages and with variable severity at the time of presentation.

Recent findings Guidelines from several medical societies for the evaluation and treatment of a child presenting with constipation have been published. It has become increasingly clear that early treatment of functional constipation is associated with improved long-term outcomes. The diagnostic role of anorectal and colonic manometry has been clarified and these tests have been standardized in the pediatric population. New medical and surgical treatments have been developed and Are leading to improved outcomes in children who fail conventional medical and behavioral interventions.

Summary Childhood constipation Requires a comprehensive therapeutic plan, comprised of education, behavioral intervention, and medication that jointly produce effective defecation. Children with chronic constipation who Are unresponsive to maximal medical

treatment benefit from further evaluation with colonic transit studies, anorectal and colonic manometry, imaging studies of the spine, and defecography—especially if more invasive interventions such as anal sphincter botulinum toxin injection, appendicostomy, cecostomy, colonic resection, ileostomy, and sacral nerve stimulation are being considered. These children Are best evaluated in specialized centers that offer a multidisciplinary approach to both the physical and psychosocial components of chronic constipation treatment.

Introduction

Functional constipation Is a common problem in children. Its worldwide prevalence ranges from 0.7 to 29.6% [1]. It Is commonly encountered in both general pediatric and pediatric gastroenterology clinics and accounts for 3–10% and up to 25% of visits in these settings, respectively [2]. Functional constipation in children Is characterized by infrequent defecation, excessive stool retention, painful bowel movements, large stool caliber, and fecal incontinence. Its etiology Varies but diet, behavioral, and psychosocial abnormalities as well as genetic factors can be contributing factors [3, 4].

Normal bowel movement frequency varies with age in children and ranges from an average of 4 per day at birth to about 1 daily in those over 3 years of age [5]. The pathophysiology of functional constipation Is related to a maladaptive response to an uncomfortable defecation. Its impact on the child's health and quality of life Is significant. The annual healthcare expenditure in the USA attributed to the care of children with constipation Is estimated to be $3.9 billion [6]. Despite these realities, the majority of children with constipation do not receive timely treatment [7]. The onset of functional constipation Is most commonly observed at three predictable developmental stages. First, when an infant transitions from exclusively formula or breast feeding to the introduction of solids. Second, when a child begins toilet training and third, at the start of school.

Constipation Is a symptom and as such it has a differential diagnosis. Other causes of disordered defecation need to be considered as the source. Signs, symptoms, and exam findings that suggest an organic etiology include constipation that starts extremely early in life, delayed passage of meconium (more than 48 h after birth), family history of Hirschsprung disease (HD), ribbon-like stools, failure to thrive, bilious vomiting, abnormal thyroid gland, severe abdominal distention, sacral dimple, gluteal cleft deviation, and tuft of hair on spine [8].

Early onset of symptoms and delayed passage of meconium should raise suspicion for HD [9]. Yet, reports indicate that up to 50% of patients with HD pass meconium within the first 48 h of life, underscoring the importance of keeping this diagnosis in the differential even when a child's history Is less classic [10].

The child's medical, surgical, developmental, and psychosocial history along with the concomitant use of medications should be obtained. Relevant family history includes presence of thyroid disease, cystic fibrosis, celiac disease, or HD. The child's developmental stage and the presence of psychosocial stressors Are other areas that should be explored. In any child with intractable constipation, it is essential to uncover a history of being bullied, physical or sexual abuse, or other events that can be significant contributors to the persistence of symptoms.

Diagnosis

The diagnosis of functional constipation Is criteria-based. According to Rome IV, it must include 2 or more of the following occurring once or more per week for a minimum duration of 1 month in a context where there has to be insufficient evidence to meet the criteria for a diagnosis of irritable bowel

syndrome. The symptoms cannot be fully explained by another medical condition after appropriate evaluation (sometimes that means no testing) [11••].

1. Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
2. At least 1 episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of large fecal mass in the rectum
6. History of large diameter stools that can obstruct the toilet

A prompt and correct diagnosis of functional constipation relies on a detailed history and a thorough physical examination. The history should include detailed information about the age and circumstances associated with the onset of constipation, defecation frequency, presence, or absence of soiling episodes, stool characteristics preferably done with the help of the Bristol stool chart, associated symptoms, psychosocial history, and medications already tried [12•]. The caregiver's observation of the child's posture and behavior around stooling is of paramount importance and should be shared with the provider. Children who experience unpleasant and painful stool evacuation often develop stool-withholding behaviors that further perpetuate the problem. Parental misinterpretation of a child's behavior and various postures as an effort to defecate rather than withhold is common. It is the provider's responsibility to inquire about these rituals that Are typical of withholding behavior.

