Evidence-based guideline development in paediatric gastroenterology

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General introduction

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General introduction

Constipation is one of the most prevalent, frustrating and long-lasting paediatric functional gastrointestinal disorders. Many differences exist between involved health care professionals with respect to diagnosing and treating children with constipation. Only recently, a survey among Dutch Paediatricians showed that “Constipation” was the most wanted topic for which a Dutch national guideline was urgently needed. The development of this national guideline concerning paediatric constipation will be discussed in this thesis.

Guideline development

Unfortunately, for many health care conditions, a gap exists between what medical science has shown to be effective practice and what is actually done by physicians. To target this problem, guidelines are of great importance since clinical practice guidelines can facilitate translation of new research findings into clinical practice. They are seen as powerful tools to achieve effective care, reduce variability in daily practice, and may reduce costs.¹ A guideline is a document with recommendations, guidance and instructions to support daily practice in health care, based on results of scientific research and the consequent discussion and formation of opinion, aimed at the explicit statement of good medical practice.² The primary aim of paediatric guidelines is to improve the health of children by ensuring that they receive up-to-date, evidence-based care. Several studies have shown that adherence to evidence-based guidelines leads to improvement in the quality of care provided.³⁻⁶ Some guideline characteristics have been shown to contribute to their use in clinical practice. It all starts with the fact that a guideline should be developed according to evidence-based principles which facilitates the acceptance and effective use in the target group.⁷ Further important characteristics are inclusion of specific recommendations, sufficient supporting evidence, a clear structure, an attractive lay out and short summaries.⁸ Guideline endorsement by a physician’s own specialty organization is also associated with improved physician’s confidence in a guideline.⁹ Physician participation in guideline development has been shown to be useful in addressing barriers owing to lack of agreement.¹⁰ In the past, guidelines developed by paediatricians were mainly based on experience and opinions of experts. In the 1990s, scientific requirements for guidelines became stricter, due to the evidence-based medicine movement.

Nowadays, there are several institutions which are producing or authorizing evidence based paediatric guidelines, e.g. the Scottish Intercollegiate Guidelines (SIGN: www.sign.ac.uk) and the American Academy of Paediatrics (AAP: www.aap.org). Furthermore, databases exist that register and link to evidence-based child health guidelines like the National Guideline Clearinghouse (NGC: www.guideline.org), the Agency for Health Care Policy and Research (ACHCPR) and the Canadian Medical Association Clinical Practice Guidelines Infobase (CMA: www.cma.ca).⁶ In the Netherlands, the Dutch Paediatric Association (NVK) started in 2000
with the development of paediatric guidelines.\textsuperscript{6} Since 2000, around 50 evidence-based guidelines have been developed or approved by the Dutch Paediatric Association. Boluyt et al. showed by questionnaires that “Constipation” was the most wanted topic by Dutch paediatricians for which a Dutch national guideline was urgently needed.\textsuperscript{11} However, to date, there is still no national guideline concerning constipation in children. Currently two international guidelines exist for the treatment of functional constipation which are based on reviews of the literature that did not apply a systematic literature search, did not incorporate quality assessment of studies, or used a language restriction.\textsuperscript{12,13} Therefore it remains unclear whether the recommendations of both guidelines are based on personal conviction of the guideline committee or on scientific evidence. An evidence-based guideline concerning one of the most prevalent, frustrating and long-lasting paediatric functional gastrointestinal disorders should therefore be needed.

How to develop a guideline?
Clinical guidelines are only valid if they are developed in a rigorous way, independently of vested interests of their developers, and if they support decision making in practice and affect actual care.\textsuperscript{14} In order to develop a valid guideline, the process of guideline development should consist of different steps as shown in table 1.\textsuperscript{15}

<table>
<thead>
<tr>
<th>Steps</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Preparation</td>
<td>- Topic selection, assess aims and target group</td>
</tr>
<tr>
<td></td>
<td>- Composition of guideline group including a chairman</td>
</tr>
<tr>
<td></td>
<td>- Identifying controversies and existence of proven solutions, formulating questions</td>
</tr>
<tr>
<td></td>
<td>- Assess method of patient involvement</td>
</tr>
<tr>
<td>2. Development of draft version</td>
<td>- Literature search by identifying existing guidelines and systematic reviews</td>
</tr>
<tr>
<td></td>
<td>- Appraising available literature for quality and applicability</td>
</tr>
<tr>
<td></td>
<td>- Formulating recommendations</td>
</tr>
<tr>
<td></td>
<td>- Writing draft version</td>
</tr>
<tr>
<td>3. Consultation</td>
<td>- External review by a sample of concerned individuals (experts, patients, managers, insurers)</td>
</tr>
<tr>
<td></td>
<td>- Pilot study</td>
</tr>
<tr>
<td>4. Authorizing</td>
<td>- Procedure of authorization, approval of involved professional organisations</td>
</tr>
<tr>
<td>5. Publication and dissemination</td>
<td>- Writing final version</td>
</tr>
<tr>
<td></td>
<td>- Assess publication and dissemination strategies</td>
</tr>
<tr>
<td>6. Implementation</td>
<td>- Assess effective implementation strategies</td>
</tr>
<tr>
<td>7. Evaluation and revision</td>
<td>- Developing indicators</td>
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<td></td>
<td>- Assess revision procedure</td>
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</table>
Preparation

Appropriate topics can be selected by the relevance and prevalence of the problem, controversy about optimal care, existence of proven solutions, barriers expected when implementing improvements and motivation and improvement skills of the care providers involved. Besides scientific also psychosocial, ethical, legal and financial aspects play a role in implementing guidelines. A systematic analysis prior to guideline development contributes to its successful application. In case of constipation, as mentioned above, this was a topic most frequently wanted by Dutch paediatricians.

A balanced guideline group with both clinical and methodological expertise is necessary to promote broad consensus and to prevent bias from conflicts of interests. These stakeholders involved in the developmental process are of great importance in disseminating recommendations before active implementation. It should also include representatives of patient groups. Furthermore, adequate staff support is needed to perform literature searches. Finally, a neutral chairman and formal group processes should be used to achieve consensus.

