Childhood constipation: new insights in testing, treatment and cost
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General introduction

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GENERAL INTRODUCTION

Constipation affects almost everyone at some point in their life. Although it is common and varies greatly in its severity, the complaint should not (and often cannot!) be ignored. The pediatrician has an important role in identifying the small fraction of children with an underlying disease causing constipation and in choosing expeditious and appropriate therapy. This is important as children with functional constipation benefit from prompt and adequate treatment interventions. Although most children will respond to conventional treatment aimed at treating their symptoms, the pathophysiology of such ‘functional constipation’ remains poorly understood. In patients with intractable symptoms, additional tests are indicated to try to elucidate the cause of colonic dysfunction, and perhaps also to define patterns of bowel dysfunction in sub-groups of patients in order to develop new therapeutic strategies.

Definition of constipation

One of the problems for clinicians and researchers is that parents’ and physicians’ perception of constipation is variable. Thus, there is need for consensus on the definition of functional constipation in order to make a diagnosis and to allow different researchers to study the same disorder. In 1999, a group of internationally recognized experts in the field of functional gastrointestinal disorders in children met in Rome and developed symptom-based criteria to diagnose a variety of different disorders, including constipation. The first of these criteria for children, the Rome II criteria (Rome I had not included children) were published in 1999 but were found too cumbersome and restrictive to use in clinical practice. In 2006 the Rome III criteria were reformulated. (Table 1) Compared to the Rome II criteria, fecal incontinence, a feature in 80% of constipated children, was now included among the criteria for the diagnosis of functional constipation. Another change was that a child must fulfill 2 of 6 constipation criteria to be diagnosed with functional constipation, instead of the

<table>
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<tr>
<th>Table 1. Diagnostic criteria for Functional Constipation</th>
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<td>Must include two or more of the following in a child with a developmental age of at least 4 years with insufficient criteria for diagnosis of IBS</td>
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<tr>
<td>Two or fewer defecations in the toilet per week</td>
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<tr>
<td>At least one episode of fecal incontinence per week</td>
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<td>History of retentive posturing or excessive volitional stool retention</td>
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<td>History of painful or hard bowel movements</td>
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<tr>
<td>History of large diameter stools which may obstruct the toilet</td>
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<tr>
<td>Presence of a large fecal mass in the rectum</td>
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*Criteria fulfilled at least once per week for at least 2 months prior to diagnosis
obligatory two criteria of retentive posturing and a defecation frequency fewer than three/week. These changes resulted in 42.1% more children with constipation who were not recognized using the Rome II criteria now being diagnosed with functional constipation.

Because the Rome III criteria were established by pediatric gastroenterologists specialized in functional gastrointestinal disorders, in theory they might not be entirely applicable for children in primary care and children with developmental disorders. One can hypothesize that for those groups different symptoms may play a more significant role. For example, for general practitioners it is likely that symptoms have not been present for at least 2 months (one of the Rome criteria) before patients consult them. Hence, the need for more validation studies of the Rome III criteria and possible modifications to ideally formulate definitions that meet the needs of practitioners, who may desire sufficiently broad criteria to include atypical cases, and researchers, who may prefer stricter criteria, in order to include more homogeneous population in their investigations.

Epidemiology
The prevalence of childhood constipation has been reported to range between 0.7% to 29.6% with no differences found between Europe, Oceania and North America. A number of studies have reported a higher number of constipated boys compared to girls but others report no difference between genders. Low maternal educational level is significantly associated with constipation, concuring with the fact that adults of lower social, economic and educational level also have a tendency towards higher constipation rates.

In contrast with the pediatric literature, studies concerning adults suggest a higher prevalence in women than in men. However, evidence of gender differences is inconsistent. The wide range in prevalence and inconsistent evidence of gender differences are likely to be explained by the lack of consensus about the definition of constipation in different studies. In general, estimates of prevalence rates are lower in studies, which use more restricted definitions for constipation. Higher prevalence rates, on the other hand, are reported when constipation is defined using combinations of measures. The use of the Rome III criteria, which provide a clinical definition of constipation based on objective symptoms will hopefully alleviate this problem in future studies.

