Evidence-based guideline development in paediatric gastroenterology

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Chapter 10

Summary & Future perspectives
Summary

Evidence-based guidelines play an important role in improving quality of care since guidelines can facilitate translation of new research findings into clinical practice. They are therefore seen as powerful tools to achieve effective care, reduce variability in daily practice, and may reduce costs. Although functional constipation is one of the most prevalent, frustrating and long-lasting paediatric functional gastrointestinal disorders, diagnostics and treatment of functional constipation are rather experience-based than evidence-based. An explanation could be that constipation is often seen as a minor problem which will either spontaneously resolve or respond to advice on diet. This attitude ignores the impact on wellbeing of the child and family life. In children, constipation and faecal incontinence can lead to social withdrawal, low self-esteem and even depression. Furthermore, lack of understanding about the condition, delayed diagnosis, and suboptimal treatment and support contribute to ongoing symptoms and multiple medical consultations. Therefore, to improve quality of care of children suffering from constipation, an evidence-based guideline is required. The aim of this thesis is to give a systematic overview of both diagnostic and therapeutic treatment options in paediatric constipation including the relatively new treatment option with "probiotics". All reviews are developed during the 1.5 year lasting process of the Dutch guideline development of the guideline “Constipation in children from 0-18 years".

Unfortunately, it is well known that many guidelines are not used in daily practice unless they are actively implemented. Therefore, this thesis also focuses on the methodology used for implementation of a national evidence-based guideline and the success factors according to specific indicators. General recommendations for future guideline implementation projects are given.

