

Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

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ABSTRACT

Background: Constipation is a pediatric problem commonly encountered by many health care workers in primary, secondary, and tertiary care. To assist medical care providers in the evaluation and management of children with functional constipation, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition were charged with the task of developing a uniform document of evidence-based guidelines.

Methods: Nine clinical questions addressing diagnostic, therapeutic, and prognostic topics were formulated. A systematic literature search was performed from inception to October 2011 using Embase, MEDLINE, the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, and PsychInfo databases. The approach of the Grading of Recommendations Assessment, Development and Evaluation was applied to evaluate outcomes. For therapeutic questions, quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation system. Grading the quality of evidence for the other questions was performed according to the classification system of the Oxford Centre for Evidence-Based Medicine. During 3 consensus meetings, all recommendations were discussed and finalized. The group members voted on each recommendation, using the nominal voting technique. Expert opinion was used where no randomized controlled trials were available to support the recommendation.

Results: This evidence-based guideline provides recommendations for the evaluation and treatment of children with functional constipation to standardize and improve their quality of care. In addition, 2 algorithms were developed, one for the infants <6 months of age and the other for older infants and children.

Conclusions: This document is intended to be used in daily practice and as a basis for further clinical research. Large well-designed clinical trials are necessary with regard to diagnostic evaluation and treatment.

Key Words: children, constipation, encopresis, enema, evidence-based, fecal incontinence, fecal soiling, functional constipation, guideline, infants, laxative

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INTRODUCTION

Functional constipation is a common problem in childhood, with an estimated prevalence of 3% worldwide (1). In 17% to 40% of children, constipation starts in the first year of life (2). Constipation is often associated with infrequent and/or painful defecation, fecal incontinence, and abdominal pain; causes significant distress to the child and family; and has a significant impact on health care cost (3). Although constipation may have several etiologies, in most children presenting with this symptom no underlying medical disease responsible for the symptom can be found. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition published a medical position paper in 1999, which was updated in 2006 (search until 2004) (4). Recommendations were based on an integration of a comprehensive and systematic review of the medical literature combined with expert opinion. In addition, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom developed a guideline in 2010, based on a best-evidence strategy, for children with constipation in primary and secondary care (5). To assist health care workers in the management of all of the children with constipation in primary, secondary, and tertiary care, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition elected to develop evidence-based guidelines as a joint effort. The present guideline provides recommendations for the diagnostic evaluation of children presenting with constipation and the treatment of children with functional constipation. It is intended to serve as a general guideline and should not be considered a substitute for clinical judgment or used as a protocol applicable to all patients. The guideline is also not aimed at the management of patients with underlying medical conditions causing constipation, but rather just for functional constipation.

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METHODS

Literature Search and Grading the Articles for Quality of Evidence

The project started in September 2011 by formulating 9 clinical questions (Table 1). Seven questions were chosen based on the Dutch guidelines for functional constipation (6). In addition, 2 new questions were added to the present guidelines: questions 5 and 8. After the questions were formulated, the guidelines committee

TABLE 1. Overview of the 9 clinical questions

Question 1: What is the definition of functional constipation?
Question 2: What are the alarm signs and symptoms that suggest the presence of an underlying disease causing the constipation?
Question 3: In the diagnosis of functional constipation in children, what is the diagnostic value of
3.1 Digital rectal examination?
3.2 Abdominal radiography?
3.3 CTT?
3.4 Transabdominal rectal ultrasonography?
Question 4: Which of the following diagnostic tests should be performed in children with constipation in order to diagnose an underlying disease?
4.1 Laboratory investigations to diagnose (cow's milk) allergy, celiac disease, hypothyroidism and hypercalcemia?
4.2 ARM or rectal suction biopsy to diagnose HD?
4.3 Use of barium enema to diagnose organic causes such as HD?
Question 5: Which of the following examinations should be performed in children with intractable constipation to evaluate pathophysiology and diagnose an underlying abnormality?
5.1 Colonic manometry
5.2 MRI of the spine
5.3 Colonic full-thickness biopsies
5.4 Colonic scintigraphy
Question 6: What is the additional effect of the following nonpharmacologic treatments in children with functional constipation?
6.1 Fiber
6.2 Fluid
6.3 Physical activity
6.4 Prebiotics
6.5 Probiotics
6.6 Behavioral therapy
6.7 Biofeedback
6.8 Multidisciplinary treatment
6.9 Alternative medicine
Question 7: What is the most effective and safest pharmacologic treatment in children with functional constipation?
7.1 Which pharmacologic treatment should be given for disimpaction?
7.2 Which pharmacologic treatment should be given for maintenance therapy?
7.3 How long should children be receiving medical therapy?
Question 8: What is the efficacy and safety of novel therapies for children with intractable constipation?
8.1 Lubiprostone, linaclotide, and prucalopride
8.2 Surgery (eg, ACE)
8.3 TNS
Question 9: What is the prognosis and what are prognostic factors in children with functional constipation?
9.1 What is the prognosis of functional constipation in children?
9.2 What are prognostic factors in children with functional constipation?

ACE = antegrade continence enema; ARM = anorectal manometry; CTT = colonic transit time; HD = Hirschsprung disease; MRI = magnetic resonance imaging; TNS = transcutaneous nerve stimulation.

was subdivided into subgroups that dealt with each question separately. Questions 1 and 2 were answered based on expert opinions and earlier published guidelines (5–9). Questions 3 to 9 were answered using the results of systematic literature searches.

Systematic literature searches were performed by a clinical librarian from inception to October 2011. The Embase, MEDLINE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, and PsychInfo databases were searched.