Constipation and obesity
The prevalence of obesity is increasing worldwide. In the past few years there have been several studies that have documented a higher prevalence of constipation in a group of obese children and vice versa; a higher prevalence of obesity in a group of
children with chronic constipation.\textsuperscript{15-17} Epidemiologic data in adults also show that obesity is associated with a wide range of chronic gastrointestinal complaints.\textsuperscript{18,19} The etiology of constipation in obese children is not clear. Several mechanisms have been proposed such as diet, hormonal changes, level of activity but no direct mechanism has been demonstrated yet.

**Healthcare costs**

Due to its wide prevalence and chronic nature, it has become clear that constipation is a significant source of health care expenses and a potential target for reducing health care cost. Cost estimation studies are critically important in medicine. They can identify important public health problems that are often not adequately considered in policy making and research. Furthermore, they may provide evidence of opportunities for savings through earlier identification and intervention along with use of less expensive and equally effective products. Several studies in the last years have addressed the economic impact of chronic constipation in adults using a variety of investigational techniques.

An analysis of 3 national surveys in the United States had estimated the constipation-related health care costs in adults to be about $235 million in 2001.\textsuperscript{20} Nyrop et al. performed a prospective study and calculated a mean annual cost for treatment of chronic constipation of $7,522 per patient.\textsuperscript{21} In the same study, total healthcare costs tended to be higher for functional constipation patients compared to IBS patients. Meanwhile, average costs of diagnostic studies for constipation have been shown to approach $3,000 per patient.\textsuperscript{22} The cost-effectiveness of treating constipation in adults with macrogol 4000 compared to lactulose was the focus of a study by Guest et al. They concluded that macrogol 4000 is clinically more effective than lactulose and therefore fits the cost-effective strategy of the British National Health Service.\textsuperscript{23} The same group found that using macrogol 3350 for disimpaction of children suffering from fecal impaction would be the least expensive and clinically effective treatment compared to enemas, suppositories or manual evacuation.\textsuperscript{24}

Other studies have looked at the economic benefit of prevention, specifically by increasing the dietary fiber intake. In Australia, Egger et al. studied the effect of a community intervention trial promoting the consumption of whole-grain bread and reported a 49\% decrease in laxative sales corresponding with a 58\% increase in sales of wholegrain bread.\textsuperscript{25} Finally, another economic component that must be considered is the indirect costs such as work absenteeism. Sonnenberg and Koch used the National Health Interview Survey to compile data regarding limitations in activity due to constipation in the
US. Annually, 0.4 days per person were lost among constipated patients because of constipation.\textsuperscript{26} Unfortunately not much data is available on the healthcare cost of children with constipation but given the wide prevalence, healthcare utilization and cost are likely to be great. Thus there is a need to evaluate the financial impact of childhood constipation.

Etiology

Less than 5-10\% of children suffering from constipation have an underlying organic cause, such as anatomic malformation (i.e. anal stenosis, imperforate anus), metabolic and gastrointestinal causes (i.e. hypothyroidism, celiac disease, and cystic fibrosis), intestinal nerve and muscle disorder (i.e. Hirschsprung disease, visceral myopathies).\textsuperscript{27} In all other children no organic disease is responsible for their symptoms. They are thought to have functional constipation, an entity whose pathophysiology is still not completely known.

