Functional defecation disorders in children
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GENERAL INTRODUCTION & OUTLINE OF THE THESIS

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INTRODUCTION

Constipation and fecal incontinence represent common problems in children. Beyond the neonatal period, only a minority of children has an organic cause for constipation and the etiology remains not well understood. Approximately 3-10% of visits to general pediatric clinics and up to 25% of referrals to pediatric gastroenterologists are related to defecation problems. Constipation rarely leads to life threatening complications, but can cause emotional and physical distress and concerns for children and their families, ultimately impairing health related quality of life. The main characteristics of constipation are infrequent painful defecation and fecal incontinence often accompanied by abdominal pain. In less than 15% of cases, children have fecal incontinence without a history and physical examination that indicates underlying constipation. These latter children are classified as functional nonretentive fecal incontinence (FNRFI).

Definition of constipation

For many years, patients, parents, but also healthcare professionals have used different definitions for constipation. The Rome II criteria, developed in 1999, attempted to provide a symptom-based definition of functional constipation, mostly based on expert opinion. Such criteria were subsequently found to be too restrictive and were revised, between 2004 and 2006, in the Rome III version of pediatric functional gastrointestinal disorders. Different studies have shown that the Rome III criteria are less restrictive than the Rome II criteria in diagnosing functional defecation disorders. Burgers et al. retrospectively evaluated patients referred for functional defecation disorders, comparing the Rome II and Rome III criteria. They demonstrated that by using the Rome III criteria, functional constipation is diagnosed more frequently compared with the Rome II criteria (87% and 34%, respectively). Recently, the Rome IV criteria have been published. To fulfill the Rome IV criteria for functional constipation, children should have two or more of symptoms described in Table 1. The Rome III Committee suggested different diagnostic criteria for constipation in infants and toddlers up to 4 years of age and for childhood constipation in older children and adolescents.

Definition of fecal incontinence

Fecal incontinence is defined as the involuntary loss of stool into the underwear in a child older than the age of 4 years. It represents an upsetting and psychologically distressing problem in children. Functional fecal incontinence can be divided into constipation-associated fecal incontinence or “overflow” incontinence,
and FNRFI. More than 80% of the children with functional fecal incontinence have retentive fecal incontinence. These findings were also observed in a Sri Lankan epidemiologic survey showing that indeed retentive fecal incontinence is 4.5 times more common than FNRFI. It is important to differentiate between retentive and nonretentive fecal incontinence because these two conditions differ in etiology and management. The diagnostic criteria for FNRFI according to the Rome IV criteria are listed in Table 2.

Epidemiology
The worldwide prevalence of constipation varies from 0.7% to 29.6%. The lack of consensus in diagnostic criteria and differences in cultural beliefs about normal bowel habits may have contributed to the worldwide variation in the prevalence.

Constipation may occur at any age, but children appear most vulnerable in one of three phases: (1) infancy, with the introduction of cereals and other solids and weaning of (breast) milk; (2) toddlers, at the time of toilet training; and (3) older children, who avoid bathrooms at school. The estimated prevalence of fecal incontinence is between 0.8% and 7.8%. The prevalence is higher among younger children, and it is significantly more common among boys, with a male to female ratio ranging from 3:1 to 6:1.

Pathogenesis
The pathophysiology of constipation in children is multifactorial and remains incompletely understood. In a small subset of patients, constipation is secondary to a known organic disorder. In more than 90% of children presenting with constipation, no obvious organic cause is found and thus classified as functional. In the majority of children, constipation results from purposely or subconscious stool withholding after the passage of a hard, painful, or frightening bowel movement. Fear of defecation leads to withholding of stool, called retentive posturing. Children often stiffen their legs, grunt, or rise on their toes and rock back and forth. In many cases, this behavior is misinterpreted by parents as an extreme effort to pass stool. Loening-Baucke reported that 45% of the constipated infants and toddlers exhibited stool-withholding behavior. A child may also refuse defecation as part of a control and independence struggle with parents during toilet training. A significant number of school-aged children refuse to use school toilets, often citing poorly maintained and unhygienic facilities. As a consequence of withholding, whatever the cause is, the rectal mucosa absorbs water from the fecal mass and the retained stools become progressively more difficult to evacuate. This process leads to a
vicious circle of stool retention. When stool retention remains untreated for a long period, the rectal wall becomes stretched and a megarectum develops. This can result in overflow fecal incontinence, loss of rectal sensation and, ultimately, loss of normal urge to defecate\textsuperscript{13}.