The inclusion criteria were as follows:

1. Study population consisting of children of ages 0 to 18 years in whom functional constipation was diagnosed, treated, or its course followed. The key words used to describe constipation were “constipation,” “obstipation,” “faecal/fecale incontinence,” “coprostitis,” “encopresis,” and “soiling.” Excluded were the studies concerning children with organic causes of constipation and children with exclusively functional non-retentive fecal incontinence.
2. A clear definition of functional constipation had to be provided by the authors.
3. To evaluate the value of tests in diagnosing functional constipation (question 3), we included systematic reviews and original studies related to the diagnostic accuracy of the specific tests. The reference standard for functional constipation had to be defined by the authors in terms of findings at history and physical examination.
4. In studies evaluating the effects of treatments or interventions (questions 6, 7, and 8), the following inclusion criterion was used: systematic reviews of randomized controlled trials (RCTs) and/or RCTs containing at least 10 individuals per arm.
5. In studies evaluating the outcome of functional constipation (questions 4, 5, and 9), the following inclusion criteria were used: systematic reviews of prospective or retrospective controlled studies and original studies with a follow-up of at least 8 weeks.

An additional strategy to identify studies involved searching the reference lists of review articles and included studies. No language restriction was applied. Furthermore, all of the guidelines members were asked to search the literature with respect to their assigned topics to possibly uncover further studies that may have been missed by the former search.

The approach of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used to identify outcomes (10). A draft version was circulated by M.T., and every workgroup member was allowed to add outcomes. Group members were asked to rate relative importance of the outcomes on a 9-point scale: limited (1–3), important but not critical (4–6), or critical (7–9) for decision making. The workgroup members were also asked to discuss personal experience. Based on the answers of the guidelines group members and patient preferences from a focus group, 8 outcome measures were selected: pain during defecation, defecation ≥ 3 times per week, fecal incontinence frequency, difficulty with defecation, worsening constipation, quality of life, possible harm from laxatives (cancer, tolerance, adverse effects), and abdominal pain.

The levels and quality of evidence were assessed using the classification system of the Oxford Centre for Evidence-Based Medicine (<http://www.cebm.net>) (diagnostic and prognostic questions) and the GRADE system (therapeutic questions) and are summarized in the online-only appendix (<http://links.lww.com/MPG/A295>). Grades of evidence for each statement are based on the grading of the literature. If no therapeutic studies were found, we decided to define the quality of evidence as “low.”

Using the GRADE system, the quality of evidence for therapeutic interventions (questions 5, 6, and 9) was graded as follows (10):

- High: Further research is unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Very low: Any estimate of effect is uncertain.

See the online-only appendix for the quality assessment of all included studies (<http://links.lww.com/MPG/A295>).

Consensus Meeting and Voting

Three consensus meetings were held to achieve consensus on and formulate all of the recommendations: September 2012, February 2013, and May 2013. Each subgroup presented the recommendations during the consensus meetings, wherein these were then discussed and modified according to the comments of the attendees. The consensus was formally achieved through nominal group technique, a structured quantitative method. The group anonymously voted on each recommendation. A 9-point scale was used (1 = strongly disagree to 9 = fully agree), and votes are reported by each recommendation (11). It was decided in advance

that consensus was reached, if >75% of the working group members voted 6, 7, 8, or 9. The consensus was reached for all of the questions.

A decision was made to present 2 algorithms (Figs. 1 and 2). In contrast to the earlier guidelines, one pertains to the infant from birth to 6 months (instead of 1 year) and the other to the older child (7,8). This decision was based on the fact that defecation problems in infants <6 months old have different diagnostic considerations compared with older children, given the possibility of congenital problems and the influence of the different feeding and developmental issues. Both algorithms relate to any child presenting with constipation of at least 2 weeks' duration and also include the evaluation and treatment options of the child with "intractable" constipation. The final draft of the guidelines was sent to all of the committee members for approval in May 2013.

Revision

This guideline should be revised every 3 to 5 years.

RESULTS

Question 1: What Is the Definition of Functional Constipation?

At present, the most widely accepted definitions for childhood functional constipation are the Rome III definitions (Table 2) (12,13). The Rome III definitions for functional constipation have been divided into 2 groups, based on the age of the patient. Infants