Normal defecation is a complex process which is triggered by stool stretching the walls of the rectum. Stool is eventually evacuated by the involuntary internal anal sphincter relaxation and voluntary relaxation of the pelvic floor muscles and contraction of the abdominal muscles. This process requires normal colonic motility, normal sensation and the volitional attempt to find an appropriate place for the act of defecation. Dysfunction at any step of this normal process, can lead to constipation. There are three periods in which the infant and developing child are particularly prone to develop constipation. The first occurs after the introduction of solid foods into the infant’s diet, the second during the period of toilet training, and the third during the start of school when children have to utilize unfamiliar toilets.\textsuperscript{28,28} Each of these steps has the potential to change defecation into an unpleasant experience, which may result in the child consciously or subconsciously withholding stool. This behavior leads to accumulation of stool in the rectum, a factor potentially leading to overflow fecal incontinence, a terribly bothersome symptom for both children and parents. It is long been thought that long-term fecal impaction resulted in a dilated rectum with loss of sensation. Our group found that children with constipation actually have normal rectal sensation but need more intra-luminal volume due to the altered elasticity (compliance) of the rectum.\textsuperscript{29} Therefore larger stool volumes are needed to trigger rectal sensation and urge to defecate. Increased rectal compliance might result in impaired rectal contractility leading to the inability to pass bowel movements on a regular basis.\textsuperscript{30} The role of rectal compliance in the pathophysiology of constipation is still controversial. A study by van den Berg et al. showed that rectal compliance in recovered patients is lower compared to patients with persistent constipation.\textsuperscript{31} However, almost half of the recovered adolescents had a rectal compliance above the
normal range suggesting that these subjects were able to recover from functional constipation despite increased rectal compliance. Therefore, rectal compliance does not seem to be a key factor involved in recovery. Prospective longitudinal studies are required to assess the clinical relevance of increased rectal compliance.

Colonic manometry (described below) has demonstrated abnormal contractions in a subset of children with severe defecation disorders. Children with no or weak colonic contractions, in the absence of generalized colonic dilatation, are thought to have a colonic myopathy, while patients with colonic neuropathy are recognized by the absence of the gastrocolonic response and abnormal or absent high amplitude propagating contractions (HAPC). Recent studies have also identified abnormalities in the enteric nervous system in patients with intractable constipation, such as reduced numbers of interstitial cells of Cajal or ganglia cells. Although this classification of “myopathic” or “neuropathic” is being used, no direct correlation with histological findings of myopathy or neuropathy has been proven yet.

Diagnostic tools

A thorough medical history and complete physical exam, including rectal digital examination, are usually sufficient to confirm the diagnosis of functional constipation. Bowel diaries recording defecation and fecal incontinence frequency are helpful to confirm the diagnosis and are useful to monitor progress or lack thereof. There are many techniques to investigate the function of the distal gastrointestinal tract.

Abdominal radiograph

Abdominal X-rays are frequently requested by primary care providers to evaluate and objectify fecal loading in children with constipation. However, conflicting data exist on the clinical value of this test. A recent systemic review showed that that stool found during rectal examination occurred almost as often in children with fecal loading on radiography as in children without fecal loading. Moreover, the low inter- and intra observer variability for assessing fecal loading on a plain abdominal X-ray makes this test of limited value in the diagnosis of functional constipation in children.

CTT

An easy and non-invasive indirect measurement of colonic motor function is colonic transit with radiopaque markers. Our clinic uses the Bouchoucha method. Patients ingest a capsule with 10 radio opaque rings for 6 consecutive days. On the seventh day an abdominal X-ray is obtained to calculate colonic transit time. (Figure 1) Total colonic transit time and segmental colonic transit time can be determined to distinguish
different transit patterns: 1) normal colonic transit time; 2) outlet obstruction; 3) slow transit constipation. In children with constipation, CTT is delayed in approximately 50% of children. The delay of transit in these children is mostly found in the anorectal region. A low defecation frequency and a high number of fecal incontinence episodes in combination with palpable stools in the rectum correlates well with prolonged total CTT and especially with recto-sigmoid transit time (RSTT). Therefore, the use of CTT is limited in the diagnostic evaluation of the constipated child. However, it is a useful test to differentiate between children with fecal incontinence secondary to constipation and children with functional non retentive fecal incontinence (FNRI). A normal CTT is found in 90% of children with FNRI.

Colonic scintigraphy or wireless pressure/ pH capsules are other more sophisticated and more costly methods to assess colonic transit, whose clinical usefulness in children is only now beginning to be explored.