**Slow transit constipation**

In a subgroup of children with constipation, a delay in total and segmental colonic transit time has been described\textsuperscript{15-17}. Slow transit constipation (STC) is characterized by delayed passage of fecal matter through the proximal colon whereas functional fecal retention describes delayed transit in the rectosigmoid region only\textsuperscript{18}. This form of constipation may comprise up to half of patients who have chronic, treatment-resistant constipation\textsuperscript{17}.

The delay in CTT might be due to dysfunctional muscles of the colon, resulting in non-powerful contractions, or to dysfunction of the enteric nervous system, resulting in non-coordinated motor activity\textsuperscript{19}.

In a number of studies it has been shown that the number of antegrade pressure waves in the colon was significantly decreased in children with STC compared with normal controls\textsuperscript{20}. However, the amplitude of the pressure waves was the same as in normal controls, suggesting that there was no intrinsic myopathic process involving colonic muscles. These studies suggested that the underlying abnormality was in neural coordination of contractile activity within the colon\textsuperscript{16}.

A reduction in the numbers and delayed maturation of interstitial cells of Cajal (ICCs) have also been suggested to contribute to the pathophysiology of STC in children, since the ICCs function as pacemaker cells that generate gut peristalsis\textsuperscript{21,22}. However, it is still unknown if ICC changes are primary or secondary to constipation, and little is known about ICC numbers in healthy children.

**Quality of life**

Although constipation is not a life-threatening condition, it can cause emotional and physical distress for the affected child and family. Multiple studies showed that constipation can result in impaired health-related quality of life (HRQoL). In the United States, children with constipation had lower mean self-reported HRQoL scores than healthy controls and children with inflammatory bowel disease and gastroesophageal reflux disease\textsuperscript{23}. Parents of constipated children reported lower perceived emotional and social scores for their children compared to parents of healthy children. Similar observations have been described in Australia and Brazil; constipation negatively affected both physical and psychological HRQoL scores\textsuperscript{24,25}. A study from China showed that FC had a significant impact on HRQoL of constipated patients and their
**Table 1**  Rome III criteria for pediatric functional constipation

<table>
<thead>
<tr>
<th>Infants up to 4 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic criteria must include:</td>
</tr>
<tr>
<td>- Two or more criteria for at least month in infants up to 4 years of age</td>
</tr>
<tr>
<td>1 Two or fewer defecations per week</td>
</tr>
<tr>
<td>2 History of excessive stool retention</td>
</tr>
<tr>
<td>3 History of painful or hard bowel movements</td>
</tr>
<tr>
<td>4 History of large diameter stools</td>
</tr>
<tr>
<td>5 Presence of a large fecal mass in the rectum</td>
</tr>
</tbody>
</table>

In toilet-trained children, the following additional criteria may be used:
- At least 1 episode/week of incontinence after the acquisition of toileting skills
- History of large-diameter stools that may obstruct the toilet

<table>
<thead>
<tr>
<th>Children of at least 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic criteria must include:</td>
</tr>
<tr>
<td>- Two or more criteria for at least once per week for a minimum of 1 months in infants of at least 4 years</td>
</tr>
<tr>
<td>- With insufficient criteria for a diagnosis of irritable bowel syndrome</td>
</tr>
<tr>
<td>1 Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years</td>
</tr>
<tr>
<td>2 At least one episode of fecal incontinence per week</td>
</tr>
<tr>
<td>3 History of retentive posturing or excessive volitional stool retention</td>
</tr>
<tr>
<td>4 History of painful or hard bowel movements</td>
</tr>
<tr>
<td>5 Presence of a large fecal mass in the rectum</td>
</tr>
<tr>
<td>6 History of large diameter stool that can obstruct the toilet</td>
</tr>
</tbody>
</table>

After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

**Table 2**  Rome III criteria for pediatric functional nonretentive fecal incontinence

| Diagnostic criteria must include at least a 1-month history of the following symptoms in a child with a developmental age older than 4 years |
| 1 Defecation into places inappropriate to the socio-cultural context |
| 2 No evidence of fecal retention |

After appropriate medical evaluation, the fecal incontinence cannot be explained by another medical condition
families, as well as their family function\textsuperscript{2}. Fecal incontinence even more negatively affects the quality of life of these children and their families\textsuperscript{26}. Children with incontinence were found to have higher rates of psychosocial problems compared to children without fecal incontinence. Furthermore, when constipation continues into adulthood, affected individuals report difficulties with social contact and intimacy of up to 20%\textsuperscript{27}. It is important to address these issues during clinical evaluation to understand the impact of constipation on the lives of affected children.