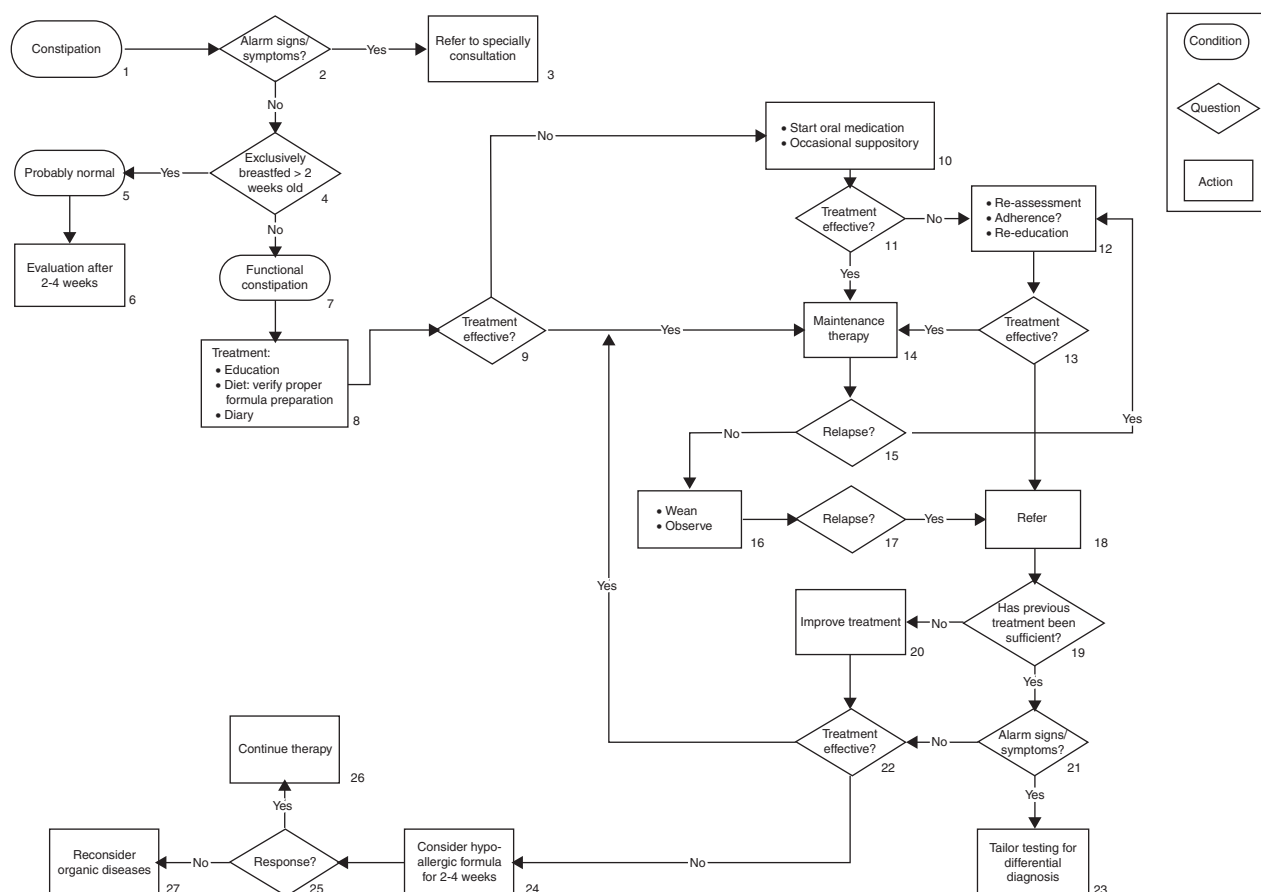


FIGURE 1. Algorithm for the evaluation and treatment of infants <6 months of age.

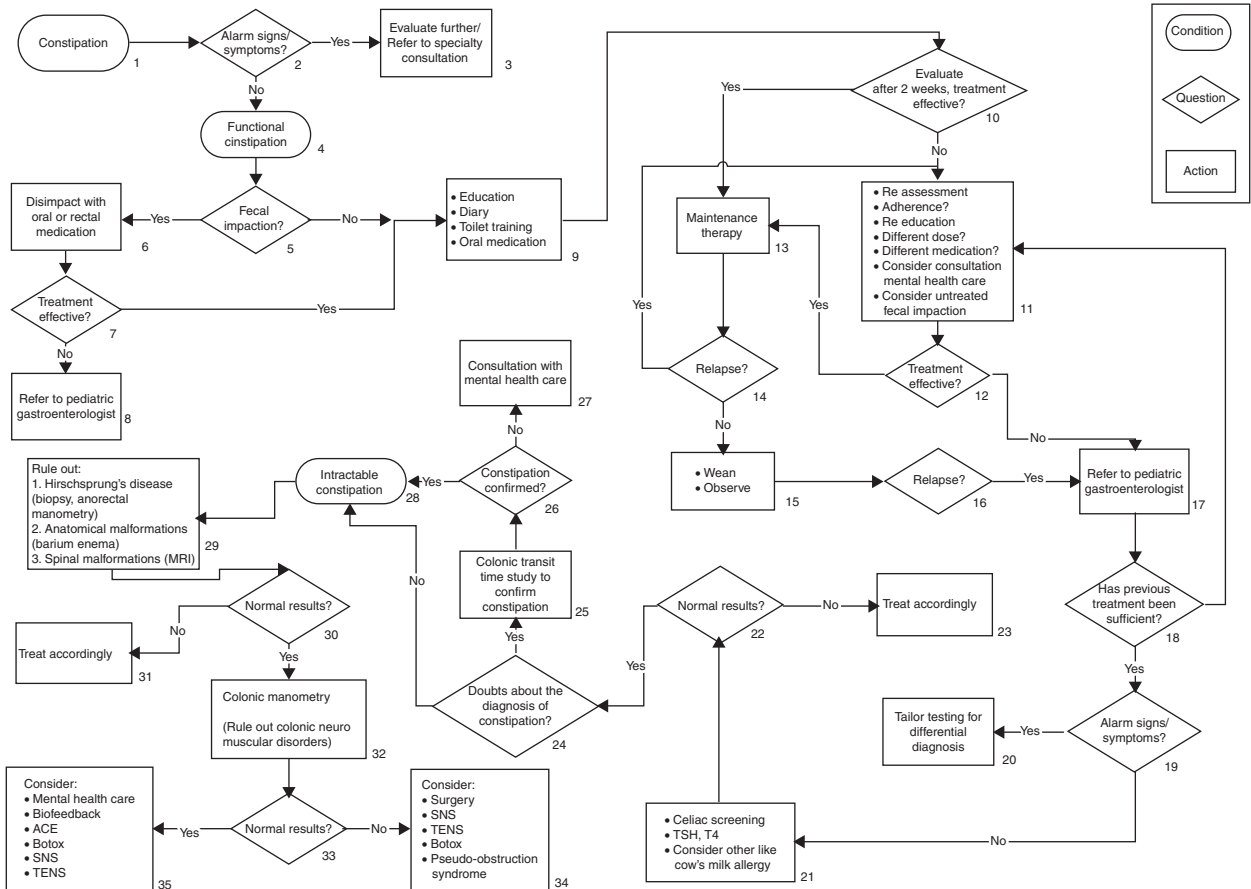


FIGURE 2. Algorithm for the evaluation and treatment of infants ≥ 6 months of age. ACE= antegrade continence enema; MRI = magnetic resonance imaging; SNS = sacral nerve stimulation; TENS = transcutaneous electric nerve stimulation; TSH = thyroid-stimulating hormone.