Abdominal radiograph

Abdominal radiography is widely used in the evaluation of a patient presenting with abdominal pain and/or difficult defecation. A few studies have investigated the value of scoring fecal loading on abdominal x-ray in diagnosing constipation. The sensitivity ranged from 70 to 80% and the specificity ranged from 43 to 90%. The reliability of abdominal radiography in making a diagnosis of constipation is therefore poor [13–17]. There are specific circumstances that may justify using an abdominal radiograph in the evaluation of a child with possible constipation. One scenario when patient's chief complaint is incongruent with the history (i.e., reports diarrhea yet the clinical history is more indicative of constipation with overflow incontinence). Another situation when radiographs Are beneficial is when a digital rectal exam cannot be performed (patient refusal or history of sexual abuse) to confirm presence of rectal fecal impaction. In this case, a radiograph may be used to demonstrate the presence of a rectal fecal mass. Finally, films Are useful when determining the need for or planning a clean-out in a child resistant to a rectal examination, as the film can be used to demonstrate the extent of the fecal load, and success of the intervention.

Colonic transit studies

Colonic transit studies are one form of diagnostic technique utilized to understand the nature of a patient's constipation. Reports indicate that the transit

time from the pylorus to the ileocolonic junction can take 2 to 4 h for ingested food [18]. Normal colonic transit is much slower than that of small bowel transit at 12–72 h [18]. Motility along the entire GI tract can be evaluated using either ingested sitz markers or radio nuclear transit scintigraphy. The sitz marker transit study relies on radio-opaque plastic rings that Are ingested orally and viewed on serial radiography. There Are different protocols of performing this transit study. Our center utilizes a protocol that involves the child ingesting a capsule of 24 markers on days 1, 2, and 3 with an abdominal x-ray on day 4 and, if necessary, on day 7 [19].

Radio nuclear transit scintigraphy may also be used for evaluation of children with chronic constipation. It is helpful in the identification of normal transit, pancolonic slow transit and fecal retention from a distal colonic or outlet obstruction. The patient is asked to stop all laxatives for 5 days and fast for 4 h prior to this study. A methacrylate-coated capsule containing indium-111 is then orally administered. Images Are taken at 4, 24, and 48 h, and geometric centers Are calculated. The resultant images Are analyzed with colonic transit estimated by both visual interpretation and identification of the geometric center (representing the median of radioactivity). This test is not widely available. Other limitations of this modality include lack of normative data, expense, and the size of the capsule which makes it impossible for young children to swallow it [20].

Anorectal manometry

Anorectal manometry, especially when performed without sedation, can be very informative. It is a test that is commonly performed in children with a history of chronic constipation. It assesses anal sphincter function, rectal sensation, anorectal reflexes, and pelvic floor function. The test is performed using a flexible catheter that has multiple sensors and a balloon at the tip. Setting appropriate expectations and addressing the patient's concerns or anxiety about the procedure is essential. The exam is typically performed with the patient on their left side [21]. The goal of placement is to have the catheter tip and attached balloon resting in the rectal vault with the high-pressure zone of the anal canal clearly identified by the pressure sensors.

The study commences by checking the resting pressure of the anal sphincter followed by having the patient squeeze as hard and as long as possible to record the maximum pressure attained and the duration of time that it can be sustained [22]. The next task is to perform balloon inflation with air and determine the presence or absence of the recto-anal inhibitory reflex (RAIR). The balloon volume is incrementally increased until a RAIR is demonstrated repeatedly or failure to do so is determined. Finally, the patient is asked to simulate defecation and push out an inflated balloon from the rectum in children mature enough to cooperate with this portion of the test.

The information gathered from this evaluation is interpreted in the context of the patient's clinical presentation. Hypertensive sphincter, sphincter weakness, non-relaxing anal sphincter, dilated rectum, hypo- or hyper-sensitive rectum, and dyssynergic defecation Are some diagnoses that manometric examination can identify. Further understanding of anorectal function during evacuation can be obtained from a fluoroscopic defecography. This test can

assist in diagnosing pelvic floor dyssynergia (PFD) and may show structural abnormalities leading to specific therapeutic interventions [23].