Development of draft version

Next, a work plan should be formulated describing the aims of the guideline, healthcare problems and settings covered, desired outcomes (like mortality, morbidity, complications, quality of life), target group involved (care providers and patient population), time schedule and division of the tasks. The literature search starts by identifying and reviewing existing guidelines and/or a systematic literature review and appraise them for quality and applicability. If none are found, a systematic review of the literature should be performed. The next step is to evaluate the scientific strength of the published research. Information about the advantages, disadvantages and costs of the studied interventions is examined. The evidence is categorized using predefined grading schemes for preventive, diagnostic, and therapeutic procedures. Table 2 shows such a grading system, as developed by the Dutch Institute for Quality Improvement in Healthcare (CBO).

Table 2. Classification of the literature according to the strength of the evidence (CBO 2000)

<table>
<thead>
<tr>
<th>For articles concerning intervention (prevention or therapy):</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 Systematic reviews of at least a few studies on the A2 level, of which the results of independent research studies are consistent</td>
</tr>
<tr>
<td>A2 Randomised comparative clinical research of good quality (randomised, double-blind, controlled trial of adequate scope and consistency)</td>
</tr>
<tr>
<td>B Randomised clinical trials of moderate quality or insufficient scope, or other comparative research (nonrandomised, cohort studies, patient-control studies)</td>
</tr>
<tr>
<td>C Noncomparative research</td>
</tr>
<tr>
<td>D Opinions of experts, such as the work group members</td>
</tr>
</tbody>
</table>
While formulating recommendations, scientific evidence and clinical experience are brought together. The following issues should be considered to ensure implementation:16
1. Strength of the scientific evidence; the balance between the advantages of a given intervention and its disadvantages. 2. Generalizability and applicability to the target population. 3. Cost-effectiveness of the proposed intervention. 4. Achievability of the intervention in terms of required skills, instruments, time, available staff, patient's preferences and legal or financial limitations. 5. Opinions, norms and values, and ethical considerations of the target users. All other used considerations in the process of developing recommendations, should be clearly presented in the guideline, because transparency is very important in order to implement the guideline in a proper way. Table 3 shows a grading system for recommendations developed by the Dutch Institute for Quality Improvement in Healthcare (CBO).

Table 3. Level of evidence of the recommendations (CBO 2000)

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Scientific evidence of level A1 or at least of 2 independent research studies of level A2</td>
</tr>
<tr>
<td>2. Scientific evidence of level A2 or at least of 2 independent research studies of level B</td>
</tr>
<tr>
<td>3. Scientific evidence of level B or C</td>
</tr>
<tr>
<td>4. Expert opinion</td>
</tr>
</tbody>
</table>

Consultation

For promoting support, the draft has to be presented at an open meeting allowing the audience to express their comments and suggestions. If no consensus is reached, a voting system can be used. To facilitate its applicability in daily care the guideline is piloted in practice. The results of the pilot and the consultation process are incorporated in the final version of the guideline.16

Authorization

The next step is authorization of the guideline by all involved professional organisations. Comments of these organisations has to be discussed in the guideline group and incorporated in the final version.15,16

Publication, dissemination, implementation

The next step is designing an accessible and attractive format with a summary of the recommendations.8,16 Clinical guidelines should be published in professional journals and posted to every possible user. Electronic versions of the guideline and tools for application (e.g. a practice summary on a plastic-laminated card) have to be developed. Furthermore, without active implementation, an evidence-based guideline will not result in changing behaviour and consequently not in improvement of quality of care.17
Evaluation and revision

Success or failure of implementation should be measured by guideline-specific indicators.\textsuperscript{18} Besides developing indicators, clinical guidelines require updating if the majority of recommendations are out-of-date due to changes in research findings and new available diagnostic or therapeutic interventions. In general, guidelines should be reassessed for validity every three years.\textsuperscript{19} As part of this thesis, we have developed a national guideline concerning paediatric constipation by using the discussed process of guideline development. During this process, we also performed a study in an attempt to get more insight into the pathophysiology of functional constipation. Colonic smooth muscle defects have been reported in patients with slow transit constipation, which probably influence colorectal motility. Histological changes as a result of constipation symptoms, however have yet to be evaluated.

Constipation

Constipation is probably the most common gastrointestinal complaint in children. In this chapter prevalence and pathophysiology, new definitions, symptomatology and treatment of constipation will be reviewed.

Prevalence and pathophysiology

Chronic constipation is a common problem in childhood with an estimated prevalence of 3\% in the Western world.\textsuperscript{20} In 17-40\% of children, constipation already starts in the first year of life.\textsuperscript{21} Constipation is a debilitating condition characterized by infrequent painful defecation, faecal incontinence, and abdominal pain. It causes distress to the child and family and can result in severe emotional disturbances, and family discord.\textsuperscript{22} The pathophysiology underlying functional constipation is undoubtedly multi-factorial, and not well understood. Normal defecation is a complex process triggered by stool stretching the walls of the rectum. Stool is evacuated by relaxation of the involuntary internal anal sphincter and voluntary relaxation of the pelvic floor muscles and contraction of the abdominal muscles. For this process normal muscle function, normal colonic motility, normal sensation and the volitional attempt to find an appropriate place for defecation are needed. Dysfunction at any level in this process can cause constipation. Withholding behaviour is in this process probably the major cause for the development of constipation; this behaviour might be triggered by the previous production of large, hard, painful stools, anal fissures, a primarily behavioural mechanism, or resistance to use another toilet than their own.\textsuperscript{22} The time of toilet training is an especially critical period when constipation may occur as a consequence of a struggle between child and parents.\textsuperscript{22} Interestingly, Borowitz et al. found no association between the development of early childhood constipation and the timing, style or techniques used for toilet training.\textsuperscript{23} However, the retained stools become progressively more difficult to evacuate leading to a vicious circle in which the rectum is increasingly distended by large
faecal contents. Finally chronic rectal distension may cause overflow faecal incontinence, loss of rectal sensitivity and, in the end, loss of normal urge to defecate. This aberrant behaviour may lead to the unconscious contraction of the external sphincter during defecation. Approximately 50% of children and adults with constipation have this abnormal defecation pattern. This paradoxical contraction of the anal sphincter complex has been considered by some to be the major pathophysiological mechanism of childhood constipation. However, normalization of this pattern with biofeedback training does not correlate with successful treatment outcome. Voskuijl et al. found that constipated children have normal rectal sensation but need more intraluminal volume as a consequence of the altered compliance of the rectum. The role of rectal compliance in the pathophysiology is still controversial. Another study showed that rectal compliance in recovered patients is lower compared to patients with persistent constipation. However, almost 50% of the recovered adolescents had a rectal compliance above the normal range suggesting that they were able to recover from functional constipation despite the increased rectal compliance. Thus, rectal compliance seems not to be an important factor involved in recovery. Further studies are necessary to assess the significance of an increased rectal compliance. 