up to 4 years have to fulfill ≥ 2 of the criteria for at least 1 month, whereas those >4 years need to fulfill ≥ 2 of the criteria for at least 2 months, and to be included in the latter group children need to have a developmental age of at least 4 years and have insufficient criteria to

fulfill the diagnosis of irritable bowel syndrome. Abdominal pain is a frequent associated symptom, but its presence is not considered a criterion for functional constipation. The role that constipation plays in children with predominant abdominal pain is not clear.

TABLE 2. Rome III diagnostic criteria for functional constipation

In the absence of organic pathology, ≥ 2 of the following must occur

For a child with a developmental age <4 years*

1. ≤ 2 defecations per week
2. At least 1 episode of incontinence per week after the acquisition of toileting skills
3. History of excessive stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that may obstruct the toilet

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety, which may disappear immediately following passage of a large stool

For a child with a developmental age ≥ 4 years with insufficient criteria for irritable bowel syndrome[†]

1. ≤ 2 defecations in the toilet per week
2. At least 1 episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that may obstruct the toilet.

* Criteria fulfilled for at least 1 month. Adapted from Hyman et al (12).

† Criteria fulfilled at least once per week for at least 2 months before diagnosis. Adapted from Rasquin et al (13).

A subgroup of young children has defecation-related difficulties and has been categorized according to the Rome III criteria as having “infant dyschezia.” This condition has been defined as occurring in an infant >6 months, with at least 10 minutes of straining and crying before successful passage of soft stools, in the absence of other health problems. Parents describe infants with dyschezia as straining for many minutes, screaming, crying, and turning red or purple in the face with effort. The symptoms persist for 10 to 20 minutes, until soft or liquid stools are passed. Stools are usually evacuated daily. The symptoms begin in the first months of life and resolve spontaneously after a few weeks. In the absence of any scientific literature evaluating this condition, infant dyschezia is not discussed in this document.

Not all of the children with defecation problems fulfill the Rome criteria, and other definitions have been proposed that are less stringent and have only included “difficulty with defecation for at least 2 weeks, which causes significant distress to the patient” (7). Although those definitions are more inclusive, they probably encompass a more heterogeneous group of patients. Several studies attempt to validate the Rome III criteria for functional constipation by comparing these criteria to other definitions. Boccia et al (14) compared the Paris Consensus on Childhood Constipation Terminology criteria (which are essentially the same as the Rome III criteria) with the Rome II criteria in 128 consecutive children presenting with disorders of defecation and found that the Paris Consensus criteria showed greater applicability than the Rome II criteria. Devanarayana et al (15) conducted a study in Sri Lanka comparing the Rome III and Rome II criteria for several functional gastrointestinal disorders and found that the Rome III criteria identified significantly more children with functional constipation. Finally, Burgers et al (16) investigated 336 children with defecation disorders and found that of the 6 Rome III criteria, 39% children had a defecation frequency ≤ 2 /week, 75% had fecal incontinence, 75% displayed retentive posturing, 60% had pain during defecation, 49% passed large-diameter stools, and 49% had a palpable rectal fecal mass. According to the Rome III criteria, 87% had functional constipation compared with only 34% fulfilling criteria for different disorders of defecation based on the Rome II definitions.

The present document includes evidence related to patients diagnosed as having constipation using the established Rome III criteria or equivalent definitions at the time of the publication. Constipation is also a prominent symptom in children who have other underlying medical conditions such as prematurity, developmental delay, or other organic diseases, but the present guideline is not intended for those patients.

Given some evidence showing early treatment favorably affects outcome, we decided to use as an entry point in the algorithms children who fulfill the Rome III criteria for constipation, except for the duration (Fig. 1, boxes 1 and 7; Fig. 2, boxes 1 and 4). Based on consensus, the group agreed that the 2-month interval listed in the Rome III criteria for older children may unduly delay treatment in some children with constipation.

Other Definitions Used in This Guideline

Intractable Constipation: Constipation not responding to optimal conventional treatment for at least 3 months.

Fecal Impaction: A hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination or excessive stool in the distal colon on abdominal radiography.

- (1) Based on expert opinion, we recommend the Rome III criteria for the definition of functional constipation for all age groups.

Voting: 9, 9, 9, 9, 9, 9, 9

- (2) Based on expert opinion, the diagnosis of functional constipation is based on history and physical examination.

Voting: 9, 9, 9, 9, 9, 9, 9

Question 2: What Are the Alarm Signs and Symptoms That Suggest the Presence of an Underlying Disease Causing the Constipation?