Colonic manometry

Colonic manometry is used to assess colonic motor function (or motility). It is performed with specially designed catheters that are placed and left in the colon for the duration of the study. Some of the indications for colonic manometry include:

1. Determine if severe constipation that is unresponsive to adequate medical therapy is due to intrinsic colonic dysmotility or has functional etiology.
2. Act as a guide to plan surgical interventions—including creation of diverting stoma, segmental colonic resection or formation of a conduit for administration of antegrade continence enemas.
3. Evaluate a diverted colon before possible takedown of an ostomy [24••, 25].

Water perfused and solid-state catheters Are the most commonly used colonic manometry catheters. The high-resolution solid state catheter has greater number of pressure sensors that Are spaced much closer to each other compared to the water perfused catheters, which enables a more precise mapping of the colonic function. The catheter is placed under anesthesia with the aid of either colonoscopy or fluoroscopy. Once the patient has fully recovered from anesthesia, the study commences based on the center's protocol (can be same or following day). Fasting and post-prandial colonic motility activity is continuously recorded [26]. Normal colonic response to ingestion of a meal (the "gastro-colonic reflex") occurs when there is an increase in motility after ingestion of a meal in excess of 600 Kcal [26]. This postprandial response is often impaired in children with intractable functional constipation [27•].

The last part of a colonic manometry is a provocative test with administration of a stimulant medication, such as bisacodyl or glycerin. The stimulant is administered directly into the colon via the central lumen of the catheter [26]. The expected colonic response to the stimulant is generation of high amplitude propagating contractions (HAPC), a distinct pattern of motor contractions associated with antegrade movement of colonic contents. Absence of HAPCs or lack of full propagation to the recto-sigmoid junction of these contractions despite these provocative measures is indicative of abnormal motility. Other types of colonic contractions deemed to be less effective in antegrade movement of stool include low amplitude propagating contractions (LAPC) and contractions that propagate for short distances or in a retrograde direction. Ideally, a trained observer should be with the patient in the room during the entire test to document everything that happens, including the child's behavioral responses as well as the parental interactions with the child and medical providers. This information is clinically relevant and essential in interpreting the manometric tracing.

Treatment

The core components of therapy Are education, behavioral modifications, and timely, regular use of oral and rectal laxatives. Treatment is a team effort with

defined roles for the clinician, the patient, and the family (Fig. 1). Once a clinical diagnosis of functional constipation is established, the clinician's most important task is to educate patient and caregivers about the condition. A discussion about the role of limited testing is important and contributes to the therapeutic plan. If a caregiver is expecting an extensive workup, failure to discuss why testing is usually unnecessary will adversely impact the effectiveness of the treatment due to misunderstanding and noncompliance. The in-person discussion ought to be augmented with written information about the diagnosis and its treatment. This discussion should focus on the chronic nature of pediatric functional constipation, the need for long-term therapy, and the importance of tailoring the treatment to achieve the desired effect. It has been reported that only 50% of children treated and followed (for up to 1 year) at a tertiary care center recovered to the point that they were taken off laxatives [28, 29]. These data should inform the discussion and justify the long-term nature of the treatment.

A child or an adolescent who presents with constipation complicated by fecal impaction and fecal incontinence should first undergo a clean out followed by initiation of daily medications. Our preferred clean out plan in a patient with fecal impaction consists of using rectal enemas or suppositories followed by high-dose oral laxatives. Some patients will be resistant to this approach or develop complications from oral clean out (aspiration or abdominal compartment syndrome). Manual disimpaction performed under sedation is sometimes necessary to remove the rectal fecal impaction prior to starting an