Colonic manometry has demonstrated possible other underlying factors. In a subset of children with severe defecation disorders, no or weak colonic contractions were seen without a generalized colonic dilatation. They are thought to have a colonic myopathy, while children with colonic neuropathy are characterized by the absence of the gastrocolonic response and abnormal or absent high amplitude propagating contractions (HAPC). Studies have also shown the occurrence of abnormalities in the enteric nervous system in patients with intractable constipation, such as reduced numbers of interstitial cells of Cajal or ganglia cells. However, to date, no direct correlation with histological findings of myopathy or neuropathy has been proven yet. Finally, a recent study showed that children with slow transit constipation, characterized by an overall delay in colonic transit time, have reduced trunk control and posture compared to controls, which indicates that clinicians should include training of trunk muscles and correction of sitting posture. There was no evidence that children with slow transit constipation exercised less than the controls.

**Definition of constipation**

The term constipation is derived from the Latin word “constipare”, meaning to crowd together. For many years, physicians, patients and parents used different definitions for constipation. For this reason, consensus on the definition was needed in order to make an appropriate diagnosis and to allow researchers to compare results of studies. Initially Rome II criteria (1999) defined functional childhood constipation as at least 2 weeks of: scybalous, pebble-like, hard stools for most of the stools; or firm stools two or fewer times a week and no evidence of structural endocrine or metabolic disease. These criteria were
not necessarily comprehensive and were found to be restrictive by some researchers.\textsuperscript{33} In 2004, the PACCT group (Paris Consensus on Childhood Constipation Terminology) modified the Rome criteria and defined childhood constipation as the occurrence of two or more of the following six criteria in the previous 8 weeks: frequency of movements fewer than 3 per week; more than one episode of faecal incontinence per week; large stools in the rectum or palpable on abdominal examination; passing of stools so large that they may obstruct the toilet; retentive posturing and withholding behaviour; and painful defecation.\textsuperscript{34} These criteria were integrated into Rome III criteria (2006).\textsuperscript{35,36} To fulfill the new Rome III criteria for functional constipation, see table 4, children > 4 years should have 2 or more of the following symptoms for at least 2 months: 1) two or fewer defecations in the toilet per week, 2) at least one episode of faecal incontinence per week, 3) stool retentive posturing, 4) painful or hard bowel movements, 5) presence of a large faecal mass in the rectum or 6) large diameter stools that may obstruct the toilet without objective evidence of a pathological condition. Infants up to 4 years of age have to fulfill two or more criteria for at least 1 month.

\textbf{Table 4. The Rome II criteria for paediatric functional constipation}

1) two or fewer defecations in the toilet per week,
2) at least one episode of faecal incontinence per week
3) stool retentive posturing
4) painful or hard bowel movements
5) presence of a large faecal mass in the rectum
6) large diameter stools that may obstruct the toilet

The limitation of the current ROME III criteria are that these definitions are based on constipation seen in referred children. Most children with constipation, however are seen in primary care, and therefore the current definitions need to be validated and confirmed in primary care. Furthermore, it is of major importance to investigate if these criteria are applicable for specific patient groups like premature and/or small for gestational age babies or mentally handicapped children.\textsuperscript{37} Besides different definitions, also many different terms for defecation related symptoms, such as soiling and encopresis are used in studies worldwide. Soiling is defined as the involuntary passage of small amounts of stools, resulting in staining the underwear. The quantity of faecal loss is the main difference between encopresis and soiling. In practice, however, parents are often unable to accurately estimate the amount of feces lost in the underwear and thus cannot differentiate between soiling and encopresis. Therefore, the more neutral term of faecal incontinence was adopted by the Rome III group rather than the terms encopresis and soiling to prevent misunderstanding. Paediatric faecal incontinence can be divided into either organic faecal incontinence (e.g., resulting from anorectal malformations or neurological damage) or functional faecal incontinence. The latter can be subdivided into constipation-associated faecal incontinence and nonretentive faecal incontinence.\textsuperscript{38}
Symptoms of constipation

Healthy term born neonates have an average of 3-4 bowel movements (bm) per day. At the age of 4-6 months it decreases to 1-2 bm per day. In children from 6 months to 2 years, a defecation frequency of 1-2 is assumed to be normal. From 2 years to 8 years, a defecation frequency of once per day seems to be normal. Up to the age of 8 years, a defecation frequency of once per day or per two days is reported in 95% of healthy children. An Italian nationwide survey was performed to assess bowel frequency and modalities of defecation in the general paediatric population. In this study, mean bowel frequency did not vary in the first two years of life, it decreased after the second year, and remained stable until the 12th year; it did not differ between sexes. Stool consistency, duration of evacuation, and frequency of episodes of painful defecation showed a significantly inverse relationship with bowel frequency.