Barostat testing

The barostat is an electromechanical computer-driven air pump that maintains a constant pressure in an intraluminal balloon. Such a balloon can be placed anywhere in the digestive system and is used to measure tone, compliance and sensitivity of
hollow organs by inflating air when the outside pressure falls and to aspirate air when
the pressure rises. In 50% of all constipated children a disturbed compliance can be
found in the rectum but as previously mentioned, the disturbed compliance does not
predict successful outcome. The role of the electronic barostat as a diagnostic tool
has therefore yet to be established.

Anorectal manometry
Anorectal manometry assesses anorectal function. Its main indication is to
demonstrate the presence of the recto-anal inhibitory reflex (RAIR). The RAIR
is absent in children with Hirschsprung disease or in children with anal achalasia
or ultrashort segment Hirschsprung disease.44 In order to elicit this reflex, a small
balloon is inflated in the rectum while simultaneously measuring pressures in the
anal sphincter. Other features that can be evaluated with this test are anal resting
pressures and defecation dynamics.

Colonic manometry
Colonic manometry is a diagnostic test performed in specialized motility centers to
differentiate between normal colonic motor function and colonic neuromuscular
disorders in the evaluation of children with intractable constipation.45 Other
indications to perform a colonic manometry are: clarifying the pathophysiology of
persisting lower GI symptoms after surgery for Hirschsprung disease, evaluation of
colonic involvement in a child carrying a diagnosis of intestinal pseudo-obstruction,
assessing function of a diverted colon prior to possible re-anastomosis and to assess
colonic motor activity prior to intestinal transplantation in order to find out whether
or not the colon should be kept at the time of transplant.32 In a study by Pensabene
et al. results of colonic manometry testing, resulted in recommendation to change
therapy (mostly surgical) in 93% of their patients.46 Finally, manometry can also help
predict whether antegrade enema treatment through a Malone stoma or cecostomy
will be successful.47

Colonic manometry measures changes in intracolonic pressure due to lumen-occluding
contractions within the large bowel. After cleaning out the bowel with cleansing
solutions, a catheter with 6-8 recording side holes (10-15cm apart) is inserted
using colonoscopy or interventional radiology. (Figure 2) The use of water perfused
catheters is currently the standard in pediatric motility testing. Perfusion is achieved
by connecting the low-compliance catheters to a pneumohydraulic pump. At a low
infusion rate of 0.15ml/minute distilled water is instilled during the test. Care is
taken to limit the amount infused to avoid water intoxication in very small children, a
problem that has been reported anecdotally. The motility testing includes at least 1
hour of fasting, 1 hour post-prandial after a finishing a high calorie meal and at least
1 hour after bisacodyl provocation. During the test the child is required to remain
in bed and it is important to have a trained observer at the bed site.

Colonic manometry tracings are analyzed in a qualitative and quantitative manner
looking for the presence of normal motility and absence of abnormalities. Colonic
motility is characterized by propagating and non-propagating contractions. These
latter contractions are thought to be responsible for mixing and shifting luminal
contents over short distances permitting adequate absorption. High amplitude
propagating contractions (HAPC) are the most recognizable feature observed during
a colonic manometry and together with a gastrocolonic response to a meal (increase
of colonic motility) it is a marker for normal colonic motility. The HAPCs are powerful
peristaltic waves, originating in the proximal colon propagating to the rectum,
with the main purpose to propel colonic content towards the rectum (Figure3). 49

They generally occur more frequently after a meal, after awakening and before
defecation. 49 In children younger than 4 years HAPC frequency is significantly higher
compared to older children. 50 In adults with constipation the frequency of HAPCs is
significantly lower compared to healthy controls but in children with constipation the
frequency does not seem to be different. 51
Colonic irritants, such as bisacodyl or glycerine, can initiate HAPCs and are therefore used as test stimulants during colonic manometry in children to evaluate whether patients have motility.\textsuperscript{52} Nevertheless, little is known about the factors that initiate spontaneous HAPCs. Physical factors such as distention secondary to colonic filling have been hypothesized as the physiologic initiators of HAPCs. This, however, has not been studied in children.