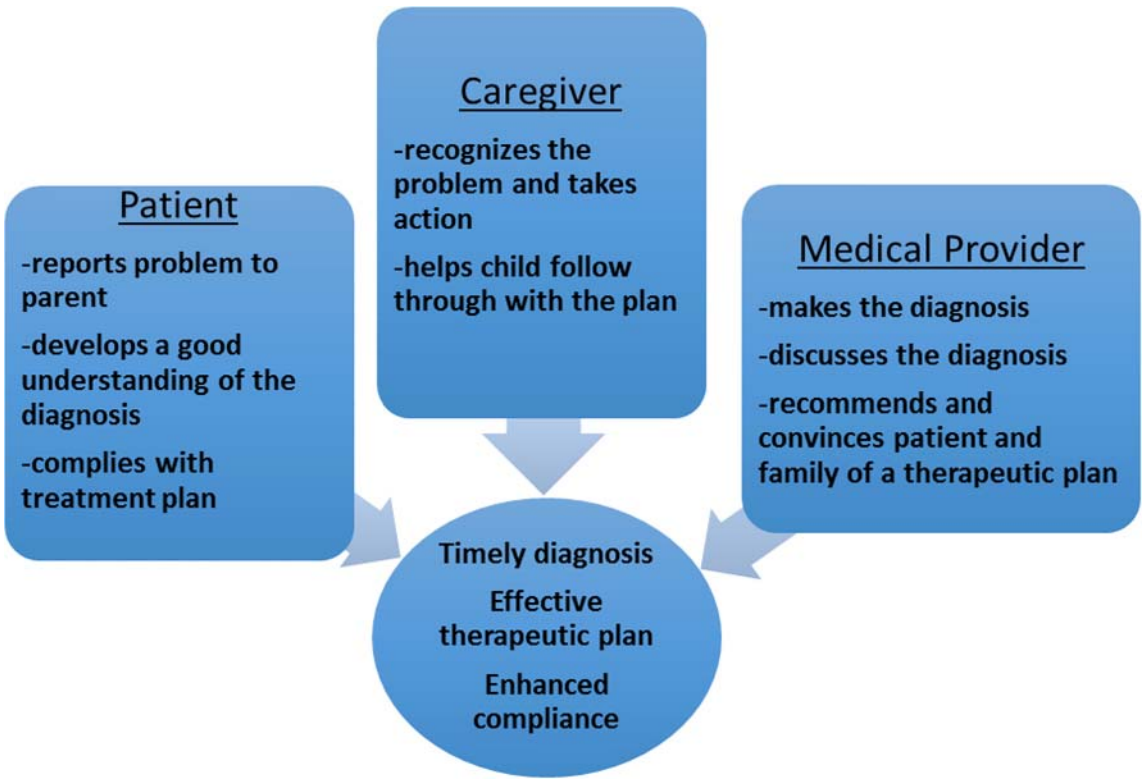

Fig. 1. Relationship of the patient, caregiver, and medical provider roles in the management of constipation

aggressive oral clean out regimen. Ultimately, the goal is to effectively empty the colon of any stool burden and allow the daily maintenance regimen to be effective.

The oral and written instructions given to the patient and caregivers should emphasize the following:

1. A healthy dietary practice that ensures adequate fiber intake to achieve soft stool consistency.
2. Oral laxatives Are meant to help evacuate stool on a regular basis. The doses of oral laxatives Are to be adjusted up or down based on the individual patient's response.
3. Rectal enemas and suppositories Are an essential part of therapy. They can be used on as-needed basis or given daily to help facilitate timely and effective stool evacuation.
4. The choice between medications given orally or rectally should be made together with the child and the parents.
5. The benefits of any pharmacologic treatment outweigh its potential adverse effects and the concern for developing "dependence" is unfounded.
6. The need to administer medications regularly and remain vigilant for a prolonged period of time should be emphasized.

Dietary therapy

It is well known that breast-fed infants have different stool consistencies from those who Are formula fed. This well-known observation underscores the role diet plays in defining the characteristics of stool. Soluble dietary fiber intake is helpful in softening the stools [30]. The American Health Foundation recommends a child's daily fiber intake in grams should be their age plus 5 (with a maximum of 25 g per day)—an amount which is not met by the majority of American children [31]. Okuda et al. studied the relationship between functional constipation and dietary habits in school-age Japanese children. The authors found significant association between poor dietary fiber intake and prevalence of functional constipation in primary and secondary school students. The same study further reported that increased bread consumption was related to higher prevalence of functional constipation [32]. Another study by Roma et al. reported that children with constipation have a significantly lower fiber intake [33]. Thus, poor fiber intake seems to be predisposing to the development of childhood constipation.

The role of juice and water intake in both causing and helping treat constipation is not well understood. Young et al. conducted a randomized trial evaluating the effect of increasing oral fluids in chronically constipated children. There were no significant changes in stool consistency or frequency when the group with increased water intake was compared with the control group [34]. The role of diet on stooling is further demonstrated in children with celiac disease. Although it is more common for children with celiac disease to present with diarrhea, some report constipation as the primary symptom. Both the diarrhea and constipation associated with celiac disease Are responsive to gluten free diet [35].

