



Evaluation and Management of Intractable Constipation in Children

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Received 2018 September 28; Accepted 2018 October 15.

Abstract

Intractable constipation has a negative impact on quality of life and well-being of children. The evaluation includes a thorough history and physical examination with diagnostic testing to rule out metabolic, systemic, anatomic, and neurological etiologies. In children with refractory symptoms who failed aggressive medical management, colonic transit studies help guide need for invasive testing. Manometric testing of the anorectum and the colon are recommended to evaluate for enteric neuromuscular compromise and guide novel medical and surgical therapies. Goals of management are to facilitate colonic emptying, ensure fecal continence, and preserve colonic neuromuscular integrity. Treatments range from aggressive medical therapy with stimulant laxatives that modify transit to antegrade continence enemas that facilitate colonic emptying. Surgery, including diverting ostomy and resection, has a limited role and should only be considered in select patients after medical and manometric evaluation. The aim of this article is to provide an update on the evaluation and management of childhood intractable constipation.

Keywords: Constipation, Children, Refractory

1. Context

The worldwide prevalence of constipation in children ranges from 0.7% to 29.6% (1). Constipation has a significant impact on public health including rising health care utilization of outpatient, emergency, and inpatient services, and associated financial burden (2, 3). Children with constipation have a lower health related quality of life including emotional, psychosocial, and physical well-being (4).

In children, constipation is considered either functional or organic in etiology. Greater than 90% of children fulfill the Rome IV criteria for functional constipation and have a reassuring history and physical examination (5). Organic etiology accounts for less than 10% of children who present with constipation and includes anatomic, neurologic, metabolic, toxic, gastrointestinal, and neuroenteric causes (6). Intractable constipation (IC) is defined as constipation that is refractory to conventional treatment with laxatives and stool softeners. Organic disease should be suspected in children who develop refractory symptoms, especially in those with concerning findings on history and physical examination.

2. Evaluation

The evaluation starts with a thorough history and physical examination. It should be tailored towards investigation of underlying organic etiology and appropriate diagnostic testing. Onset and duration of symptoms should be evaluated in the context of the child's age, development, and toileting habits. A detailed history includes stool consistency and frequency, presence and severity of fecal incontinence, withholding behavior, response to laxatives, and medications that may alter colonic transit. Alarming gastrointestinal symptoms include nausea, vomiting, abdominal distention, weight loss, bloody stools, and recurrent fecal impactions. Laboratory testing is indicated in those with symptoms of hypothyroidism, celiac disease, lead poisoning, or derangement of calcium and potassium.

Refractory constipation in neonates and infants, and in children with associated anomalies should raise concern for anorectal malformations. Anorectal malformations are commonly identified during neonatal examination, however, 13 - 25% may present beyond the neonatal period and are associated with morbidity and mortality (7, 8). The perianal examination should focus on anal placement, symmetry of radial corrugations, cremasteric/anal reflexes, and rectal tone/caliber. Flat buttocks, deviation of the gluteal

crease, and midline spinal defects (tufts, dimples) are suggestive of anorectal and sacral malformation.

History of delayed passage of meconium (> 24 - 48 hours), recurrent obstructions, enterocolitis, vomiting, abdominal distention, and poor growth are concerning for Hirschsprung disease (HD). There should be a higher index of suspicion for children with chromosomal abnormalities (trisomy 21) and syndromes (Waardenburg, congenital central hypoventilation) (9). While considered primarily a neonatal disease, in a retrospective review of national inpatient databases, Aboagye et al. reported that 6.5% of HD cases presented within the 1st week of life, 60% by the end of 1st year, and 93% by 13 years of age (10). Therefore, HD should be suspected in any child or adolescent with IC. Patients with suspected HD should undergo anorectal manometry to evaluate for the recto-anal inhibitory reflex. If absent, rectal suction or full thickness biopsy is performed to exclude HD by the presence of ganglion cells and normal acetylcholinesterase and calretinin staining (11). In centers without manometric capability, contrast enema may be used to identify the transition zone. A normal contrast enema does not rule out HD, especially in the neonatal period and in those with short-segment disease. Patients who have a normal rectal biopsy and a non-relaxing internal anal sphincter (IAS) are diagnosed with IAS achalasia.