**Associated factors**

**Behavior problems**

Behavior problems are frequently reported in children with functional defecation disorders\textsuperscript{28}. Likewise, gastrointestinal problems like constipation, abdominal discomfort and reflux seem to be particularly common in children with behavioral and developmental disorders, such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD)\textsuperscript{29,30}. The association between behavioral factors and functional defecation disorders has increasingly been studied, but the question whether behavior problems result in constipation or vice versa is still not answered yet. It can be hypothesized that behavior problems may result in a complicated period of toilet training, which is known as a possible critical phase in the development of FDD. On the other hand, FDDs might give rise to a considerable level of stress for the child and family, which may lead to behavioral changes.

**Obesity**

Obesity and functional constipation seem to share a common biopsychosocial model of causation. A relationship between constipation and an increasing body mass index in children has been reported several times\textsuperscript{31-33}. Lifestyle factors such as diet and physical activity are assumed to play an important role in the pathophysiology of both functional constipation and overweight\textsuperscript{34}. Other possible shared etiological factors are a disordered eating pattern, low fiber intake, hormonal dysfunction, gut microbiota, genetic predisposition, and psychological and socioeconomic factors\textsuperscript{31,35,36}.

**Clinical evaluation and diagnostic testing**

The clinical presentation of constipation in children is obvious in the majority but may be subtle and nonspecific in a subset of children. The physician should be aware of symptoms and signs of organic causes or red flag symptoms.
**Medical history**

The medical history should include questions about the time of the first bowel movement after birth, to discriminate functional constipation from Hirschsprung’s disease. Other important questions include the age of onset; frequency, consistency, and size of stools; whether the child experiences pain during defecation or exhibits retentive posturing; and whether blood is present on the toilet paper. Large caliber stools, which may be large enough to clog the toilet, may cause anal fissures, commonly manifested as blood on the toilet paper. Information about the incontinence frequency and day and/or nighttime soiling must be obtained. An assessment of stool pattern, using a defecation diary in combination with the Amsterdam Infant Stool Scale (AISS) or Bristol Stool Scale (BSS), can be used to estimate the severity of constipation\(^{37,38}\). The AISS is developed for use in infants and children who are not yet toilet trained. In the AISS, the stool consistency, the amount, and color of stools are described. The BSS, on the other hand, is not age specific and only describes stool consistency. Physicians should ask about the presence of abdominal pain or distention, loss of appetite, fever, nausea, vomiting, weight loss or poor weight gain, problems with neuromuscular development, and psychological or behavior problems. Furthermore, urinary incontinence and urinary tract infections are reported in a considerable number of children with constipation\(^{39}\). Dietary history and the history of previous treatment strategies for constipation should be investigated. Finally, it is essential to ask about important life events that might contribute to the development of retentive behavior such as death in family, birth of a sibling, school problems, and sexual abuse\(^1\).

**Physical examination**

A thorough physical examination should be performed in all children. Physical examination should start with measurement of weight and height. Abdominal examination gives valuable information concerning the accumulation of gas or feces. A palpable fecal mass is present in 50% of children with chronic constipation\(^40\). Evaluation of the perianal region provides valuable information about the position of the anus, evidence of fecal incontinence, skin irritation, eczema, fissures, hemorrhoids, and signs of possible sexual abuse. The anorectal digital examination assesses the perianal sensation, anal tone, size of the rectum and the contraction and relaxation of the anal sphincter. The lumbosacral area should be inspected for the presence of a sacral dimple, a tuft of hair or asymmetry of the buttocks, which may indicate spina bifida occulta.
Laboratory investigations
The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) formulated in their recommendations that routine laboratory testing to screen for hypothyroidism, celiac disease and hypercalcemia is not recommended in children with constipation in the absence of alarm symptoms. These recommendations are in line with a recent study showing that only a minority of the children with constipation who undergo routine laboratory testing are diagnosed with an organic disease. Only 1.7% of the children was diagnosed with celiac disease, only 0.6% with hypothyroidism and none with hypercalcemia. The likelihood of finding patients with an organic cause decreases even further in children who present with constipation as their only symptom.

Radiological investigations
Abdominal radiography, including colonic transit time (CTT) measurement and abdominal ultrasound are frequently used to diagnose childhood constipation. Nevertheless, a systematic review evaluating the additional value of these investigations found insufficient evidence for a diagnostic association between clinical symptoms of constipation and fecal loading on abdominal radiographs, CTT and rectal diameter on ultrasound scanning in children.

Abdominal radiography
The sensitivity and specificity of abdominal radiography in diagnosing childhood constipation ranges from 60-80% and from 43-90%, respectively. Based on the currently available evidence, the National Institute for Health and Clinical Excellence guideline and the new ESPGHAN/NASPGHAN constipation guideline concluded that abdominal radiography should not be recommended as an additional test for constipation in children and therefore has no role to diagnose functional constipation. Radiography is only useful to determine the presence of a fecal rectal mass when there is uncertainty as whether the patient is constipated and rectal examination is not possible because of obesity, refusal or psychological factors (sexual abuse) that make a rectal examination to traumatic.