The medical literature was reviewed extensively by Tabbers et al. as part of the evidence-based recommendations from ESPGHAN and NASPGHAN in 2014. They concluded that the use of additional fiber beyond the recommended daily intake was not helpful in the treatment of functional constipation based on the available evidence. In the same report, experts also found no beneficial role of pre- or probiotics in the treatment of constipation in children [8].

Behavioral and pelvic floor therapy

Children with constipation may present with behavioral challenges that Are directly associated with defecation. Little et al. conducted a study in preschool age children in which they assessed differences in sensory processing patterns between those with chronic constipation and a control group. They found that those with chronic constipation had significantly higher sensory scores and concluded that children with chronic constipation have abnormal underlying sensory characteristics complicating their toileting behaviors [36••]. It Is not uncommon for children to develop stool withholding and soiling as they Are going through toilet training [37]. Interventions that focus on positive reinforcement, avoidance of negative terms and language to refer to feces as well as use of a child-oriented approach to toileting can help shorten the period of toileting refusal [38].

Pelvic floor dyssynergia in children with functional constipation is common and can be difficult to address effectively. Two approaches to treat fecal incontinence associated with functional constipation Are pelvic floor physical therapy and biofeedback therapy. Pelvic floor physical therapy has been reported to be effective in improving fecal incontinence in the majority of children who had the intervention [39]. In a multicenter randomized controlled trial, authors found that pelvic physiotherapy (PPT) was significantly more effective than standard medical care, which consisted of education, toilet training, and laxatives in children 5 to 16 years old [40••]. Biofeedback therapy has also been reported to have clinical efficacy in children with constipation and PFD [41].

Medications

Polyethylene glycol (PEG) is one of the most commonly used medications in the treatment of children with constipation. It is a stool softener that can be used alone or in combination with a stimulant drug. Its dose should be titrated to achieve a soft stool consistency. Advantages include that it can be mixed in the child's fluid of choice, is palatable, and generally well tolerated. In a randomized, double-blinded, placebo-controlled study investigating PEG efficacy, Modin et al. demonstrated that treatment with PEG is significantly more effective than placebo to prevent constipation recurrence during long-term maintenance treatment [42•]. This study included a 24-week follow-up period and monitored the incidence and severity of adverse events related to PEG. None were identified during this interval. Two other randomized, placebo-controlled studies have also investigated the effect of PEG on childhood functional constipation and attest to its effectiveness [43, 44]. Nurko et al. tested the efficacy of three doses in their dose-ranging study. They recommended a starting dose of 0.4 g/kg/day, which showed good efficacy and fewer side effects (looser stools and abdominal cramping) when compared with the higher dose of

0.8 g/kg/day. It is important to underscore that the initial recommended dose is a starting dose and should be adjusted based on the clinical response. There have been public concerns regarding neuropsychiatric events occurring with PEG 3350. Williams et al. reported that daily PEG 3350 therapy in the pediatric population was not associated with sustained elevation of ethylene glycol, diethylene glycol, and triethylene glycol blood levels when compared to matched controls [45••]. Lactulose and milk of magnesia Are other osmotic drugs that soften stools and Are taken orally.

Senna is a stimulant laxative commonly used in the treatment of children and adolescents with constipation. Its primary mechanism of action targets intestinal smooth muscle increasing intestinal contractility. The use of senna as a long-term laxative seems to be safe. The only reported side effect is perianal dermatitis in children on high-dose senna and prolonged skin contact with stool [46•]. Oral Bisacodyl is another commonly used stimulant medications. It can be used alone or in combination with other medications intended to soften the stools. It is available in multiple forms; orally as a tablet or rectally as a suppository or enema. The liquid rectal version can also be delivered in an antegrade manner via a cecostomy or an appendicostomy. Stimulant medications such as bisacodyl, senna, and glycerin Are effective in generating propagated colonic contractions, such as HAPCs. These strong and sustained colonic contractions can be felt as abdominal cramping by the patient at times. Some children have a negative response to this cramping sensation. They may complain, withhold, and squander the opportunity to have a bowel movement rather than proceed to the toilet to defecate and relieve the colon from its burden. Thus, education is paramount to inform the patient, and their family, about the nature of the cramping, desired response and need to make adjustments to the dose if the cramping is severe.