Propagating contractions with an amplitude < 60 mmHg are defined as low amplitude propagating contractions (LAPC) (Figures 3). Their role is not completely understood but they are thought to be involved in the transport of liquid and gas.\textsuperscript{53}

Developments in microtransducer technology have allowed the production of manometry catheters incorporating miniaturized strain gauge transducers which are capable of prolonged intraluminal recording of gastrointestinal motor activity on portable solid state data logging devices.\textsuperscript{54} Such catheters permit to study colonic motility in ambulant patients and offer an attractive alternative to traditional water perfused stationary manometry. Although the potential of solids state catheters seem promising, their strengths and weaknesses compared to the current gold standard, stationary water perfused manometry, has not been evaluated yet for colonic manometry in children.

Solid state manometry not only allows the child to walk around freely, but also allows prolonged recordings. Given the wide physiologic variations in colonic motility over 24 hours, longer observation might detect clinically relevant information.\textsuperscript{55}

Figure 3. High amplitude propagating contractions (HAPCs) following bisacodyl stimulation in a girl with chronic constipation. Contractions are propagating from the cecum to the sigmoid colon.
Prolonged ambulatory manometry has the additional advantage of assessing motility during normal activities (eating/fasting, sleeping/awake, and active/resting) and of correlating motility abnormalities with infrequent symptoms. Recently, King et al. performed 24 hours colonic manometry in 18 children with slow transit constipation with a catheter introduced through a previously formed appendicostomy. They compared their data to data obtained from motility studies in 16 young adult controls. Children with slow transit constipation showed significantly fewer antegrade propagating contractions and no significant increase in frequency immediately following awaking or eating. In contrast to adults with constipation, the amplitude, propagation distance and velocity of those antegrade contractions were normal. Furthermore, the frequency of HAPCs was not decreased, suggesting that a normal frequency of HAPCs is insufficient to provide normal colonic motility in some children with slow transit constipation. Apart from increasing our knowledge of normal and abnormal motility patterns, prolonged recordings might also provide useful diagnostic information in patients who need colonic motility evaluation. It could possibly shed light on those children who eventually do well despite colonic manometry showing abnormal colonic motility or those children who remain symptomatic despite having normal motility on current testing.

**Diet**

Although it is a widespread concept that lack of fiber is a common cause of constipation, only a few pediatric trials have been performed to evaluate the efficacy of fiber therapy. Conflicting reports exist about constipated children having a lower, equivalent or higher intake of dietary fiber compared to non-constipated children. The recommended minimum daily fiber intake for children older than 2 years is age in years plus 5 g. Recent standardized trials in children have shown the beneficial effects of fiber supplementation in children with chronic constipation. Compared to a placebo group, Castillejo et al. found a decrease in colonic transit time in children who had a basal prolonged colonic transit time and received cocoa husk. They also observed a reduction in the percentage of patients who reported hard stools. It has to be noted that these constipated children had a mean fiber intake near the recommended amount of total fiber for the specific age groups. Glucomannan supplement also led to more frequent and softer stools with an improved response to laxative treatment. One of the main factors that has limited the long-term efficacy of dietary fibers in children has been the poor adherence to treatment due to the fact that most fiber agents like cellulose fiber, guar gum and pectin fiber have to be consumed in large quantities to be effective and that they are unpalatable. The fibers used in the previously mentioned trials had a good acceptance rate and did not have any notable side effects. While lack of fibers is probably not the cause of chronic constipation.
constipation in general, it may be a contributory factor in a subgroup. Therefore, a balanced diet containing whole grains, fruits, and vegetables is recommended as part of the treatment of constipation, without forceful implementation of fiber in the diet.\textsuperscript{45} Increased fluid intake is another widely recommended therapy and is based on the assumption that additional oral intake of fluids leads to an increased contribution to colonic fluids, which would enhance increased stool output. A study looking at 108 constipated children who were randomized to a control group and 2 interventional groups, where 1 group was instructed to increase their daily water intake by 50\%, did not show any changes regarding stool frequency, consistency or ease of defecation.\textsuperscript{62} The reason that the increased fluid did not result in a change in bowel habits might have to do with the large adaptive absorptive capacity of the small and large bowel in response to acute or chronic challenges.\textsuperscript{63, 64} The solutes, not water, contribute to ileal effluents. Consequently minor modifications in liquid intake will not significantly alter stool consistency. There is no evidence that constipation can be successfully treated by increasing fluid intake; unless there is evidence of dehydration, constipated children should not be forced to drink more than normal.