Colonic transit time (CTT)
One of the underlying mechanisms of idiopathic constipation is thought to be a disturbance of intestinal motility. Consequently, colonic transit time is assumed delayed in children with idiopathic constipation in comparison to healthy children.
Colonic transit time can be measured with the following non-invasive techniques: radiopaque sitz (plastic) markers, scintigraphy (transit of radioisotopes), and by tracking the movement of a pressure, pH, temperature capsule (Wireless Motility Capsule). Three different patterns of colonic transit time can be described on colonic transit studies. These include normal colonic transit, colonic inertia (also known as slow-transit constipation with slow propagation throughout all colonic segments), and outlet obstruction (delay is mainly in the rectosigmoidal region). Outlet obstruction is the most commonly encountered form in pediatric functional constipation. However, a colonic transit study is not recommended to diagnose constipation, but may only be useful to discriminate between functional constipation and FNRFI and in situations in which the diagnosis is not clear. Furthermore it is important to emphasize that CTT may be normal in up to 50% of children with constipation and in 90% of the children with FNRFI. De Lorijn et al showed that a bowel diary is sufficient to diagnose constipation. A low defecation frequency and/or a high fecal incontinence frequency recorded with a bowel diary correlated with total CTT, measured with radio-opaque markers.

**Defecography**

Fluoroscopic defecography is a dynamic radiological test performed during voluntary defecation of the rectum, to assess the anorectal function at rest and during defecation. The strength of defecography is that it allows assessment of the rectal functional with the patient in sitting position during the procedure, to achieve a more physiological defecation. Since the introduction by Wallden in 1952, the technique has been further improved and simplified, but currently consensus regarding the optimal examination technique is still lacking. Recently, it has been shown that defecography can be a useful tool in understanding the pathophysiology of defecation disorders and it may provide information that impacts the management of children with intractable defecation disorders.

**Ultrasonography**

Based on the assumption that fecal retention is one of the main features of constipation, assessment of stool retention and size of rectum and colon can be measured using abdominal ultrasonography. A rectal diameter larger than 30 mm is considered as enlarged and some studies demonstrated that the diameter of the rectum is significantly larger among constipated children compared to healthy children. Although this test is considered to be a simple, non-invasive technique to demonstrate fecal retention, there is insufficient evidence that the transverse diameter can be used as a predictor of
constipation and fecal impaction. On the other hand, transabdominal ultrasound has been shown a reliable alternative to assess the rectal filling state, and might replace digital rectal examination in the evaluation of fearful children with constipation.

**Manometry**

*Anorectal manometry*

Anorectal manometry measures pressures in the anorectal region and provides a way to quantify the function of the internal and external anal sphincters. Anorectal manometry is only indicated to demonstrate the presence of the recto-anal inhibitory reflex, which is absent in children with anal achalasia or in children with Hirschsprung’s disease (HD). When the recto-anal inhibitory reflex is absent, the diagnosis of HD has to be confirmed by histochemical evaluation of the rectum. Anorectal manometry can be useful in differentiating between constipation associated fecal incontinence and FNRFI. It has been shown that children with constipation associated fecal incontinence have higher thresholds for rectal sensation than those with FNRFI.

*Colonic manometry*

Colonic manometry is a diagnostic test only performed in specialized motility centers to differentiate between normal colonic motor function and colonic neuromuscular disorders in the evaluation of children with intractable constipation. Colonic manometry may be useful in children with long-standing and intractable constipation if a gastrointestinal motility disorder is suspected. This test is used in clinical practice in children with severe constipation when medical therapy fails, to identify children who may benefit from surgery, such as the creation of an antegrade continence enema. In this select patient group, colonic manometry leads to recommendations to change therapy (mostly surgery) in 93% of patients. Several studies have used low-resolution colonic manometry to record contractile activity in children with constipation, commonly reporting a reduced frequency of high amplitude propagating contractions (HAPCs) and an absent or diminished meal response. Such findings indicate that a potential colonic neuropathy may exist. More recently, studies using high-resolution colonic manometry have emerged. One of the advantages of high-resolution manometry is that we are now able to characterize many more propagating motor patterns, than we could previously using the low-resolution recordings.
**Magnetic resonance imaging (MRI)**

To date evidence does not support the use of MRI of the spine in patients with intractable constipation without other neurological abnormalities\(^4\)\(^1\). A recent study involving children with defecation disorders (constipation, constipation associated FI and FNRFI) reported spinal cord abnormalities (such as an intradural lipoma or tethered cord) only in 3% of affected children. Imaging of the spinal cord is therefore only recommended in children presenting with neurologic complaints or physical symptoms, such as gluteal cleft deviation, suggestive of spinal cord abnormalities\(^6\)\(^2\). Rosen et al. reported improvement in constipation after the spinal cord abnormalities were surgically corrected\(^6\)\(^3\).