Although diagnosis of constipation is based on the history and physical examination, subjective symptom description is unreliable in infants and many children <8 years of age, and some purported symptoms of constipation in infants and children are nonspecific. The major role of history and physical examination in the evaluation of constipation is to exclude other disorders that present with difficulties with defecation and to identify complications (Figs. 1 and 2, boxes 2 and 3). The information that should be actively sought includes age of onset of symptoms, success or failure of toilet training, frequency and consistency of stools (preferably expressed according to existing stool scales such as the Bristol scale (17) or the Amsterdam infant stool scale (18) or the Lane scale, which is the modified Bristol Stool Form Scale for children (19,20)), pain and/or bleeding when passing stools, coexistence of abdominal pain or fecal incontinence (if present, whether it is also nocturnal), withholding behavior, dietary history, changes in appetite, nausea and/or vomiting, and weight loss. The age of the child when symptoms began is one of the easiest and most important pieces of information to obtain in the evaluation of the problem. Onset of symptoms in infants <1 month old raises the suspicion of the presence of an organic condition such as Hirschsprung disease (HD) (21). The timing of passage of the first meconium is especially relevant to the risk of having HD; delayed passage of meconium by 48 hours in a term neonate suggests the need for definitive testing to rule out the diagnosis. Although 99% of healthy term neonates pass their first meconium before 48 hours of life (22), 50% of children with HD also pass meconium within 48 hours of birth (23). Thus, the failure of passage of meconium within the first 48 hours of life, although suggestive of HD, does not establish the diagnosis.

The information should also be obtained regarding previous and present treatment. Ideally, based on expert opinion, a 3-day diary should be used to better evaluate dietary and fluid intake. Medication history should be collected, including the use of oral laxatives, enemas, suppositories, herbal treatments, behavioral treatment, and other medications.

The general development and psychosocial history, such as disruption of child or family life and activities, interaction with peers, and temperament, is also relevant. Family history should be carefully taken, searching for gastrointestinal diseases (HD, food allergies, inflammatory bowel disease, celiac disease, urinary bladder disease) and for abnormalities of organs such as the thyroid, parathyroid, kidneys, or systemic diseases such as cystic fibrosis. Physical examination should specifically focus on the growth parameters, abdominal examination (muscle tone, distension, fecal mass), inspection of the perianal region (anal position, stool present around the anus or on the undergarments, erythema, skin tags, anal fissures), and examination of the lumbosacral region (dimple, tuft of hair, gluteal cleft deviation, sacral agenesis, flat buttocks). Digital rectal examination evaluates the presence of an anal stenosis or of a fecal mass. The evacuation of explosive stools after withdrawal of

the examining finger is suggestive of HD (a result of its hypertonic sphincter). Anal and cremasteric reflex and lower limb neuromuscular examination including tone, strength, and deep tendons reflexes should be ascertained. Extreme fear during anal inspection and/or fissures and hematomas in combination with a history of smearing feces should raise the suspicion of sexual abuse.

The differential diagnoses are listed in Table 3. The key points of history and physical examination to guide in the evaluation of constipation are listed in Table 4. Alarm signs that should alert the medical provider to a possible underlying condition responsible for the constipation are listed in Table 5.

- (3) Based on expert opinion, we recommend using Tables 3, 4, and 5 for alarm signs and symptoms and diagnostic clues to identify an underlying disease responsible for the constipation.
Voting: 7, 8, 8, 8, 9, 9, 9

Question 3: In the Diagnosis of Functional Constipation in Children, What Is the Diagnostic Value of the Following (3.1–3.4)

3.1 Digital Rectal Examination

One study was included evaluating the value of digital rectal examination in diagnosing clinically defined childhood constipation. Beckman et al (24) aimed to determine whether clinical variables accurately identify children with radiographically proven constipation. In this study, the ability of the clinical examination to discriminate between radiographically constipated and nonconstipated children was evaluated in a cross-sectional study and reported

TABLE 3. Differential diagnoses of constipation in infants/toddlers and children/adolescents

Celiac disease*
Hypothyroidism, hypercalcemia, hypokalemia*
Diabetes mellitus†
Dietary protein allergy*
Drugs, toxics
Opiates, anticholinergics
Antidepressants*
Chemotherapy
Heavy metal ingestion (lead)
Vitamin D intoxication*
Botulism
Cystic fibrosis*
HD*
Anal achalasia*
Colonic inertia†
Anatomic malformations
Imperforate anus*
Anal stenosis*
Pelvic mass (sacral teratoma)
Spinal cord anomalies, trauma, tethered cord*
Abnormal abdominal musculature (prune belly, gastroschisis, Down syndrome)*
Pseudoobstruction (visceral neuropathies, myopathies, mesenchymopathies)
Multiple endocrine neoplasia type 2B†

HD = Hirschsprung disease.

* More likely in the younger child.

† More likely in the older child.

a sensitivity of 77%, a specificity of 35%, and a likelihood ratio (LR, which means the likelihood that a given test result would be expected in a patient with functional constipation compared with the likelihood that that same result would be expected in a patient without functional constipation) of 1.2 (95% confidence interval [CI] CI 1.0–1.4). An LR of 1 indicates that a finding occurs as often in children with constipation as in children without constipation. A diagnosis of constipation as made by the clinician was not defined. None of the individual symptoms had a clinically relevant (LR ≥ 2 or ≤ 0.5) and statistically significant association with constipation on abdominal radiography. The best discriminator was “stool present on rectal examination” with an LR of 1.6 (1.2–2.0).

In conclusion, evidence does not support the use of digital rectal examination to diagnose functional constipation.

3.2 Abdominal Radiography

Demonstration of the presence or absence of fecal impaction has important therapeutic implications (Fig. 2, boxes 5 and 6).