It is assumed that children with functional constipation are only suffering from a low defecation frequency. However, in general they will suffer from many other symptoms. Table 5 shows clinical signs of constipation. Defecation frequency below three times per week is found in 64-88% of constipated children and faecal incontinence is reported in 75-90%. Van Dijk et al. showed that stool withholding behaviour occurred in 68% of the constipated children and painful defecation in 65% which make them also important

Table 5. Clinical presentation of constipation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal incontinence</td>
<td>75–90</td>
</tr>
<tr>
<td>Defecation frequency &lt; 3/wk</td>
<td>75</td>
</tr>
<tr>
<td>Large stools</td>
<td>75</td>
</tr>
<tr>
<td>Straining during defecation</td>
<td>35</td>
</tr>
<tr>
<td>Pain during defecation</td>
<td>50–80</td>
</tr>
<tr>
<td>Retentive posturing</td>
<td>35</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10–70</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>20–40</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10–25</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>25</td>
</tr>
<tr>
<td>Enuresis/Urinary tract infection</td>
<td>30</td>
</tr>
<tr>
<td>“Psychological problems”</td>
<td>20</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>- Abdominal mass</td>
<td>30–50</td>
</tr>
<tr>
<td>- Anal prolapse</td>
<td>3</td>
</tr>
<tr>
<td>- Fissures/hemorrhoids</td>
<td>5–25</td>
</tr>
<tr>
<td>- Faecal impaction</td>
<td>40–100</td>
</tr>
</tbody>
</table>
features of constipation. A rectal scybalus found either by abdominal palpation or rectal examination is present in 30-75% of the constipated toddlers and older children. As table 2 shows, 20% of the children with constipation have psychosocial co-morbidity. If present, they are generally secondary to social consequences and humiliation experienced by these children due to the presence of faecal incontinence.

**Diagnostic tools**

In general, a thorough medical history and complete physical exam including a rectal digital examination, are usually sufficient to confirm the diagnosis of functional constipation. De Lorijn et al. showed that a bowel diary (www.poeppoli.nl) is sufficient in diagnosing constipation. Further investigations should only be performed in case of doubt, to exclude an underlying disease. Less than 5% of children with constipation have an underlying cause, such as anatomic malformation (i.e. anal stenosis, imperforate anus), metabolic and gastrointestinal disorders (i.e. celiac disease, hypothyroidism and cystic fibrosis), intestinal nerve and muscle disorder (i.e. Hirschsprung’s disease, visceral myopathies). In the majority of patients, children with organic constipation will not only present with constipation but also with other specific symptoms belonging to their underlying disease. It is assumed that only in these selected cases, a further diagnostic work-up is indicated. A systematic review is currently lacking investigating and summarizing the quantity and quality of the current evidence concerning the value of different diagnostic tools like a rectal ultrasound, or assessing colonic transit time using radiopaque markers in determining the diagnosis functional constipation. A systematic review has been performed in 2005 reporting the value of an abdominal X-ray in the diagnosis of childhood constipation. This extensive review concluded that an abdominal X-ray is not worthwhile in assessing the diagnosis. The diagnostic value was related to the methodological quality of the four included studies. Studies of low quality showed a higher diagnostic value. Sensitivity and specificity of the abdominal X-ray were ranging from 60 to 80% and from 43 to 90% respectively. Despite these data, many physicians are still using an abdominal X-ray in their diagnostic work-up of constipation. Therefore, a national guideline with all available evidence concerning diagnostics will be helpful in an attempt to change behaviour leading to an improvement of quality of care and saving costs.

**Treatment**

The objectives of treating children with constipation are: to restore a regular defecation pattern (soft and painless stools) without faecal incontinence and to prevent relapses. In 1999 NASPGHAN published a position paper in which four important steps in the treatment of childhood constipation were recommended: 1) education, 2) disimpaction, 3) prevention of re-accumulation of feces and 4) follow-up.
Education

Treatment of childhood constipation starts with demystification, education and a non-accusatory approach by parents and physicians. Information should be given about prevalence and symptoms including the recurrent periods of improvement and deterioration. This information should also contain explanation to parents and child about the aetiology of faecal incontinence. Faecal incontinence is due to overflow of loose stools in an impacted rectum and not the result of the child’s behaviour. A clear explanation will help parents and child in understanding this frustrating paediatric gastrointestinal symptom and should be therefore easier to accept. A systematic review showed that only 50% of all children followed for 6 to 12 months are found to recover and were successfully taken off laxatives. However, none of the included studies were conducted in primary care. Parents and child have to be informed about this percentage before start of the treatment. Besides education, dietary advices should be given consisting of a normal fluid and normal fibre intake. The recommended daily fluid intake depends on many factors like age and weight. Furthermore, specific circumstances like diarrhea or fever require more fluid. In general, an infant needs 150 ml/kg fluid per day. From a weight of 10 kg or more, a healthy child needs 1000-1500 ml fluid per day. The recommended fibre intake in children over age 2 years is calculated as the age in years plus 5 grams/d. However, it is generally accepted by doctors and patients that lack of fibre, fluid and also physical movement are common causes of constipation. But is there scientific evidence available for these interventions? We do know that the current evidence regarding the effect of fibre for instance is based on few and small studies with different study designs and different outcomes. In chapter 3, 4 and 5 of this thesis, we will discuss the available evidence for the use of fibre, fluid and physical movement in a systematic way. Furthermore, all children with a developmental age of at least 4 years have to be instructed to try to defecate on the toilet for 5-10 minutes after each meal (3 times a day) and to complete a standardized bowel diary daily. Bowel diaries recording data about the defecation pattern are useful to confirm the diagnosis, to quantify therapeutic progress and to enhance motivation. Introducing a rewarding system linked to the defecation diary, is often an effective tool in the treatment. If education, dietary measures, bowel diary with rewarding system is not sufficient within two weeks, medical treatment has to be started. Aim is to soften the stools to facilitate defecation.

Disimpaction

Faecal disimpaction prior to maintenance treatment with oral and/or rectal laxatives is recommended to increase success, and reduce the number of faecal incontinence episodes. For many years, it has been assumed that omission of initial disimpaction, treatment with oral laxatives will paradoxically result in an increase in faecal incontinence due to overflow incontinence. A recent randomised controlled trial has shown that enemas daily and polyethylene glycol orally (1.5 g/kg per day) for 6 consecutive days were equally effective in treating rectal faecal impaction in children with functional constipation. Indeed,
compared with enemas, polyethylene glycol (PEG) caused more faecal incontinence, with comparable behaviour scores. The same behaviour scores are quite remarkable, because in earlier studies faecal incontinence is associated with lower quality of life reported by parents and children as well. An explanation could be that in the study of Bekkali et al., enemas were given in a familiar environment, namely at home by the parents instead of a nurse in the hospital which is more commonly done in practice. So, these treatments should be considered equally effective as first-line therapy for rectal faecal impaction.