**Treatment**

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\(^6\)\(^4\)\(^,\)\(^6\)\(^4\). The recently published ESPGHAN/NASPGHAN guideline includes 4 important phases in the treatment of chronic constipation: 1) education, 2) disimpaction, 3) prevention of re-accumulation of feces and 4) follow-up\(^4\)\(^1\).

**Education**

The treatment starts with education and includes explanation to parents and child of the anatomy and physiology of defecation and its associated disorders, explanation of the prevalence of constipation and fecal incontinence, and discussion of the related shame, embarrassment, and social issues. The physician must explain that constipation leads often to a vicious cycle that results in stool withholding, fecal retention and eventually fecal incontinence. It is important to clarify to the family that fecal incontinence is due to rectal impaction and beyond the child’s control. 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\(^6\)\(^5\). In most cases, a detailed plan eliminates parents’ and the children’s frustration and improves compliance for the prolonged treatment necessary. Without this compliance, the recommended therapy will not be successful.

**Disimpaction**

Fecal impaction is defined as a large hard mass palpable in the lower abdomen or on digital rectal examination that is unlikely to be spontaneously passed\(^6\)\(^6\). Children with chronic constipation, who undergo disimpaction before
Maintenance therapy is started, are more likely to improve with treatment compared to those who do not\textsuperscript{67}. Therefore, disimpaction, or removal of the fecal impaction, is recommended prior to maintenance therapy\textsuperscript{61}.

Fecal disimpaction can be accomplished with oral, nasal or rectal agents. Orally administration of laxatives is less invasive and is more cost effective than rectal enemas or manual disimpaction\textsuperscript{68}. Parents however should be informed that in contrast to rectal enemas their child will experience an increase in fecal incontinence episodes during the first week of treatment. After successful disimpaction the number of fecal incontinence episodes decreases significantly and the same laxative, but in a lower dose, should be continued.

Rectal enemas and suppositories have been widely used to treat fecal impaction for many years as well. Although the onset of action is faster than oral therapy, the method of delivery is more invasive.

**Maintenance therapy**

After disimpaction has been accomplished, the next step of treatment focuses on the prevention of recurrence. This can be achieved through a combination of dietary changes, behavioral interventions and medication.

**Dietary interventions**

*Fiber & fluid*

A common recommendation to parents is to increase the amount of their child’s daily fluid intake. Conflicting evidence can be found regarding the association between a low dietary fiber intake and constipation. Some studies demonstrated low fiber intake in constipated children compared to healthy controls, but others did not support this finding\textsuperscript{69–71}. Literature further shows that current recommendations for dietary fiber intake in children vary substantially among organizations\textsuperscript{72}. A well-balanced diet rich in whole grains, fruits and vegetables remains the most reasonable advice to parents and children\textsuperscript{41}.

**Behavioral interventions**

Parents should be encouraged to be positive and supportive throughout the treatment. This can be helpful in reducing the child’s defecation anxiety and toileting avoidance\textsuperscript{73}. The child is encouraged to do toilet training, in which the child is encouraged to sit on the toilet up to 5 minutes, three times a day following meals to take advantage of the gastrocolic reflex. A daily diary to keep record of bowel movements, fecal and urinary incontinence, and medication is helpful to monitor progress and compliance. Sometimes positive reinforcements or rewards for compliant behavior using stickers or small gifts can
further encourage children\textsuperscript{74}. The presence of coexisting behavioral problems often is associated with poor treatment outcome. Psychological referral is indicated in children with severe emotional problems who fail intensive medical treatment.

Biofeedback training is a technique that can be used to teach children how to control their perianal muscles in order to pass bowel movement more efficiently. It is based on making a physiological mechanism of which patients are unaware of noticeable and measurable to them. A systematic review, however showed that biofeedback when used together with laxative therapy does not add any long-term benefit in children with non-organic fecal incontinence and constipation\textsuperscript{75,76}.

**Oral laxatives**
Oral daily laxative therapy should be started immediately after disimpaction. The laxative dose should be adjusted as needed to reach the desired stool consistency and frequency.

**Osmotic laxatives**
Osmotic laxatives (lactulose, magnesium hydroxide, polyethylene glycol) soften the stools by retaining water within the colon through osmosis. PEG-based laxatives are the most commonly used laxatives worldwide\textsuperscript{77}, possibly due to its ease of administration and palatability. Two randomized controlled trials showed that PEG 3350 was more effective than placebo in increasing stool frequency and reducing the number of hard stool and pain during defecation\textsuperscript{78,79}.