One review was found (25). Five studies were included assessing the value of scoring fecal loading on abdominal radiography in diagnosing clinically defined childhood constipation. All studies evaluated the value of abdominal radiography to diagnose functional constipation, using as a reference the clinical definition of constipation. Barr et al (26) was the first to develop an abdominal radiography score to diagnose functional constipation. The Barr scoring system ranges from 0 to 25, with a total score of >10 , indicating excessive fecal retention. Barr et al reported a sensitivity of 80% (95% CI 65–90) and a specificity of 90% (90% CI 74–98) using their scoring system. Benninga et al (27) also used the Barr scoring system and reported a lower sensitivity of 60% (95% CI 46–72) and a specificity of 43% (95% CI 18–71). Subsequently, Leech et al (28) developed a scoring system in which an abdominal radiograph is divided into 3 segments. Each segment is scored from 0 to 5, with a score range of 0 to 15. A total score of 8 to 15 indicated constipation. Application of this scoring system by Leech et al yielded a sensitivity of 76% (95% CI 58–89) and a specificity of 75% (95% CI 63–85). de Lorijn et al (29) also used the Leech scoring system and reported a sensitivity of 75% (95% CI 61–86), and a specificity of 59% (95% CI 42–75). Çayan et al (30) rated fecal loading on abdominal radiography defined by the Blethyn scoring method (31). Fecal loading is scored on a scale from 1 to 3. They reported a sensitivity of 70% (95% CI 35–93) and a specificity of 90% (95% CI 95–100). Among these studies, only the study by de Lorijn et al (29) presented an area under the curve (AUC). An AUC of 1 indicates perfect discrimination between children with and without constipation. An AUC of 0.5 indicates no discrimination at all. The AUC of 0.68 (0.58–0.80) in this study indicated poor discriminative value.

One additional study defined constipation based on colonic transit time (CTT) (32). The ability of scoring fecal loading according to Barr on abdominal radiography to discriminate between radiographically constipated (CTT > 60 hours) and nonconstipated children (CTT ≤ 60 hours) was evaluated and reported a best AUC of 0.84 (95% CI 0.79–0.89; scored by a consultant). The discriminative power was dependent on the level of experience of the radiologist (Barr scores of the junior physician and the student were poorer, with AUCs of 0.76 and 0.61 (95% CI 0.69–0.82 and 0.53–0.69).

In conclusion, evidence supports not using an abdominal radiography to diagnose functional constipation.

3.3 CTT (Fig. 2, Box 25)

Four studies were included evaluating the value of CTT in diagnosing clinically defined childhood constipation. Gutiérrez et al

TABLE 4. Key points of history and physical examination to guide in the evaluation of constipation in infants/toddlers and children/adolescents

Infant/toddler	Child/adolescent
<p>Functional constipation</p> <p>History</p> <ul style="list-style-type: none"> Starts after a few weeks to months of life (not at birth) Obvious precipitating factors coinciding with the start of symptoms: fissure, change of diet, timing of toilet training, infections, changing house, starting nursery Normal passage of meconium <p>Examination</p> <ul style="list-style-type: none"> Generally well, weight and height within normal limits Normal growth Normal appearance of anus and surrounding area Soft abdomen Normal appearance of the skin and anatomical structures of lumbosacral/gluteal regions Normal gait, tone strength, and reflexes of lower limbs <p>Toilet phobia</p> <p>Cystic fibrosis</p> <ul style="list-style-type: none"> Respiratory problems Failure to thrive <p>Celiac disease, hypothyroidism</p> <ul style="list-style-type: none"> Family history Growth delay, developmental delay <p>Dietary protein allergy</p> <ul style="list-style-type: none"> Personal and family history (allergy) <p>Eczema</p> <p>HD</p> <ul style="list-style-type: none"> Onset of symptoms <1 mo Passage of meconium >48 h Bloody diarrhea, bilious vomiting Failure to thrive Abdominal distension Tight empty rectum in presence of palpable abdominal fecal mass Explosive stool and air from rectum upon withdrawal of examining finger <p>Anatomic malformations</p> <ul style="list-style-type: none"> Anal stenosis: ribbons stools, tight anal canal on rectal examination Abnormal anal position <p>Sacral teratoma</p> <ul style="list-style-type: none"> Sacral agenesis <p>Spinal cord anomalies</p> <ul style="list-style-type: none"> Weakness in legs, locomotor delay Pilonidal dimple covered by a tuft of hair Gluteal cleft deviation Absent anal and cremasteric reflex Decreased lower extremity tone and/or strength Abnormal deep tendon reflexes of lower extremity <p>Prune belly, gastroschisis, Down syndrome</p> <ul style="list-style-type: none"> Abnormal abdominal musculature <p>Pseudoobstruction</p> <ul style="list-style-type: none"> Reported from birth or first few weeks of life Failure to thrive Abdominal distension and bilious vomiting Urinary bladder distension 	<p>Functional constipation</p> <p>History</p> <ul style="list-style-type: none"> Starts after a few weeks to months of life (not at birth) Sometimes precipitating factors coinciding with the start of symptoms: fissure, change of diet, infections, changing house, starting school, fears and phobias, major change in family, new medicines, travel Normal passage of meconium <p>Examination</p> <ul style="list-style-type: none"> Generally well, weight and height within normal limits, fit and active Normal growth Normal appearance of anus and surrounding area Soft abdomen (palpable fecal mass possible) Normal appearance of the skin and anatomical structures of lumbosacral/gluteal regions Normal gait, tone strength, and reflexes of lower limbs <p>Sexual abuse</p> <ul style="list-style-type: none"> Social history Extreme fear during anal inspection/rectal examination, anal scars, fissures, hematomas <p>Depression</p> <ul style="list-style-type: none"> Personal and family history <p>Anorexia</p> <p>Cystic fibrosis</p> <ul style="list-style-type: none"> Respiratory problems Difficulty gaining weight <p>Celiac disease</p> <ul style="list-style-type: none"> Family history Growth delay <p>HD</p> <ul style="list-style-type: none"> Reported from birth or first few weeks of life Passage of meconium >48 h Growth delay, abdominal distension, bilious vomiting Massive abdominal distension Tight empty rectum in presence of palpable abdominal fecal mass Explosive stool and air from rectum upon withdrawal of examining finger <p>Sacral teratoma</p> <ul style="list-style-type: none"> Sacral agenesis <p>Spinal cord anomalies, trauma</p> <ul style="list-style-type: none"> Weakness in legs, abnormal motility Pilonidal dimple covered by a tuft of hair Gluteal cleft deviation Absent anal and cremasteric reflex Decreased lower extremity tone and/or strength Abnormal deep tendon reflexes of lower extremity <p>Prune belly, gastroschisis, Down syndrome</p> <ul style="list-style-type: none"> Abnormal abdominal musculature <p>Pseudoobstruction, MEN type 2B</p> <ul style="list-style-type: none"> Family history Reported from birth or first few weeks of life Failure to thrive Abdominal distension and bilious vomiting Urinary bladder distension