Novel medical treatments

Plecanatide, linaclotide, lubiprostone, and prucalopride Are some of the newer medications that have recently entered the market after being approved by the FDA for the treatment of constipation and constipation predominant irritable bowel syndrome in adults. The first three Are intestinal secretagogues. Plecanatide and linaclotide Are guanylate cyclase-C (GC-C) agonists, while lubiprostone is a chloride-channel-2 activator. They all act by drawing fluid into the intestinal lumen via osmotic gradient, and thereby help soften the stool. Diarrhea is the most common adverse effect of plecanatide and linaclotide and systemic exposure to these drugs is negligible due to their poor intestinal absorption [47, 48]. Lubiprostone, a prostaglandin E1 analog, has more adverse effects including nausea in 29%, diarrhea in 12%, and headache in 11% [49]. Prucalopride is a selective 5-hydroxytryptamine 4-receptor agonist that was not found to be superior to placebo in a large randomized, placebo-controlled study in children despite reported efficacy in constipated adults [50].

Surgical interventions

Some children with chronic, intractable constipation fail to improve despite aggressive therapy including high-dose oral laxatives, rectal enemas, and

behavioral interventions. Constipation and fecal incontinence can become so severe that the child's ability to socialize with peers and quality-of-life are adversely impacted. Surgical intervention should be considered in these refractory cases. A variety of surgical procedures can be employed to address defecation problems in such children. They include anal dilation, internal anal sphincter myectomy, anal sphincter botulinum toxin injection (chemical sphincterotomy), Malone appendicostomy or cecostomy creation for antegrade continence enema (ACE) administration, segmental colonic resection, stoma formation, and sacral nerve stimulation [51•]. Anorectal manometry can diagnose outlet and pelvic floor dysfunction or a non-relaxing anal sphincter suggesting the need for intra-anal sphincter botulinum toxin injection with or without biofeedback therapy. Injection of botulinum toxin was found to be as effective as myectomy without being as invasive as the latter [52]. The safety of anal sphincter botulinum injection is reported to be excellent [53]. Colonic manometry helps guide what specific interventions Are most likely to be effective. Rodriguez et al. reported that colonic manometry helps in predicting the outcome of an ACE and that colonic motility improves following therapy with antegrade enemas [54]. An antegrade continence enema regimen completely evacuates the colonic stool reducing the chance for fecal incontinence and giving the child a much improved quality of life and function. Our experience has been that antegrade continence enemas Are most helpful when the cleansing solution consists of a mix of a stimulant laxative such as bisacodyl or glycerin and a carrier such as tap water, normal saline, or a PEG containing fluid. Children with intractable constipation due to total colonic inertia often need colonic diversion with an ileostomy. Ultimately, the decision to pursue surgery and choice of procedure should be tailored to the individual child and should be made after a collaborative discussion among the family, surgeon, and gastroenterologist.

Emergency presentations

The vast majority of children with constipation Are successfully managed in the outpatient clinic setting. Clinicians should be open to trial of various approaches and medication combinations to determine an effective regimen. There Are, however, rare circumstances that mandate immediate intervention. Children and adolescents whose symptoms go untreated can present with severe constipation complicated by vital sign changes, marked abdominal distention, abdominal compartment syndrome, colonic perforation, and shock (Fig. 2) [55]. Etiologies for these life-threatening cases can include inadequate therapy, noncompliance with use of medications, lack of follow-up, behavioral challenges, and undiagnosed underlying organic pathology such as HD.

The safest and most effective intervention in children who present with marked rectal fecal impaction and excessive colonic stool burden begins with administration of rectal enemas or manual disimpaction under sedation or anesthesia [55]. Rarely, emergent surgical decompression is required. Only after a substantial amount of stool is successfully evacuated from the rectum, should an oral clean out be started. The clean out can be accomplished orally or via a cleansing solution administered through a nasogastric tube. A complete clean out alone is inadequate treatment. It should be one component of a