Maintenance therapy (prevention of re-accumulation of feces)

After the short disimpaction phase, maintenance therapy is started to prevent re-accumulation of feces. Several oral laxatives, and sometimes enemas, can be prescribed consisting of osmotic laxatives, like lactulose and PEG, or stimulant laxatives, like bisacodyl or senna. Only two randomised controlled trials have been performed comparing oral laxatives versus placebo. Both studies using macrogol (PEG 3350) showed that this compound was more effective than placebo in increasing number of defecations, reduction of hard stools and in reduction of pain- and straining during defecation. Furthermore, several randomised controlled trials were carried out comparing PEG and lactulose. Disappointingly all these trials used different inclusion criteria, outcome measures, dosages and study designs which make it difficult to draw firm conclusions.

Currently two international guidelines for the treatment of functional constipation exist which are based on reviews of the literature that did not apply a systematic literature search, did not incorporate quality assessment of studies, or used a language restriction and were therefore rather experience-based than evidence-based. A systematic review is lacking investigating and summarizing the quantity and quality of the current evidence for the effect of laxatives. More well-designed, large randomised controlled trials are necessary to determine and understand the role of different medical treatments in constipated children.

Behavioural therapy

As discussed previously, all children with a developmental age of at least 4 years have to be instructed to try to defecate on the toilet for 5-10 minutes after each meal (3 times a day) and to complete a standardized bowel diary daily. Introducing a rewarding system linked to the defecation diary, is often an effective tool to enhance compliance. Aim of these behavioural interventions in combination with laxatives, is to reduce the level of distress and to develop or restore normal bowel habits by positive reinforcement. A recent randomised trial compared behavioural therapy by a child psychologist (learning process to reduce phobic reactions related to defecation consists of 5 sequential steps: know-dare-can-will and do) versus conventional treatment by a paediatric gastroenterologist (education, diary, toilet training with rewarding system) over 22 weeks including 12 visits. Both groups used similar laxative therapy. Although a statistically significant increase in defecation frequency and a statistically significant reduction in faecal incontinence episodes were found
in both groups, no significant differences were seen in defecation frequency at 22 weeks and 6 months, or in the number of episodes of faecal incontinence between both groups. Furthermore no significant difference in success rates was found between both groups. After 6 months, the percentage of children with behavioural problems was significant lower in the behavioural therapy group compared to the conventional treatment group (11.7% versus 29.2%). Therefore the authors concluded that psychological referral is only indicated in constipated children with severe emotional problems, scored upon the child behaviour checklist. Furthermore behavioural therapy might be helpful in those cases were laxative therapy failed.

Non-pharmacological treatments
The treatment of constipation is long-lasting and relapses are common. Therefore it is not surprising that parents of children with functional defecations disorder seek help from other health care professionals. Non-pharmacological treatment includes fibre, fluid, physical movement, behavioural therapy, multidisciplinary treatment, pre-and probiotics and alternative medicines (including acupuncture, homeopathy, mind-body therapy, musculoskeletal manipulations like osteopathic and chiropractic manipulations and spiritual therapies like yoga). Only recently, Vlieger et al. showed that 36.4% of children with functional constipation used some form of complementary medicine such as acupuncture and homeopathy.

Multidisciplinary treatment
Due to the multi-factorial pathophysiology underlying functional constipation, which is often a combination of physical, behaviour and psychological factors, many hospitals are using multidisciplinary teams. Based on clinical experience, multidisciplinary behavioural treatment could be an important and valuable supplement to the standard medical treatment of children. However, randomised trials in children with functional constipation are lacking.

Prebiotics
Prebiotics are short-chain carbohydrates that alter the composition, or metabolism, of the gut microbiota in a beneficial manner. It is therefore expected that prebiotics will improve health in a way similar as probiotics, whilst at the same time being cheaper, and carrying less risk and being easier to incorporate into the diet than probiotics. To date, however there is only one randomised trial comparing a formula containing a high concentration of sn-2 palmitic acid, a mixture of prebiotic oligosaccharides and partially hydrolyzed whey protein with a standard formula in 38 constipated infants, aged 3-20 weeks. It found no statistical difference in defecation frequency, neither in improvement of stool consistency nor in painful defecation. Further studies are necessary to elucidate the role of prebiotics in the treatment of constipation.
Probiotics