HD = Hirschsprung disease; MEN = multiple endocrine neoplasia.

(33) found that in constipated children the mean CTT was significantly prolonged compared with the control group (mean \pm standard deviation [SD] 49.57 ± 25.38 versus 29.08 ± 8.3); CTT was inversely related to the number of defecations per week. Zaslavsky et al (34) found that in constipated children the mean

CTT was significantly different from the mean in the control group (mean \pm SD 58.25 ± 17.46 compared with 30.18 ± 13.15). de Lorijn et al (29) presented an AUC of 0.90 (range 0.83–0.96), indicating that CTT is a good discriminator between children with and without clinical constipation who were referred to a pediatric

TABLE 5. Alarm signs and symptoms in constipation

Constipation starting extremely early in life (<1 mo)
Passage of meconium >48 h
Family history of HD
Ribbon stools
Blood in the stools in the absence of anal fissures
Failure to thrive
Fever
Bilious vomiting
Abnormal thyroid gland
Severe abdominal distension
Perianal fistula
Abnormal position of anus
Absent anal or cremasteric reflex
Decreased lower extremity strength/tone/reflex
Tuft of hair on spine
Sacral dimple
Gluteal cleft deviation
Extreme fear during anal inspection
Anal scars

HD = Hirschsprung disease.

gastroenterology department. In the study by Benninga et al (27), a CTT of ≥ 62 hours had a sensitivity of 52% (43–61) and a specificity of 91% (85–97), indicating that a CTT <62 hours rules out constipation. The choice for a case-control design in all studies indicates that all results are at risk for serious bias. In all of the studies, children with constipation were compared with healthy controls or symptomatic children in whom constipation was excluded. This study design is likely to overestimate diagnostic accuracy.

In conclusion, evidence does not support the routine use of colonic transit studies to diagnose functional constipation.

Comment: The working group concluded that demonstration of a normal CTT with the prompt passage of markers suggests either nonretentive fecal incontinence (a condition in which children have fecal incontinence without having functional constipation) or an unreliable medical history.

3.4 Transabdominal Rectal Ultrasonography

Four studies were included evaluating the value of transabdominal rectal ultrasonography in diagnosing childhood constipation. Bijoš et al (35) calculated a rectopelvic ratio by dividing the transverse diameter of the rectal ampulla by the transverse diameter of the pelvis. In children with functional constipation, the mean rectopelvic ratio was 0.22 ± 0.05 compared with healthy controls 0.15 ± 0.04 . The difference was statistically significant in all age groups.

In the study by Singh et al (36), the impression of the rectum behind the urinary bladder seen as a crescent was measured; the median rectal crescent in children with constipation was 3.4 cm (range 2.10–7.0, interquartile range [IQR] 35.3) compared with 2.4 cm (range 1.3–4.2, IQR 0.72) in healthy controls. Cutoff values for constipation were not presented. In the study by Joensson et al (37), it was possible to visualize the transverse diameter of the rectum at least 3 hours after the last bowel movement in all of the included children. The children with constipation had a significantly larger rectal diameter than healthy children (mean \pm SD 42.1 ± 15.4 vs 21.4 ± 6.0 mm). Using a cutoff value for constipation of 33.4 mm, 13 children would be misclassified. After laxative treatment, the rectal diameter of the children with constipation

decreased significantly (from [mean \pm SD] 42.1 ± 15.4 to 26.9 ± 5.6 mm). Klijn et al (38) found a statistically significant difference in mean rectal diameter between the constipated group (4.9 cm) and the control group (2.1 cm). The cutoff value was 3.3 cm, where >3.3 cm indicated constipation. The study by Singh et al (36) reported an AUC of 0.85 (0.79–0.90), indicating that measuring rectal diameter on ultrasound examination is a moderate-to-good discriminator between children with and without constipation.

In conclusion, evidence does not support the routine use of rectal ultrasound to diagnose functional constipation.