The presence of urologic and neurologic symptoms should raise concern for spinal anomalies including masses, dysraphism, and tethering. Spinal anomalies have been reported in 3 - 9% of children with IC (12, 13). Patients may present with urinary incontinence and retention, fecal incontinence, back pain, changes in gait and sensation, and progressive neuromuscular deficits of the lower extremities. A neurological examination of anal and cremasteric reflexes is recommended. The presence of anal spasms on anorectal manometry was demonstrated by Siddiqui et al. to be predictive of spinal abnormalities on MRI in 60% of their pediatric cohort (14). Manometric findings of neuropathy include abnormal intra-anal pressures and prolonged IAS relaxation and/or recovery with serial and sustained balloon inflations (14, 15).

Once metabolic/systemic, anatomic, and neurological etiologies have been addressed patients should undergo appropriate radiographic and manometric evaluation for possible neuromuscular compromise of the colon.

Abdominal radiographs (AXR) are commonly used in the evaluation of children with constipation. The current ESPGHAN-NASPGHAN consensus guidelines do not recommend the routine use of AXR to diagnose constipation (5). In a systematic review of six studies, Reuchlin-Vrolage et al. demonstrated variable sensitivity (60 - 80%) and specificity

(35 - 90%) of the AXR in discriminating children with and without clinical symptoms of constipation (16). There is poor correlation between symptoms and severity of constipation and findings of fecal impaction and degree of stool loading on AXR (16-18). Poor sensitivity/specificity and inter/intra-observer variability have been reported with different scoring systems (Barr, Leech, Blethyn, etc.) (16, 17, 19). An AXR could be considered in instances of unreliable history, inaccurate abdominal or rectal examination, suspicion of colonic distention, and concern for obstruction.

In children with refractory constipation the evaluation of colonic transit is valuable prior to moving forward with invasive testing. Colonic transit can be assessed using radiopaque marker (ROM) study or colon transit scintigraphy.

Colon transit scintigraphy is limited by cost, availability, and lack of normative pediatric data. Studies demonstrate that scintigraphy is feasible in the children and report three patterns normal transit, slow transit (segmental, total colonic), and anorectal retention (20, 21). In children with severe constipation, Mugie et al. demonstrated a poor level of agreement (kappa 0.34) between colonic manometric and scintigraphy findings (22). While scintigraphy may serve as an adjunct to manometric evaluation of the colon, future studies are needed to validate its diagnostic and therapeutic utility in children with IC.

There are limited studies using ROM to evaluate colonic transit in children (23, 24). The ROM study is readily available, simple, and well tolerated in children, however pediatric protocols and normative data are lacking. Children can be classified as having normal transit, slow transit, or anorectal retention (25). In patients with anorectal retention the markers are distributed in the rectosigmoid and indicate withholding and/or pelvic floor dysfunction. In their cohort of 24 children with constipation, Tipnis et al. reported that a normal ROM study correlated with a normal colonic manometry testing. However, an abnormal ROM study was not predictive of abnormal colonic manometry (26). Children with abnormal ROM study who fail aggressive medical therapy should undergo colonic manometry (CM) testing. CM evaluates the neuromuscular integrity of the colon by characterizing colonic response to meal (gastrocolic response) and the presence of high amplitude propagating contractions (HAPCs) during fasting, meal, or with bisacodyl administration. CM is used to differentiate colonic neuroenteric abnormalities, such as neuropathy and myopathy, from functional constipation (27, 28). Abnormalities on CM may be total or segmental and include absence of gastrocolic response to a meal and abnormal amplitude and/or propagation of HAPCs (28). Colonic inertia is characterized by absence of

gastrocolic response and HAPCs (28).

3. Management

The goals of management are to facilitate colonic emptying, ensure fecal continence, and preserve colonic neuromuscular integrity. Fiber, fluids and physical activity, and pre and pro-biotics have a limited role. Pediatric studies have not demonstrated additional benefit of combining biofeedback and behavioral therapy to conventional medical therapy (5, 29). Recently, pelvic floor therapy/physiotherapy has been shown to improve symptoms of functional constipation and fecal incontinence (30, 31), however its utility in children with intractable symptoms has not been studied.

Optimization of medical therapy is the initial mainstay of management. Fecal impaction should be addressed prior to dose escalation or initiation of new medications. Polyethylene glycol (PEG) and rectal enemas have been demonstrated to be equally effective for treatment of fecal disimpaction (5) with the caveat that PEG may cause increased fecal incontinence. The treatment of IC relies heavily on stimulant laxatives, such as sennosides and bisacodyl, and selective chloride channel-2 agonist lubiprostone (Amitiza, Takeda).