**Stimulant laxatives**
Stimulant laxatives, like bisacodyl, increase intestinal motility and interfere with epithelial transport of water and electrolytes. Literature is lacking high-quality randomized controlled trials evaluating the use of stimulant laxatives in childhood constipation\textsuperscript{80}. Stimulant laxatives can cause abdominal discomfort and cramping. Despite intensive medical treatment, only 50% of all children followed for 6–12 months completely recover from constipation and are successfully taken off laxatives\textsuperscript{81}.

**New laxatives**
Several new compounds have been evaluated for adults with constipation, including serotonergic enterokinetic compounds and chloride channel activators. Serotonin is involved in regulating gut motility, visceral sensitivity and intestinal secretion through serotonin 5-HT4 receptors, which are mainly expressed
by enteric nervous system interneurons. Prucalopride, is a selective, high-affinity 5-HT4 receptor agonist, with enterokinetic properties, and has been shown to be successful for the symptomatic treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief\textsuperscript{52,83,84}. Prucalopride stimulates colonic motility by increasing high-amplitude propagated contractions and accelerates colonic transit in healthy volunteers and adult patients with constipation. However, a large multicenter RCT in children with functional constipation showed that prucalopride, although well tolerated, was not more effective than placebo\textsuperscript{85}. The first chloride channel activator, lubiprostone, stimulates intestinal fluid secretion without increasing serum electrolyte levels. This compound showed a significant improvement in bowel habits compared to placebo in several studies in adults with constipation\textsuperscript{86–88}. The main reported side effect was nausea. Currently, only one open label study exists in children of different ages with constipation. This study showed that lubiprostone was efficacious and well tolerated in 127 children and adolescents with constipation, with minor side effects as nausea and vomiting\textsuperscript{89}. A large randomized placebo controlled trials is currently conducted in Europa and United States in children with functional constipation.

**Retrograde enemas**

Little is known about the role of retrograde enemas in the maintenance phase of childhood constipation. One randomized controlled trial compared the clinical effectiveness of additional treatment with rectal enemas to conventional treatment alone in 100 children aged 8-18 years with at least 2 years symptoms of functional constipation. After 1 year of treatment, the overall success rate was 47.1% in the enema group versus 36.1% in the conventional control group, suggesting there is no additional effect of enemas compared with oral laxatives alone as maintenance therapy for severely constipated children\textsuperscript{90}.

**Transanal irrigation**

Transanal irrigation with Peristeen\textsuperscript{®} is a relatively new rectal irrigation system that can be used at home in children with constipation and fecal incontinence. After inserting the rectal catheter, a balloon attached to the catheter is inflated with air to secure the position of the catheter in the rectum. Then, after infusion of the irrigation fluids into the colon, the balloon is deflated and both stools and irrigation water are evacuated from the rectum. By irrigating the colon, accumulation of large quantities of stools is prevented which consequently results in a decrease in the number of fecal incontinence episodes, thereby improving the quality of life in these children\textsuperscript{91}. 

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Surgical management

Although conventional therapy usually successfully treats children with functional constipation, a small group continues to have intractable symptoms. Surgical interventions may benefit this minority. Surgery is generally performed in a step-up approach, beginning with the least invasive procedure and proceeding to more invasive treatment options only after failure of the previous step.

Sacral nerve modulation

Sacral nerve modulation (SNM) is a promising new treatment option for patients with intractable functional constipation. SNM involves percutaneous placement of an electrode in the third sacral foramen and implantation of a stimulating device under the skin in the buttocks. Clinical results for SNM in constipation are mostly limited to adults. In literature success rates vary between 47-90% in adults with constipation or fecal incontinence. A study by van Wunnick et al. demonstrated that constipation symptoms in 13 patients between 10-18 years of age improved after SNM. Minor complications include pain after implantation, displacements of the leads and infection. Recently, a study in children with chronic constipation refractory to conservative treatment, showed that SNM has beneficial effects on defecation frequency and abdominal pain over prolonged period of time, as improvement of symptoms sustained during a median follow-up of 22.1 months in 42.9% of patients. Neuromodulation of the bowel to treat constipation has also been achieved using methods of stimulation across the skin known as transcutaneous electrical stimulation (TES). A randomized control trial examining the effect of TES, (delivered by physiotherapists three times per week for one month) and sham stimulation on 40 slow transit constipation children improved intestinal transit measured by scintigraphy and improved quality of life. Surprisingly, there was no change in the number of spontaneous bowel movements. Improvement lasted for more than 2 years in 30% of the patients. The level of evidence, however for neuromodulation of pediatric constipation is low with a clear need for well-designed studies with larger numbers of patients and longer follow up.