Probiotics are currently gaining worldwide popularity for their presumed health-promoting effects. The term “probiotic” is a Greek word meaning “for life”. Probiotics are defined as live micro-organisms which when administered in adequate amounts confer a health benefit on the host. The exact working mechanisms of probiotics are not well understood. There are some hypotheses why probiotics might have therapeutic potential for the treatment of constipation. Firstly, a dysbiosis in the gut flora in constipated patients has been suggested which might improve after the ingestion of probiotics. However, it remains important to understand if dysbiosis is a secondary manifestation of constipation, or is it a factor contributing to constipation? Furthermore, probiotics can lower pH of the colon by producing lactic, acetic and other acids. A lower pH enhances colonic peristalsis and subsequently decreases colonic transit time. Interestingly, lactulose has a similar “probiotic” working mechanism. Lactulose is a synthetic sugar consisting of the monosaccharides fructose and galactose. In the colon, lactulose is broken down primarily to lactic acid, and to small amounts of formic and acetic acids, by mainly Lactobacilli, which results in an increase in osmotic pressure and slight acidification of the colonic contents. This in turn causes an increase in stool water content and softens the stool. To date, only a few of the potential health benefits attributed to probiotics, such as modifying the composition of colonic microflora and acting against enteric pathogens, have been confirmed in well-designed, well-conducted, randomised, controlled trials. A daily intake of $10^6$ to $10^9$ colony forming units is reportedly the minimum effective dose for therapeutic purposes. A dose-effect relationship has been suggested, but pharmacokinetic studies on probiotics are lacking and therefore needed. Furthermore, the influence of other aspects (food and other host factors like the composition of individual gut microbiota and previous use of antibiotics) on the efficacy of probiotics should be investigated. In recent years probiotics have been increasingly used for functional gastrointestinal disorders like constipation and functional abdominal pain. But to date, only three small randomised controlled trials have been performed in children in order to determine the efficacy of probiotics on constipation. One study showed an increase in defecation frequency and a decrease in abdominal pain compared to placebo using the probiotic Lactobacillus casei rhamnosus. However, another trial showed that Lactobacillus rhamnosus GG (LGG) was not effective as adjunctive treatment with lactulose. The third trial showed that infants receiving Lactobacillus reuteri (DSM 17938) had a significantly higher frequency of bowel movements than infants receiving a placebo. All three paediatric trials did not report any adverse events in the probiotic group. In contrast to the few paediatric studies, several studies have performed in adults. They suggest that adults with constipation might benefit from ingestion of B. lactis DN-173 010, L. casei Shirota, and E. coli Nissle 1917. All studies showed an increased defecation frequency and improved stool consistency. These findings, however, are not directly applicable to the paediatric population due to the fact that constipation in children differs considerably from that in constipated adults with regard to its prevalence, onset, aetiology, symptoms, treatment, and prognosis.
Therefore, more trials are necessary in children to unravel the efficacy of different probiotic strains and different dosages in childhood constipation. According to the available data, it is assumed that the risk of infection with lactobacilli or bifidobacteria is similar to risks with commensal strains.\textsuperscript{65,70} Vlieger et al. showed in a randomised trial that the use of a prebiotic-containing starter formula supplemented with \textit{L. paracasei ssp. paracasei} and \textit{B. animalis ssp. lactis} in early infancy (first 3 months of life) had no adverse effects on growth and infant behaviour.\textsuperscript{70} However, there is an ongoing concern that the use of probiotics may result in harmful events in at-risk populations like immunocompromized subjects or in patients with other life-threatening illnesses, who were admitted in the intensive care unit.\textsuperscript{66,71}

\textit{Complementary and alternative medicine}

In the paediatric population complementary and alternative medicine are often used, especially when facing a chronic illness for which treatment options are limited. The term “COMPLEMENTARY and alternative medicine” (CAM) refers to a spectrum of diagnostic and therapeutic modalities that complement mainstream medicine by contributing to a common whole by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine.\textsuperscript{72} CAM incorporates many different approaches and methodologies, ranging from traditional Chinese medicine, ayurvedic medicine to chiropractic, homeopathy, spiritual healing, and bodymind medicine. A review designed to assess the effect of Traditional Chinese Medicine (TCM) on the management of functional constipation in adults included randomised controlled trials and controlled clinical trials.\textsuperscript{73} Many different TCM modalities are available such as Chinese herbal medicine, herbs, herbal diet, acupuncture, moxibustion (a traditional Chinese medicine technique that involves the burning of mugwort, a small, spongy herb, to facilitate healing ), acupressure, massage, tuina (a form of Chinese manipulative therapy), auricular point therapy, qi gong (various Chinese systems of physical and mental training for health, martial arts, and self-enlightenment), yoga and t’ai chi (an internal Chinese martial art practiced for both its defense training and its health benefits).

The definition used for constipation, namely “TCM and/or conventional medicine criteria such as the Rome II criteria”, in this systematic review was rather vague. TCM interventions appear to be useful in managing constipation. Only 21 (eighteen were Chinese herbal medicine and three were acupuncture trials) of the 137 publications identified attained high quality scores. The authors concluded that significant positive results like the “total effective rate” and the “scores of the constipation” were found in 15 high-quality studies. Both definitions, total effective rate and scores of the constipation, were highly variable among the studies. There was heterogeneity in diagnostic procedures and interventions among the studies. Outcome indicators were also different. Hence, the results should be interpreted cautiously. Furthermore, it is not known if these results are applicable to the paediatric population with functional constipation. In chapter 4, we will discuss a systematic review concerning complementary treatments used for childhood constipation.
Future drug therapies
Advancements in the understanding of the gastrointestinal enteric nervous system and epithelial function have led to the development of new classes of drugs for treatment of chronic constipation. These include substances that bind to serotonin receptors or are chloride channel activators.

Tegaserod (5-hydroxytryptamine (5-HT) is a selective serotonin receptor agonist that acts at 5-HT4 receptors in the gut wall.\textsuperscript{74} Serotonin is an interesting therapeutic target because it plays an important role in modulating motility, visceral perception, and intraluminal secretion in the gastrointestinal tract.\textsuperscript{74} Liem et al. showed in a retrospective study that tegaserod increased the defecation frequency and decreased faecal incontinence episodes in 44 children using tegaserod for non-functional and functional gastro-intestinal diseases.\textsuperscript{75} Of these patients 42% fulfilled the criteria for functional constipation. Adverse events were observed in 32% of the children. Most of them were self-limiting diarrhea and abdominal pain. However, tegaserod has been withdrawn from the market in 2007 due to possible cardiovascular adverse events. A retrospective analysis of data from clinical studies showed a significant difference in cardiovascular ischemic events in adult patients taking tegaserod compared with adults taking placebo (incidence 0.11% in tegaserod group versus 0.01% in placebo group).\textsuperscript{76}

Prucalopride is a 5-HT4 receptor agonist which enhances colonic motility.\textsuperscript{77,78} Four randomised, placebo controlled trial in 2274 adults with chronic constipation were performed in which they received in three trials 2 mg or 4 mg prucalopride or placebo, once daily, for 12 weeks.\textsuperscript{79,80,81} One trial randomised patients to prucalopride (1, 2, or 4 mg once daily) or placebo for 4 weeks.\textsuperscript{82} Significantly more patients taking prucalopride 2 or 4 mg than placebo had three or more SBMs per week. Also the proportion of patients with an increase of ≥ 1 SBMs per week was significantly higher in patients taking prucalopride compared to placebo. Patients’ satisfaction with their bowel function and treatment and QOL were also significantly higher in the prucalopride group compared to placebo. The most frequent treatment-related adverse events were headache, abdominal pain and diarrhea. There were no significant cardiovascular effects of treatment. In children, no clinical trials have been performed yet.