The pathophysiology underlying functional constipation is not well understood. In order to elucidate possible underlying pathophysiological mechanisms for functional constipation in childhood, we have evaluated in chapter 1 rectal suction biopsies in patients with functional constipation, with Hirschsprung’s disease (HD) and controls. This study showed a thicker rectal muscularis mucosae in children with functional constipation compared to children with HD and controls. No differences were found between characteristics of the muscularis mucosae of controls and children with HD. We did find a correlation between duration of functional constipation symptoms and thickness of the muscularis mucosae. This finding could suggest that the rectal muscularis mucosae hypertrophy could be secondary to constipation. As a result of long-lasting rectal faecal impaction, this muscle layer remains presumably contracted with consequential hypertrophy. In chapter 2 a systematic literature review has been carried out to evaluate the additional diagnostic value of an abdominal X-ray, colonic transit time (CTT) and abdominal ultrasonography in the diagnosis of functional constipation in children. It found sufficient evidence to recommend that an abdominal X-ray...
is a redundant investigation in the diagnosis functional constipation in children. Furthermore, this systematic review found no evidence to recommend colonic transit time (CTT) measurement and abdominal ultrasonography in the diagnosis of functional constipation in children. In \textit{chapter 3}, a systematic review has been performed investigating the effect of laxatives and dietary measures on functional constipation in children. Due to a lack of placebo-controlled trials we found insufficient evidence for an effect of any one laxative or dietary treatment of childhood constipation. Although, PEG achieved more treatment success compared to all other laxatives, the results on defecation frequency were conflicting. Based on the results of this review a recommendation could not be given to support one laxative over the other for childhood constipation. \textit{Chapter 4} described a systematic review concerning non-pharmacological treatments including fibre, fluid, physical movement, pre-and probiotics, behavioural therapy, multidisciplinary treatment and alternative medicines (including acupuncture, homeopathy, mind-body therapy, musculoskeletal manipulations like osteopathic and chiropractic manipulations and spiritual therapies like yoga) in childhood constipation. In this review we found some evidence that fibre may be more effective than placebo in improving both the frequency and the consistency of stools and in abdominal pain reduction. Compared to normal fluid intake, no evidence was found that water intake increase or hyperosmolar fluid is more effective in increasing stool frequency or in decreasing difficulty in passing stools. Furthermore no evidence was found to recommend the use of pre-or probiotics in childhood constipation. Behavioural therapy with laxatives is not more effective than conventional treatment in the treatment of childhood constipation. We found no randomised studies concerning physical movement, multidisciplinary treatment and alternative medicines. This study clearly shows that there is a lack of well-designed controlled trials of high quality concerning non-pharmacological treatments including alternative treatments in children with functional constipation. In \textit{Chapter 5}, we evaluated the effectiveness of behavioural treatments (such as biofeedback), anorectal manometry, surgical disimpaction and effectiveness and safety of anal dilatation. It found that behavioural treatments, such as biofeedback, diaries, toilet training or anorectal manometry, or anal dilatation, have no benefit in the treatment of these children, but the evidence is limited. We found no evidence assessing the effectiveness of surgical disimpaction in the treatment of faecal impaction. In \textit{chapter 6} we have performed a systematic review concerning the effect of placebo in children with functional gastrointestinal disease including irritable bowel syndrome (IBS) and functional constipation. It showed that in children with IBS, Lactobacillus GG was more effective than placebo with respect to reduction in pain frequency and decrease in perceived abdominal distension. Compared to placebo, peppermint oil seemed to be more effective in improving symptoms related to IBS. Placebo and amitriptyline were equally effective in response to treatment (child’s assessment of pain relief and sense of improvement) in children with IBS. In a small randomised trial, however, amitriptyline was more effective compared to placebo in improvement of the overall quality of life score in children with IBS. In children with functional constipation, fibre may be more effective
than placebo in improving bowel movements, in improvement stool consistency and in the reduction of abdominal pain. Macrogol was more effective than placebo in increasing number of defecations, reduction of hard stools and in reduction of pain and straining during defecation. Based on this review, we concluded that there is a lack of placebo-controlled trials of high quality in children with IBS and functional constipation. More well-designed, large randomised controlled trials are necessary to determine and understand the role of placebo in children with these functional gastrointestinal disorders. In chapter 7, we have reported the results of a randomised, double-blind, controlled multicentre trial concerning the effect of the probiotic strain *Bifidobacterium lactis* strain DN-173 010 in constipated children. It demonstrated that in children with functional constipation with a defecation frequency of <3 times/week and one or more of the other ROME III criteria, the fermented dairy product containing *Bifidobacterium lactis* strain DN-173 010 did increase stool frequency, but this increase was comparable with the one seen in the control group. Across all other clinical outcomes, the differences between both groups were small and not statistically significant with the exception of “flatulence” in favour of probiotics. These clinical outcomes were rate of success (≥ 3 more bowel movements per week and < than 1 faecal incontinence episode in 2 weeks over the last 2 weeks of product consumption), rate of responders (with a responder defined as a subject reporting a stool frequency ≥ 3 episodes during the last week of product consumption), and over 3 weeks were calculated: stool frequency, stool consistency, frequency of episodes of faecal incontinence, frequency of pain during defecation, frequency of digestive symptoms (abdominal pain and flatulence), and frequency of intake of bisacodyl.

This study shows insufficient evidence to recommend fermented dairy products containing *Bifidobacterium lactis* strain DN-173 010 in children with constipation. There were no serious adverse events related to probiotics. Chapter 8 described an uncontrolled pilot study in which the probiotic strain *Bifidobacterium breve* was investigated in constipated children with a defecation frequency of <3 times/week and one or more of the other ROME III criteria. It showed that *Bifidobacterium breve* was safe and effective in increasing stool frequency in children with functional constipation. Furthermore, it has a positive effect with respect to stool consistency, decreasing the frequency of episodes of faecal incontinence and in diminishing abdominal pain. A large randomised placebo-controlled trial is now necessary to confirm these encouraging results. Chapter 9 described the national implementation of an evidence-based paediatric guideline on first-choice fluid for resuscitation in hypovolemia. We have learnt from this process, that stakeholders involved in the developmental process are of great importance in disseminating recommendations before active implementation. Therefore, to successfully implement guidelines and reduce costs of active implementation, any guideline development should consider implementation right from the beginning. Implementation strategies should target identified barriers and will therefore always be guideline specific.
Future perspectives