Antegrade continence enemas

The use of antegrade continence enema (ACE) has been reported as a successful therapeutic option for children with constipation when maximal conventional therapy is not successful. The antegrade delivery of enemas enables the patient to evacuate the colon at regular intervals, avoiding impaction of feces and reducing fecal incontinence. Since its introduction in 1990 by Malone et al, many surgical modifications have been made, with a recent
trend towards more minimally invasive procedures\textsuperscript{100}. The use of ACE in children with functional constipation has proven to be effective, but success rates vary among different studies\textsuperscript{101}. A wide variety of enema solutions can be used, including saline and PEG. Complications include skin lacerations, stoma stenosis, granulation tissue, leakage of enema solution and tube dislodgement.

**Colonic resections and ostomies**

Currently, the choice for surgery is generally based on severity of symptoms, lack of response to intensive (non)pharmacological treatment and results of diagnostic investigations. Since there are no guidelines for surgery in children with intractable FC, the choice of surgical intervention is challenging and the approach differs among centers. Temporary or permanent ileostomies and colostomies have been described in children with functional constipation\textsuperscript{102}. The rationale for diversion is to relieve symptoms and to decompress the colon, giving the diverted colonic segment time to recover. Several studies have shown that diversion of a dysmotile colonic segment can lead to improvement of colonic motility in that segment\textsuperscript{103,104}. Segmental and total colonic resections have also been described in this setting\textsuperscript{102}. Although outcomes of colon resections and anastomosis were considered largely successful in 84\% of patients with a failure rate of 16\%, the included studies in this systematic review were all retrospective case series with a small number of patients\textsuperscript{102}. Before surgical interventions are considered in patients with intractable functional constipation, families should be counseled by an experienced multi-disciplinary team, including a pediatric gastroenterologist, a pediatric surgeon, a stoma nurse, child psychologist and a social worker.

**Other surgical interventions**

Long term follow up has shown that anal dilatation does not benefit children with functional constipation\textsuperscript{105}. Another treatment option for intractable constipation is an intrasphincteric injection of Botulinum toxin (BoTox). BoTox reduces the contraction of muscles locally in a temporary manner. The injection of BoTox serves both as a diagnostic test that indicates if the internal anal sphincter hypertonia is what is producing the obstructive symptoms, and as a treatment for chronic functional constipation. It can be repeated if necessary\textsuperscript{106}.
Treatment of fecal incontinence

The treatment of nonretentive fecal incontinence has not been well defined\textsuperscript{107}. The treatment consists of education, keeping a bowel diary and toilet training 4 times a day following meals and immediately after coming home from school. To date, there are no clinical trials evaluating dietary changes in FNRFI. As described above, the main aim of medical treatment for constipation associated fecal incontinence is to empty the impacted rectum and to maintain soft stools during follow-up. In contrast, FNRFI responds poorly to laxatives\textsuperscript{108}. The softened stools even may worsen symptoms of fecal incontinence. Sometimes antidiarrheal drugs, like loperamide, are prescribed for children with fecal incontinence to reduce the fecal output\textsuperscript{109}. In contrast to adults, experience with loperamide childhood fecal incontinence is limited\textsuperscript{11}.

Behavioral therapy, toilet training in combination with a reward system, is the most important step in the management of FNRFI. One long-term follow-up study described that after two years of intensive medical and behavioral treatment only 29\% of the children were successfully treated. Children should be motivated to adhere to an intensive toilet training program. Keeping record completed toilet training and bowel movements in a dairy can enhance motivation\textsuperscript{110}.

Currently, surgical interventions have no place in the treatment of children with FNRFI.

Follow-up

It is a misconception that constipation is self-limiting. Most children treated for constipation are eventually cured, although the time required varies and relapses are not uncommon. Therefore it is important to provide support and encouragement through regularly scheduled office visits. Progress should be assessed and, if necessary, dosage adjustments need to be made. After regular bowel habits are established, the medication dosage is gradually decreased. A systematic review found that only half of all children with constipation followed for 6-12 months after therapy were doing well without laxatives. Treatment needs to resume if constipation or fecal incontinence recurs. Early age of onset of constipation and family history were predictive of persistence of symptoms\textsuperscript{111}. There is little evidence about the long-term outcome in children with FNRFI.

In one study children with FNRFI were followed for 10 years. Only 29\% of children were having less than one episode of fecal incontinence in 2 weeks after 2 years of medical and behavioral therapy. At the age of 18 years, 85\% of patients with FNRFI were symptom free. However, this indicates that 15\% of children progress to adulthood with fecal incontinence. No prognostic factors for success were found in this study\textsuperscript{110}. 
OUTLINE OF THE THESIS

The majority of children with functional defecation disorders respond well to conservative treatment, such as laxatives and behavior therapy. Challenging is the small subgroup of patients who are not responsive to conventional treatment and continue to have symptoms. Part I of this thesis discusses which outcome measures should be measured in trials regarding functional constipation. Part II focuses on new diagnostic tests and Part III on therapeutic strategies for pediatric functional defecation disorders. In Part IV associated (behavior) problems are discussed.