Sennosides A and B (active molecules of senna), is an anthraquinone laxative that is activated in the colon by enteric bacteria. It increases fluid secretion and alters colonic motility and transit (32, 33). A recent pediatric randomized controlled crossover trial was terminated early due to clear benefit observed with senna over PEG during interim analysis in children with anorectal malformations (34). It has been shown to be safe for long term use in children, however severe perianal skin rash and blistering has been reported (35). Bisacodyl is a diphenylmethane laxative with primarily colonic site of action. It increases colonic fluid secretion (36), decreases colonic transit (37), and stimulates colonic motor activity. Bisacodyl has been reported to increase stool frequency and consistency in the treatment of acute (38) and chronic constipation (39). Stimulant laxatives may be combined with stool softeners to augment stool consistency.

Novel pharmacological agents, under investigation but not FDA approved in children, include prosecretory agents such as lubiprostone, linaclotide, and plecanatide and serotonergic agents such as prucalopride. Lubiprostone selectively activates chloride channel-2 and enhances intestinal fluid secretion. In a multicenter open-label study of 109 children with functional constipation, lubiprostone significantly increased stool frequency with the most common side effects being nausea (18.5%) and

vomiting (12.1%) (40). In our experience, lubiprostone has been effective when co-administered with stimulant laxatives particularly in children with retentive fecal incontinence. Linaclotide and plecanatide enhance intestinal fluid secretion via cyclic GMP mediated activation of CFTR channels (41). Linaclotide is contraindicated in children less than 6 years of age and not recommended in 6-18 years of age. There are no published pediatric studies to date. Prucalopride is a highly selective 5-HT₄ receptor agonist that enhances colonic transit and motility, however pediatric studies to date are conflicting (42, 43).

IAS botulinum toxin (BT) injection has been demonstrated to be a safe and effective for children with IAS achalasia (44, 45). Chumpitazi et al. reported a 65% short-term and 88.3% long-term clinical improvement following IAS BT injection where response to initial BT injection was a predictor of favorable long-term outcome (45). There is very limited data evaluating the efficacy of intra-anal BT injection in children with IC who do not have IAS achalasia (46). In a retrospective study of 142 children with severe constipation, Zar-Kessler et al. reported a 71% response rate to IAS BT injection in children without manometric evidence of IAS achalasia (47). Its routine use in children with IC without evidence of IAS achalasia is not recommended given lack of longitudinal pediatric data.

In children with functional constipation, SNS has been shown to decrease the use of laxative and antegrade continence enemas with reported closure of the conduit in 25% of patients (48). SNS improves quality of life (48, 49), increases defecation frequency, and improves abdominal pain (50, 51). van der Wilt et al. reported long-term efficacy in 42.9% of children and adolescents with IC at median follow up of 22.1 months (50). Loss of efficacy necessitating surgical intervention was reported in 40% of children and 31.1% of adults (51). Complications such as infection, lead displacement, and pain/discomfort requiring repeat surgery have been reported in up to 25% of children (52). Randomized controlled studies are warranted to delineate the long-term efficacy and safety of SNS in children.

4. Rectal Therapy

Rectal therapies such as suppositories and enemas may be used daily in children who have failed oral medical therapy and are amendable to rectal treatment. A rectal approach is not appropriate in children with history of sexual abuse and may not be possible in children with behavioral or neurodevelopmental challenges. Stimulant based rectal therapies such as bisacodyl suppository and enemas are preferred. Over the counter and prescription enemas include glycerin, docusate, and sodium phosphate

as the active ingredients. Caution should be used when administering sodium phosphate enemas in children with colonic dysmotility and poor recto-sigmoid emptying as retention of enema in the setting of renal or cardiac compromise may lead to hyperphosphatemia, hypocalcemia, and hypokalemia (53, 54). In our experience rectal therapies are effective in children who have IC with concomitant fecal incontinence. Suppositories and low volume enemas allow for predictable recto-sigmoid emptying, social continence, and independent administration in older children.

If response to the abovementioned rectal therapies is ineffective, we recommend a trial of trans-anal irrigations (TAI), where a high-volume enema is administered using a rectally inserted device. Commonly used systems include continence enema catheter (#24/26 French non-latex urinary foley with a distal balloon) and Peristeen® transanal irrigation system (Coloplast Group, Denmark). TAIs have been shown to increase quality of life and improve constipation and fecal incontinence in children with organic and functional constipation (55).