Lubiprostone is an oral bicyclic fatty acid that activates selectively chloride channels in the apical membrane of the gastrointestinal epithelium, resulting in luminal chloride secretion and consequently resulting in water movement.\textsuperscript{83} Two randomised placebo controlled trial investigated the efficacy and safety of lubiprostone in 479 adults with chronic constipation for 4 weeks.\textsuperscript{84,85} In both trials, the lubiprostone-treated patients reported higher spontaneous bowel movements (SBMs) at all weeks compared with the placebo-treated patients. Also among lubiprostone-treated patients, significantly higher percentages were
seen having SBMs within 24 h of the first dose compared with placebo. Stool consistency, straining, and constipation severity, as well as patient-reported assessments of treatment effectiveness, were significantly improved with lubiprostone compared with placebo at all weeks. Gastrointestinal-related disorders were the most common adverse events in both treatment groups. In children, no clinical trials have been performed yet.

Linaclotide is a minimally absorbed peptide agonist of the guanylate cyclase-C receptor that stimulates intestinal fluid secretion and transit and reduces pain in animal models. Recently, a placebo-controlled study has been performed in 310 adults with chronic constipation.\(^86\) Patients were randomly assigned to groups given 75, 150, 300, or 600 μg oral linaclotide or placebo once daily for 4 weeks. All doses of linaclotide improved the weekly rate of SBM compared with placebo; the increases in overall weekly number of SBMs from baseline were 2.6, 3.3, 3.6, and 4.3 for linaclotide doses of 75, 150, 300, and 600 μg, respectively, compared with 1.5 for placebo (\(P \leq 0.05\) for each pair-wise comparison of a linaclotide dose to placebo). Linaclotide significantly improved the weekly rate of SBMs, stool consistency, straining, abdominal discomfort, bloating, global assessments, and quality of life. The most common adverse event was diarrhea. In children, no clinical trials have been performed yet.

**Surgery**

Although most children will respond to some therapeutic measure, a small minority will continue to suffer from constipation which may dramatically affect their daily life. In these selected cases, intensive surgical procedures may be recommended like appendicostomy, cecostomy, colostomy, segmental or total colonic resection.\(^87-89\)

**Appendicocecostomy for antegrade continence enemas (ACE)**

In childhood and adolescence, faecal incontinence represents a psychologically devastating problem. Physical and emotional distress associated with daily rectal enemas is minimized by the introduction of a cecostomy tube for colonic cleansing with antegrade colonic enemas. Appendicocecostomy for antegrade continence enemas (ACE), described by Malone et al. has expanded the treatment options for constipation.\(^90\) ACE successfully treat both faecal incontinence and chronic constipation in children, with particular success in faecal incontinence. The commonest reasons for using ACE are spina bifida, anorectal anomalies, and Hirschsprung’s disease, with increasing use in chronic idiopathic constipation. It has been suggested that colonic dysmotility, as seen in slow transit constipation (STC) is less likely to respond to ACE. However, King et al. showed that ACEs were successful in 34 (81%) of 42 children with STC, contradicting views that ACE are less effective in patients with colonic dysmotility.\(^91\) In King’s study, all children had a mean symptom duration of 7.5 years before appendicostomy. Both quality of life and continence score significantly improved with ACE. Faecal incontinence episodes decreased in 32 of 42 children (11/32 completely continent). Complications included granulation tissue (33/42), stomal infection
(18/42), and washout leakage (16/42). A total of 15 out of 42 children ceased using the appendicostomy (7/15 symptoms resolved). In addition, Wong et al. showed that “button” cecostomies in 69 paediatric patients with faecal incontinence secondary to spina bifida (n = 43), anorectal malformations (n = 17), Hirschsprung’s disease (n = 3), trauma (n = 1), and also intractable functional constipation (n = 5) lead to a significant higher patient/parents satisfaction and also in a significant improvement of quality of life. Complications included tube dislodgement (n = 9), development of granulation tissue (n = 11), decubitus ulcer (n = 5), and infection (n = 3).

**Anal dilation and internal anal sphincter partial myectomy**

In children, anal dilation or internal anal sphincter partial myectomy under anesthesia have been done for constipation because of the perception that there is a degree of hypertrophy and increased activity of the internal anal sphincter as part of the pathophysiology of the idiopathic megarectum. It is believed that these procedures reduce the anal sphincter tone and allow pain-free defecation.

**Anal dilation**

There is only one randomised trial concerning anal dilatation in children with constipation. This RCT, which compared anal dilatation versus no dilatation, has been performed in 68 children who failed to respond to medical treatment for functional constipation. A drawback of this study was that no information was provided with respect to individual outcomes (e.g., increased defecation or reduced faecal incontinence). Instead the investigator used their own scoring system to assess overall symptom severity. This system combined scores for difficulty and pain on passing stool, delay in defecation, faecal incontinence problem, intensity of laxative treatment and general health (parent rated: 0 = worst, 65 = best). The RCT found no significant difference between groups at 12 months in change in symptom severity scores. Disappointingly, no information was given on adverse effects as could be expected of this rather invasive therapy. To date, there is no evidence for the use of anal dilatation in children with constipation. It is an invasive treatment and should therefore not be used.