**Therapy**

The lack of randomized controlled studies in children has made the treatment of constipation largely based on clinical experience rather than on evidence based controlled clinical trials. Acute simple constipation is traditionally treated with a high fiber diet and sufficient fluid intake, filling out a bowel diary and toilet training. The recently updated NASPGHAN recommendations include 4 important phases in the treatment of chronic constipation: 1) education, 2) disimpaction, 3) prevention of re-accumulation of feces and 4) follow-up.\textsuperscript{45}

Education and support for parents and children is an important component of treatment of functional constipation. The parents need to be reassured and counseled regarding normal range of frequency of bowel movements within the population, the etiology of constipation, and its prevalence in childhood. If fecal incontinence is present, it is important for parents to understand that this is caused by overflow diarrhea and is not an act of willful and defiant behavior. Parents should have a non-accusatory approach and use positive reinforcement to motivate their children. Before treatment is started, parents should be reassured that recovery is possible with adequate, often protracted, treatment. It should also be stressed that the timing of successful treatment is often unpredictable and 50\% of treated patients experience a relapse within 1 year while the duration of maintenance therapy usually takes 6-24 months.\textsuperscript{9}
Rectal disimpaction with removal of the often present large fecal mass before initiation of maintenance therapy is recommended to prevent increase in abdominal pain and an increase in fecal incontinence due to overflow diarrhea once treatment has started.\textsuperscript{45} Uncontrolled clinical trials have shown successful disimpaction by the oral route, rectal route, or a combination of the two methods.\textsuperscript{65-68} There are no randomized controlled studies that have compared methods of disimpaction. Randomized trials showed polyethylene glycol (PEG) at doses of 1-1.5g/kg/day to be effective for disimpacting children, with good acceptance by children and parents.\textsuperscript{67-69} No abnormalities in the serum osmolality and electrolytes or renal function tests were reported. Other agents that have been used successfully, but for which controlled trials are lacking include magnesium hydroxide, magnesium citrate, lactulose, sorbitol, senna and bisacodyl.

Rectal disimpaction is widely performed with phosphate soda enemas, saline enemas, or mineral oil enemas followed by a phosphate enema. Both ways of disimpaction, either orally or rectally, have advantages and disadvantages, with the first method being less invasive but requiring more time than the latter. The choice of treatment is best determined after discussing the options with the family and child.

Once disimpaction has been accomplished, the goal is to produce soft, painless bowel movements once or twice per day. Regularity for a longer period of time is important to prevent recurrent impaction and recurrence of stool withholding behavior. This usually requires maintenance laxatives in combination with behavioral therapy over an extended period, which may last for months or years. Despite the high prevalence and the chronicity of constipation only a small number of randomized controlled trials (RCTs) have been performed evaluating the effect of any laxative treatment in children.\textsuperscript{67,70,71}