5. Antegrade Continence Enema (ACE)

In children with IC who have failed aggressive medical therapy and have segmental or total colonic dysmotility on CM, an antegrade continence enema (ACE) is the next treatment of choice. It provides independence and should be considered in children who have failed retrograde enemas. Siddiqui et al. demonstrated successful ACE outcomes in 68% of children who failed bowel management before the ACE (56).

Following ACE placement patients report improved quality of life (57, 58), defecation frequency, and fecal continence (56, 57, 59). Approximately 69 - 91% of children attain long-term bowel success (56, 59) and 6 - 15% are able to discontinue the ACE (56, 59, 60). However, Siddiqui et al. demonstrated that 64% of their pediatric patients relapsed with mean time to first relapse of 88 months (56). Decreasing efficacy of the ACE has been demonstrated by Yardley et al., who reported that at mean follow up of 11 years greater than 40% of patients were not using the ACE of which 56% reported lack of effectiveness (61). Failure of the ACE is seen in 7 - 31% secondary to complications, lack of effectiveness, and poor compliance (56, 57, 59, 60). Complications have been reported in up to 63% of patients and range from site infections, stoma stenosis, leakage, and granulation tissue to abscess, intestinal obstruction, and peritonitis (56, 59, 62).

CM is an important diagnostic tool in patients undergoing evaluation of ACE or those with unsuccessful bowel

outcomes following ACE. The presence of bisacodyl induced HAPCs on CM was shown to be a predictor of cecostomy success (63). The absence of HAPCs (63) and/or abnormal CM (59) has been associated with poor ACE outcomes. Improvement and normalization of colonic motility has been demonstrated with ACE use (64, 65). Rodriguez et al. reported that baseline CM was not predictive of ACE use or discontinuation, but normal repeat CM was associated with ability to decrease ACE use (65).

6. Surgery

There is a limited role for surgery beyond the ACE in children with IC. Findings on CM can help guide surgical decision making including segmental or total colonic resection and diverting ileostomy or colostomy (66-68).

A repeat CM is recommended in children who failed ACE to further delineate the degree of colonic neuromuscular compromise. Patients with persistent segmental abnormalities despite optimization of ACE flushes should be considered for segmental resection. In their cohort who failed ACE, Bonilla et al. reported clinical improvement in 9 and poor outcomes in 3 children following segmental/total resection. CM testing prior to surgery was abnormal in all children (67). Diverting ostomy should be considered in patients with total colonic dysfunction particularly if associated with marked colonic dilation.

Patients with refractory symptoms, who have failed the ACE or were poor candidates for ACE (severe colonic distention and colonic inertia on CM) should undergo diverting ileostomy or colostomy. Christison-Lagay et al. reported poor long-term outcomes in children who underwent primary resection (22%) when compared to the ACE (65%) and the diversion groups (95%) (69). Diversion allows for return of colonic function by effectively decompressing the colon. In their cohort of 12 children with diverting ostomies, Villarreal et al. reported resolution of colonic dilation in 92% and improved colonic manometry in 75% of patients (68). Similarly, Christison-Lagay et al. reported improved colonic contractility in all 19 patients who had a diverting ostomy (69). Complications related to the stoma have been reported in 5 - 81% including stoma prolapse, pain and leakage at the stoma, ileus, and infection (70, 71).

Patients who have success with a diverting ostomy and have normalization of colonic motility on repeat CM should be considered for re-anastomosis. Total colonic or partial segment resection should only be considered if there is no recovery of colonic function on repeat CM, the child is experiencing significant complications from the ostomy, and/or great desire for ostomy closure. Moreover, a child who fails diverting ostomy a

small intestinal dysmotility should be suspected and they should undergo evaluation for chronic intestinal pseudo-obstruction (CIPO). Generalized hypotonia and visceral organ involvement especially megabladder should raise concern for CIPO.

7. Conclusion

Intractable constipation in children has a significant impact on quality of life. Methodical evaluation and implementation of appropriate diagnostic tests are necessary to decrease the morbidity associated with erroneous diagnoses and ineffective treatments. Medical management should be guided by the clinical context and diagnostic testing. Surgical options should only be considered after failure of medical therapy within the appropriate clinical setting with manometric guidance. Prospective studies are needed in children to validate new diagnostic tools and evaluate the efficacy and safety of novel pharmacological and surgical treatments.

Footnotes

Authors' Contribution: Lusine Ambartsumyan: Study concept and design; data collection and analysis; manuscript draft and final approval. Leonel Rodriguez: Study concept and design; data analysis; manuscript final draft approval.

Financial Disclosure: No disclosures.

Funding/Support: No funding received for this manuscript.

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