**Myectomy of internal anal sphincter (IAS)**

Sphincterotomy and sphincter myectomy involves division or excision of the upper half of IAS, respectively. These procedures have only been performed in children to treat idiopathic constipation where anal dilation has been unsuccessful. However, RCTs are lacking. In a retrospective review of 61 children, forceful anal dilation and anorectal myectomy were reported for the treatment of intractable constipation. This study showed that 14 of 16 (87.5%) children who underwent anorectal myectomy benefited from the procedure with no reports of faecal incontinence when followed up for at least 6 months postoperatively. Of 33 children who had anal dilation the symptoms improved in 22 (67%) and 5 patients required further myectomy with good results. The improvement of symptoms were attributed to
shortening and widening of the functional anal canal after anal stretch and myectomy which allowed the faecal bolus to reach the sensory sampling area and be expelled easily. However, the detrimental effects of any procedure that weakens the sphincters may not become apparent for many years. Therefore every effort should be made to avoid these procedures.

Colorectal resection
Colorectal resections should be reserved for the most extreme cases who have failed to respond to the care provided by an experienced interdisciplinary team involved in the management of idiopathic constipation in childhood. Surgery, rarely required, takes the form of colonic resection but only for patients with a demonstrated ability to have voluntary bowel movements, although with enormous laxative requirements. Removal of the rectosigmoid in this situation can reduce or eliminate the need for laxatives. Most reported complication is a pelvic hematoma.96

Neuromodulation
- Transcutaneous electrical stimulation
Interferential therapy (IFT) is a form of transcutaneous electrical stimulation where 4 surface electrodes are applied (2 abdominal, just below the costal margin; 2 paraspinal, over muscles between T9 and L2) that produce 2 sinusoidal currents that cross within the body. This treatment is non-invasive and painless. Its proposed mechanism of action is via neuromodulation. A RCT showed that transcutaneous electrical stimulation (TES) was effective in improving colonic activity, faecal incontinence, and quality of life in children with slow transit constipation (STC) and who had also chronic constipation according the Rome II criteria.97,98 In this RCT, 33 children were randomised to receive either 12 real or placebo IFT sessions for a 4-week period. After a 2-month break, they all received 12 real IFT sessions-again for a 4-week period. Colonic transit, using nuclear transit studies was significantly faster in children given real treatment when compared to their pre-treatment NTS at 24 (mean CG, 2.39 vs 3.04; P ≤ 0.0001), 30 (mean CG, 2.79 vs 3.47; P = 0.0039), and 48 (mean GC, 3.34 vs 4.32; P = 0.0001) hours. In contrast, no significant change in colonic transit was found in those children receiving placebo. Furthermore, the child-perceived quality of life was significantly improved after real IFT compared with baseline but not after placebo IFT.97,98 No adverse events were reported. A pilot study investigated the efficacy and safety of transcutaneous electrical stimulation (TES) (3 sessions/wk) over the abdomen at home.99 In 11 patients with slow-transit constipation a portable machine was applied 1 hour daily at home. All children completed more than 1 month of treatment after baseline recording. Defecation increased in 9 of 11 children, and faecal incontinence decreased in 4 of 11 children. There was a significant increase in total episodes of defecation per week (mean ± SD, 2.5 ± 2.1 vs 6.7 ± 4.4; P = 0.008) and a nonsignificant decrease in faecal incontinence (3.8 ± 1.6 vs 1.1 ± 0.5 episodes/wk, P = 0.1). No adverse events occurred.
- Sacral nerve stimulation

Another emerging treatment option is sacral nerve stimulation (SNS). Although similar to IFT, in that its proposed mechanism of action is via neuromodulation, SNS requires the implantation of a pulse generator and electrodes. Briefly, percutaneous transforaminal access to the third sacral spinal nerve (S3) is achieved, and once an appropriate neurological response is elicited a quadripolar tined lead is implanted. A tunneled subcutaneous extender connects the lead to an external neurostimulator device for programming to begin with the stimulation. If there is a good response, a second procedure will be performed in which the implanted pulse generator is placed in the upper lateral gluteal region. Sacral nerve stimulation has been used with a reported success rate varying between 47 and 90% in adults with either constipation or faecal incontinence. Although these results are promising, SNS electrode placement requires general anesthesia, and as yet, its use has not been investigated in children.

Follow-up

Despite an often long-lasting medical and behavioural therapy only 50% of all children followed for 6 to 12 months are found to recover and were successfully taken off laxatives. Another study even showed that 25% of patients who developed constipation before the age of 5 years continued to have severe complaints of constipation, infrequent painful defecation and faecal incontinence, beyond puberty. Furthermore, in 50% of the patients using laxative therapy, adverse side-effects were registered such as: abdominal pain, bloating, flatulence, diarrhea, nausea and bad taste. No data exist concerning possible long-term adverse effects of the different existing laxatives such as electrolyte disturbances, mucosal damage and habituation. Based on these data, developing new treatment strategies are of great importance for this specific chronic disorder.

Implementation

Without active implementation, an evidence-based guideline will not result in changing behaviour and consequently not in improvement of quality of care. Therefore, active implementation is of great importance. Several systematic reviews have shown that there is no ‘magic bullet’ for implementation success. Implementation strategies can be categorized into three groups showing consistent, variable, or little or no effectiveness. Those interventions that consistently have shown effectiveness include interactive educational meetings, educational outreach visits, reminders, and multifaceted interventions. Interventions with variable effectiveness include audit and feedback, use of local opinion leaders, local consensus processes, and patient-mediated interventions. Interventions with little or no effect are didactic educational meetings and educational materials. To date, there is little experience with the implementation of paediatric evidence-based guidelines and the specific strategies featuring success are not well known. However, active implementation is
time consuming and costly. We have received a grant for developing a guideline concerning constipation but not yet for active implementation of this guideline. For this reason, we will discuss in this thesis the implementation of another paediatric guideline and will give recommendations for future implementation of guidelines. In 2000, a Dutch multidisciplinary national committee developed an evidence-based guideline on the first-choice fluid for resuscitation of hypovolemic shock due to dehydration, sepsis, trauma, and hemorrhage in critically ill neonates and children up to 18 years. In 2004, it was updated. The guideline recommends normal saline as the first-choice treatment for all forms of hypovolemic shock. In 2004, after receiving a grant, we started an implementation project with two objectives. Our first goal was to successfully implement the guideline’s recommendations. Our second aim was to learn some important lessons for the implementation of future paediatric guidelines like constipation.
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32


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