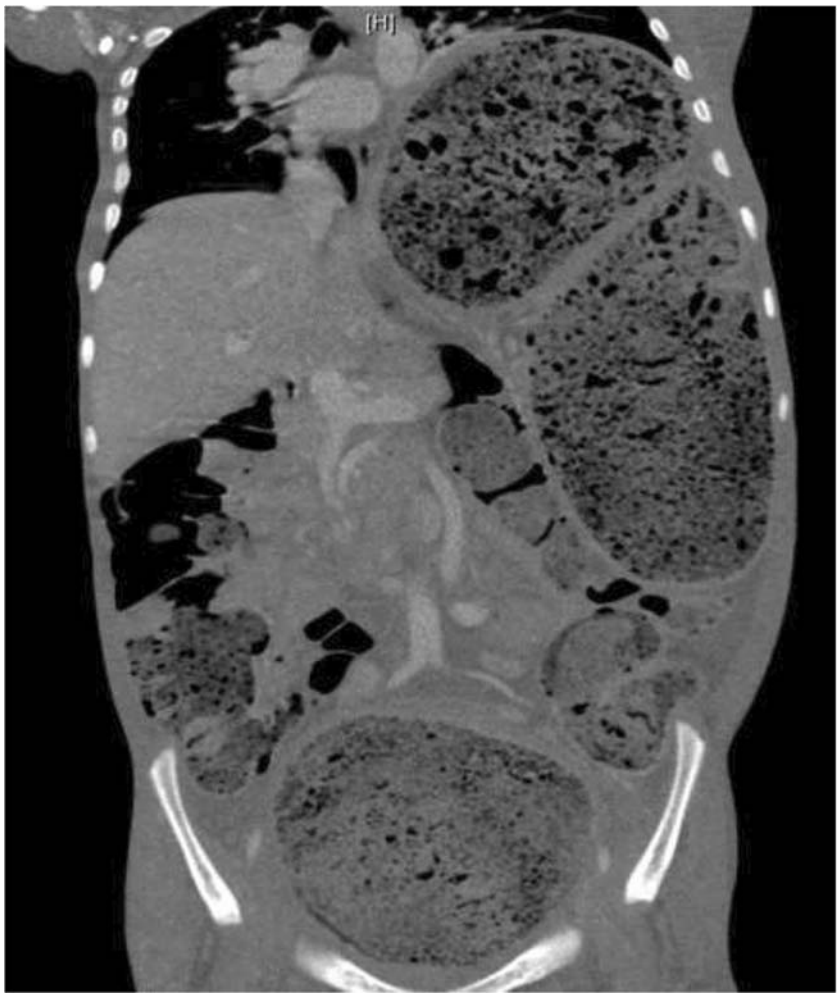

Fig. 2. Computerized tomography (CT) of the abdomen demonstrating severe colonic stool burden and rectal fecal impaction

comprehensive diagnostic and management strategy. The most important element is an effective maintenance regimen. The patient and their family must be educated about the importance of adhering to the recommended therapy and regular follow-up as well as the possible life threatening complications of untreated constipation. In the most severe presentations, further evaluation including use of anorectal manometry, colonic manometry, lumbar spine MRI, and laboratory testing should be considered after the child's condition has been stabilized.

Directions for future research

Future research should aim to improve identification of gaps in care at the primary care level, further understand the impact of familial perceptions regarding the behavioral and physiological components of childhood constipation (there Are numerous myths and misconceptions about this condition!), and determine how adherence to prescribed therapy as well as diet and physical

activity recommendations influence outcomes. High-resolution, solid state, and fiber-optic colonic manometry catheters with closely spaced sensors continue to increase our understanding of different colonic motor events. It is paramount that we explore these newly identified motor contractions and develop an understanding their clinical significance. Another area in need of clarification through additional research in pediatrics is deeper understanding of dyssynergic defecation disorders and the therapies that Are most effective in their treatment. Finally, the roles of surgical intervention and colonic neuromodulation in the treatment of functional constipation should be explored further with well-designed studies.

Conclusions

Functional constipation is a common problem in the pediatric population. It affects children of all ages. It is primarily a clinical diagnosis based on a detailed history, physical exam, and knowledge of the pediatric Rome criteria. The majority of children with constipation Are responsive to treatment and do not require additional testing. Imaging and transit studies as well as manometric evaluations Are used to assess children with refractory constipation or a dramatic initial presentation. The timing and choice of these studies should be discussed with pediatric gastroenterologist and surgery specialists. Treatment for constipation is most effective when started early and subsequently maintained. Initially, this usually involves a cleanout followed by a regimen of maintenance medication. Behavioral interventions and dietary changes can provide added benefits leading to successful treatment. Lastly, invasive therapies should be reserved for cases that are refractory to standard treatments or require urgent intervention at the time of presentation.

Compliance with Ethical Standards

Conflict of Interest
Desale Yacob declares that he has functioned as a consultant for QOL, Inc. Carlo Di Lorenzo declares that he has functioned as a consultant for QOL Inc., Mallinckrodt, Mahana, Sucampo, Allergan, Shire.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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