An evidence-based guideline can facilitate translation of new research findings into clinical practice and is therefore a powerful tool to achieve effective care, reduce variability in daily practice, and to reduce costs. A balanced central working group and guideline group with both clinical and methodological expertise is necessary to promote broad consensus and prevent bias from conflicts of interests. Formation of such a multidisciplinary guideline development committee should consist of all stakeholders’ representatives and should also include representatives of patient groups. During 2008 and 2009, we have developed a Dutch guideline for paediatric constipation. Guideline development should always start with assessing the quality of existing international guidelines by using the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument. The AGREE instrument consists of six domains: 1) Scope and purpose, 2) Stakeholder involvement, 3) Rigor of development, 4) Clarity of presentation, 5) Applicability and 6) Editorial independence. Since the two existing guidelines on childhood constipation did not address sufficiently the issues covered by the AGREE instrument, we went on to develop a new guideline for childhood constipation. Guideline development is costly, time-consuming and the scientific writing often difficult. In practice, many guideline development committee members are not trained in developing a guideline and do not have any experience in appraising the available literature for quality and applicability. Besides the lack of skills, guideline members do have their own job and have to combine their daily work with developing a guideline. For these reasons and experiences in the past with other guidelines, we have incorporated a novel strategy. Our central working group consisted of four persons; two paediatric gastroenterologists, a general paediatrician-epidemiologist and a general practitioner-epidemiologist. They were responsible for all literature searches, for evaluating and categorizing all scientific strength of the published research and writing the guideline. Furthermore, they were responsible for the communication with the other guideline members during the whole process. All guideline members actively participated in formulating questions during preparation of the guideline, during formulating recommendations and developing indicators. This new strategy resulted in a guideline of good quality which was completed within the expected time-frame.

We have learned from our implementation study that stakeholders involved in the developmental process are of great importance in disseminating recommendations already before active implementation as well. Therefore, all guideline group members should be made responsible for dissemination and active implementation of the guideline on their departments and in regional hospitals. To successfully implement guidelines and reduce costs of active implementation, any guideline development should consider implementation right from the beginning. Consequently, while receiving a grant for developing a guideline, a grant for active implementation should also be included.
During the development of the Dutch paediatric constipation guideline, the National Institute for Health and Clinical Excellence (NICE) developed an English paediatric constipation guideline. Their guideline however, used other research questions as well. Although guideline recommendations are evidence-based, these recommendations are also based on other considerations which are local (for example the organization of the health care system) and different among cultures. Consequently the same scientific evidence might formulate different recommendations for local practice. However, for some parts of the development of the guideline, such as literature reviews, collaboration between the developers of the different countries could lead to saving time and reduction in costs. Therefore, it is of major importance to become as a national paediatric organization, a member of the International Guidelines Network (www.g-i-n.net) to improve quality of care by promoting systematic development of guidelines and their application into practice, by supporting international collaboration in guideline development.

Based on the findings described in the systematic reviews of this thesis, recommendations will be given to perform studies investigating epidemiology, symptomatology, new diagnostic and therapeutic strategies and long-term follow-up in childhood constipation. It is of great importance that researchers use the same methods according to standardized protocols as suggested by international experts in the field of both adult and paediatric functional gastrointestinal diseases. In this way, the quality of care will be improved by an earlier and better recognition of constipation and by improved diagnostic and therapeutic strategies. To achieve this goal, homogeneous patient populations and outcome measures should be used, including the standard definition for functional constipation as described in the Rome III criteria. Well designed larger studies are needed with greater methodological rigor not only performed in tertiary centres but more importantly executed in primary and secondary care. Studies involving this chronic condition, should also consider long-term outcomes.