PART I  Associated problems
Behavior problems are frequently reported in children with FDD\textsuperscript{28}. Likewise, gastrointestinal problems like constipation, seem to be particularly common in children with behavioral and developmental disorders, such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD)\textsuperscript{29,30}. A prior study found that 29\% of children with FDD scored positive on ASD screening-questionnaires\textsuperscript{29}. Whether positive screens correctly identify ASD in children with FDD is unknown. The aim of Chapter 1 is to prospectively assess whether positive screening-surveys for ASD in children with FDDs accurately identify ASD. In Chapter 2 we prospectively assess the prevalence of ADHD in children presenting with FDDs, and the prevalence of FDDs in children with a known diagnosis of ADHD.

Several studies have suggested that there is an association between FDDs and overweight and/or obesity in children\textsuperscript{33,36}. To date, no comprehensive systematic review has been published to evaluate the potential association between FDDs and overweight/obesity in children. Therefore, the aim of Chapter 3 was to systematically review currently available literature regarding the association between FDDs and overweight/obesity in children.

PART II  Outcome measures
In order to compare results from clinical trials, uniform definitions and outcome measures are required. The use of inappropriate outcome measures and/or their definitions can compromise the utility of a trial, by representing misleading information on the relevance of the outcome measures, or by overestimating or underestimating trial results. Moreover, comparison between trials and meta-analysis is not possible if uniform outcome measures are not used. Only
few studies have been performed to address the choice of outcomes in clinical trials in children. Therefore, our aim of Chapter 4 and Chapter 5 systematically assess how definitions and outcome measures are defined in therapeutic randomized controlled trials of children with functional constipation. The inconsistencies and bias mentioned above could be tackled by the development of agreed standardized sets of outcomes, known as core outcome sets. A core outcome set should be measured and reported as a minimum in all trials for a specific clinical area. In Chapter 6 we will describe the core outcome set that we developed for childhood functional constipation.

PART III Diagnostics
Colonic manometry has increased the knowledge of the pathophysiology of gastrointestinal disorders and changed diagnosis and treatment of chronic constipation in children. Several studies have used low-resolution manometry to record contractile activity in children with constipation, commonly reporting a reduced frequency of high amplitude propagating contractions and an absent or diminished meal response. More recently, studies utilizing high-resolution manometry have emerged and described abnormalities in colonic motor patterns in adults with slow transit constipation. Whether or not such motor pattern abnormalities exist in children with chronic intractable constipation has not yet been established. Therefore in Chapter 7, our aim is to quantify the colonic motor patterns in such children utilizing high resolution colonic manometry. Recently cine-magnetic resonance imaging (MRI) was introduced as imaging technique for visualizing colon motility. A study by Kirchhoff et al, including 10 healthy adult volunteers, showed that cine-MRI allows for visualization and reliable recording of high amplitude propagating contractions (HAPCs) using intraluminal bisacodyl administration compared to colonic manometry.

PART IV Treatment
In tertiary care centers, 50% of children referred to a pediatric gastroenterologist are still symptomatic after 5 years, and 20% still struggle with symptoms after 10 years. Symptoms can even persist into adulthood despite intensive laxative treatment. Children with intractable functional constipation may eventually require alternative therapeutic interventions including surgery. It is therefore necessary to uncover new and more effective interventions for children with constipation. Transanal irrigation is a relatively new treatment modality and has been shown to be effective in children with constipation due to organic causes.
Data however, on children with functional constipation are scarce. Therefore we evaluated in Chapter 8 the treatment efficacy of transanal irrigation and parental satisfaction in children with intractable functional constipation treated with Peristeen®.

The use of antegrade continence enemas (ACE) has been reported as a successful therapeutic option for patients with long-lasting constipation when maximal conventional therapy is not successful. In Chapter 9 we provide an overview of the existing literature regarding the outcomes of the ACE procedure, and we assessed current practices of physicians worldwide regarding the use of an ACE.

Although children with intractable functional constipation may eventually require surgery, there are no evidence-based guidelines for the surgical management of intractable functional constipation in children. Therefore, our aim of Chapter 10 was to assess the diagnostic and surgical approach of pediatric surgeons and pediatric gastroenterologists towards children with intractable functional constipation. In Chapter 11 we describe the experience of our tertiary care center with the surgical management of children with intractable functional constipation.
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