Osmotic laxatives include milk of magnesia, lactulose and polyethylene glycol powder (PEG). Their mechanism is derived either by salts of poorly absorbable cations and anions (magnesium, phosphate), molecules that are not absorbed but to some extent metabolized in the colon (lactulose), or metabolically inert compounds. Magnesium hydroxide/sulphate or “milk of magnesia”, as it is known in the United States, is an osmotic laxative that has a long history of its use. Both magnesium hydroxide and magnesium sulphate are too poorly absorbed salts that act either by osmosis or by a secretory effect on prostaglandins or cholecystokinin thereby enhancing colonic motility.\textsuperscript{72, 73} Lactulose, another widely used laxative, is a disaccharide derived from lactose and is effective in increasing defecation frequency and normalizing stool consistency.\textsuperscript{74,75} Polyethylene glycols (PEG) are synthetic, nonabsorbable compounds with a high molecular mass (3000 and higher), and are not metabolized by colonic bacteria. They work by osmosis and volume expansion in the colon. PEG is available in powder form and is tasteless, colorless and odorless. It is available in combination
with or without electrolytes. PEG without electrolytes has the advantage to be tasteless, a factor which can play a great role in increasing compliance with a prolonged treatment in children. In two multi-centre RCTs, PEG with electrolytes was compared with lactulose and was shown to attain a higher short-term success rate (50% vs. 29%) with better stool consistency, appetite and fewer fecal impactions and need for enema use. The PEG with electrolytes had significant fewer adverse effects such as abdominal pain, nausea, flatulence and diarrhea compared to lactulose but children complained about the bad taste. A randomized trial comparing PEG without electrolytes with milk of magnesia in 49 children with functional constipation and fecal incontinence demonstrated similar effectiveness after follow-up at 1, 3, 6, and 12 months in increasing bowel movement frequency, decreasing fecal incontinence episodes, and decreasing abdominal pain.70 PEG was more palatable and better tolerated than milk of magnesia (33% of children refused to take milk of magnesia, whereas none refused PEG). No side effects from PEG were reported but data on long-term use of PEG (beyond 6 months) are lacking. Since PEG is more and more prescribed and is available over the counter, studies about its long-term use are required. Parents should be counseled that after starting laxative treatment some leakage of feces may continue at first or even worsen, especially if the child fears or continues to resist having a bowel movement.

Stimulant laxatives such as senna and bisacodyl were developed decades ago and the studies investigating those drugs do not meet current criteria of therapeutic clinical trials making a review for comparison analysis not possible.76 In contrast to previous mentioned osmotic laxatives, these stimulant laxatives are generally not encouraged for long term daily treatment. One of the common side effects is cramping.77 Their use is often necessary intermittently, for short periods, to avoid recurrence of impaction.

It is still controversial whether anthraquinone containing laxatives, such as senna, may lead to morphologic changes of the autonomous nervous system of the colon. Melanosis coli, an easily visible brown discoloration of the colon, may occur within months of regular use and can last for months after discontinuing laxatives.78,79 This pigmentation is caused by the uptake of laxative stained cell debris by submucosal macrophages but this discoloration does not seem to have any functional consequences.80 A reasonable and often utilized regimen is to use stimulant laxatives when no spontaneous bowel movement has occurred after 48 or 72 hours in combination with daily osmotic laxatives.

The combination of behavioral intervention combined with laxative treatment has the goal to lower the level of distress and to develop or restore normal bowel habits by positive reinforcement. A commonly used practice is “toilet retraining” where the child is instructed to sit on the toilet for 5-10 min after each meal (to take advantage
of the gastrocolonic reflex), attempting to defecate. The child is encouraged to strain actively while placing his feet on a footrest. The child needs to understand that responding to the defecatory urge and not holding back is the key for the success of the treatment. Another frequently used aid is to let the child keep a bowel diary to objectify complaints, quantify therapeutic progress and to enhance motivation. Small, age appropriate reward systems are established for successful compliance. Behavioral modification has been studied for constipation-related fecal incontinence. A randomized controlled trial of 87 children compared three treatment modalities: intensive medical therapy, intensive medical therapy with enhanced toilet training, or intensive medical therapy with enhanced toilet training and biofeedback therapy. After 12 months, no statistically significant difference was found in the success rate among the three interventions.\textsuperscript{81} A recent large randomized controlled trial evaluating the clinical effectiveness of behavioral therapy with laxatives for functional constipation therapy compared to standard therapy did not find an additional effect of the behavioral therapy.\textsuperscript{82} Psychological referral is indicated in children who fail intensive medical treatment and in those with severe emotional problems or serious family problems. Although many children with constipation will respond to these therapeutic measures, a small group of children continues to have intractable symptoms that makes further diagnostic testing or surgical treatments necessary. Furthermore, approximately 30% of children with constipation will continue to have constipation symptoms into adulthood although not a small group will consult a doctor for their complaints.\textsuperscript{9} It is therefore necessary to conduct carefully designed randomized controlled trials and to uncover new and more effective interventions for children with constipation.