A high placebo response between 25-80% has been described in recent efficacy studies in both children and adults with functional gastrointestinal disorders. Despite these high placebo response rates, there is a paucity of large patient sample, placebo-controlled studies reporting the efficacy of nutritional or laxative regimens in the treatment of paediatric patients with constipation or IBS. The lack of these studies is because many parents are unwilling to consent their children being involved in placebo-controlled trials. The key reason why parents refuse participation in such trial is the possibility of receiving placebo instead of the active drug. Other reasons might be the duration of the study and its associated pretreatment period in the face of a strong desire for immediate symptom relief. The association of placebo effects with RCTs’, however, has caused confusion because the response in the placebo group is not necessarily a genuine psychosocial response to the simulation of treatment. In fact, the reported response to placebo in RCTs might reflect the natural course of disease, fluctuations in symptoms, regression to the mean, response bias
with respect to patient reporting of subjective symptoms, or other concurrent treatments. Future placebo controlled studies in children with functional gastrointestinal disorders should include a third arm receiving no treatment or being on a waiting-list to control for natural history and regression to the mean, making it difficult to discern a genuine placebo effect.

To evaluate the efficacy and safety of new compounds in patients with functional gastrointestinal disorders, every clinical trial should be performed according to the principles of good clinical practice to ensure that results are relevant for daily clinical practice. Patient inclusion must be based on strict criteria as set by the Rome III committee to guarantee a homogenous patient population. This allows comparability of patients among centres and to make comparisons with other populations. Confounders such as comorbidity that could affect the response to therapy should also be assessed. The use of the maximum blinding possible will ensure the validity of the primary outcome measure and is therefore recommended. Furthermore, the method of randomisation should be clear. As discussed previously, a placebo control group is essential. The parallel-group design is the optimal one for evaluation of efficacy for most treatments. Treatment duration should be 4-12 weeks because it reflects the periodicity of symptoms and expected treatment mechanism. In case of chronic drug use, trials with a minimum of 6 months should be performed to assess long-term efficacy and safety. One or two primary outcome measures should be defined in advance with at least the defecation frequency included. Patients should be classified as responder or non-responder based on clinically meaningful change in symptoms. Furthermore, patient-reported outcome assessment should be included which should be validated before their use. For this assessment, patients should be instructed clearly about the use of a diary. All adverse events, both expected and unexpected, should be reported. Secondary outcomes should be selected based on the study question and should be explained by describing them in the analysis plan before start of the trial. QOL assessments are also very important secondary outcomes. Including both a baseline generic and a pre post disease-specific QOL-instrument is therefore necessary. Furthermore, including cost-effectiveness analysis is preferable. While reporting a trial, researchers should adhere to the CONSORT statement (www.consort-statement.org).

Recent well-designed large placebo-controlled studies in adults with either constipation or IBS-C have shown promising results of new compounds such as lubiprostone, prucalopride and linoclitate. Therefore, international collaboration is necessary to confirm the efficacy of these compounds in children of different ages with constipation. These multicentre studies are necessary in order to include large amounts of patients in a shorter time. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) reviewed and updated the legislation on how medicines for children were regulated. These instances aim to stimulate the development of new medicines for children, ensure that medicines used
Probiotics, as an adjunct to enteral nutrition, have raised high expectations and are currently gaining worldwide popularity for their presumed health-promoting effects. In constipation, a dysbiosis in the gut microbiota has been suggested as possible mechanism to develop constipation, which might improve after the ingestion of probiotics. Interestingly, there is a lack of knowledge about the composition of the normal gut flora of healthy children. Therefore, future studies should focus on the normal gut microbiota in healthy children and compare these data with the bacterial composition of the gut in children with functional gastrointestinal disorders such as irritable bowel syndrome and constipation. Subsequently, well designed large placebo-controlled trials should be performed in order to determine which probiotic strain will be of interest to investigate in a randomised controlled trial in children with functional gastrointestinal disorders.

In conclusion, based on the data described in this thesis, there is a lack of well-designed studies evaluating the role and place of diagnostic procedures in the work-up of childhood constipation. Moreover, well-designed studies, containing large patient samples including children of different age groups, evaluating the effect and short- and long-term side effects of food products and laxatives are not available in the current literature. In order to perform such trials, national and international collaboration is warranted. This will lead to better information to parents and improve the quality of care of these children.
Reference List