- (4) Based on expert opinion, if only 1 of the Rome III criteria is present and the diagnosis of functional constipation is uncertain, a digital examination of the anorectum is recommended.
Voting: 7, 8, 8, 8, 9, 9, 9, 9
- (5) Based on expert opinion, in the presence of alarm signs or symptoms or in patients with intractable constipation, a digital examination of the anorectum is recommended to exclude underlying medical conditions.
Voting: 7, 8, 8, 8, 8, 9, 9, 9
- (6) The routine use of an abdominal radiograph to diagnose functional constipation is not indicated.
Voting: 8, 8, 9, 9, 9, 9, 9, 9
- (7) Based on expert opinion, a plain abdominal radiography may be used in a child in whom fecal impaction is suspected but in whom physical examination is unreliable/not possible.
Voting: 6, 7, 7, 7, 8, 8, 9, 9
- (8) Colonic transit studies are not recommended to diagnose functional constipation.
Voting: 7, 8, 9, 9, 9, 9, 9, 9
- (9) Based on expert opinion, a colonic transit study may be useful to discriminate between functional constipation and functional nonretentive fecal incontinence and in situations in which the diagnosis is not clear.
Voting: 8, 8, 8, 8, 8, 9, 9, 9
- (10) Rectal ultrasound is not recommended to diagnose functional constipation.
Voting: 7, 8, 8, 9, 9, 9, 9, 9

Question 4: Which of the Following Diagnostic Tests Should Be Performed in Children With Constipation to Diagnose an Underlying Disease?

4.1 Laboratory Investigations to Diagnose (Cow's Milk) Allergy, Celiac Disease, Hypothyroidism, and Hypercalcemia? (Fig. 2, Box 21)

The search identified 164 studies. Five of them fulfilled our inclusion criteria.

The association between cow's-milk protein allergy and constipation has been vigorously debated since the study by Iacono et al (39), in which the authors found that 78% of children affected by constipation and cow's-milk protein allergy improved after cow's-milk protein (CMP) elimination diet. These data were partially confirmed by a further study from the same group in which 18 of 44 children responsive to the CMP elimination diet were found to have positive specific immunoglobulin E antibodies to cow's-milk antigens (40). These studies were, however, performed in an allergy center, a fact that could have led to an overestimation of the

prevalence of this association. Furthermore, the authors did not use the double-blind provocation test that is considered the gold standard method to diagnose allergy to a food antigen. A subsequent prospective study conducted by Simeone et al (41) in 91 patients affected by chronic constipation did not confirm this association. El-Hodhod et al (42) suggested that cow's-milk allergy should be considered a common etiologic factor for constipation in infants and children and that cow's-milk tolerance is often achieved after at least 12 months of strict cow's-milk elimination. Finally, a study from Irastorza et al (43) found a prevalence of 51% patients responding to a CMP elimination diet, but no significant differences were noted between the group of responders and nonresponders regarding atopic/allergic history and laboratory results.

In conclusion, evidence is conflicting for allergy testing to diagnose cow's-milk allergy in children with functional constipation.

No published evidence met our inclusion criteria on the prevalence of hypothyroidism, celiac disease, and hypercalcemia in children with functional constipation.

4.2 Anorectal Manometry (ARM) or Rectal Suction Biopsy to Diagnose HD (Fig. 2, Box 29)

Based on retrospective studies, the present diagnostic approach recognizes rectal suction biopsy as the gold standard for the diagnosis of HD. ARM is not recommended as the sole diagnostic tool to diagnose HD in neonates and infants; however, ARM is a useful screening test in older children presenting with constipation and further symptoms suggesting HD (empty rectal ampulla, nonresponsiveness to standard therapy, early-onset constipation). The presence of the rectoanal-inhibitory reflex (RAIR) excludes HD, although a false-positive RAIR is possible. The latter may occur because of displacement of the sensor positioned at the level of the sphincter upon rectal balloon inflation or as a consequence of relaxation of the external anal sphincter rather than the internal anal sphincter. In the absence of the RAIR, a rectal biopsy is needed to confirm the diagnosis of HD. When the RAIR is abnormal and a normal distal rectal biopsy is found, the diagnosis of anal achalasia is made (44,45).

The search identified 210 studies. None fulfilled our inclusion criteria.

4.3 Use of Barium Enema to Diagnose Organic Causes Such As HD (Fig. 2, Box 29)

Based on retrospective studies, a barium enema should not be performed as an initial diagnostic tool because it does not represent a valid alternative to rectal biopsy or ARM to exclude or diagnose HD, regardless of age, but it could be used to assess extent of the aganglionic segment before surgery (46).

The search identified 86 studies. None fulfilled our inclusion criteria.

- (11) Routine allergy testing is not recommended to diagnose cow's-milk allergy in children with functional constipation.
Voting: 7, 7, 8, 8, 9, 9, 9, 9
- (12) Based on expert opinion, a 2- to 4-week trial of avoidance of CMP may be indicated in the child with intractable constipation.
Voting: 6, 6, 7, 7, 8, 8, 8, 9

- (13) Based on expert opinion, we do not recommend routine laboratory testing for hypothyroidism, celiac disease, and hypercalcemia in children with constipation in the absence of alarm symptoms.
Voting: 7, 8, 8, 9, 9, 9, 9, 9
- (14) Based on expert opinion, the main indication to perform ARM in the evaluation of intractable constipation is to assess the presence of the RAIR.
Voting: 7, 8, 8, 8, 9, 9, 9, 9
- (15) Rectal biopsy is the gold standard for diagnosing HD.
Voting: 9, 9, 9, 9, 9, 9, 9, 9
- (16) Based on expert opinion, we do not recommend performing barium enema as an initial diagnostic tool for the evaluation of children with constipation.
Voting: 7, 7, 7, 7, 8, 8, 9, 9

Question 5: Which of the Following Examinations Should Be Performed in Children With Intractable Constipation to Evaluate Pathophysiology and Diagnose an Underlying Abnormality?

5.1 Colonic Manometry (Fig. 2, Box 32)

Colonic manometry allows discrimination between normal colonic physiology and colonic neuromuscular diseases. Case series have shown that colonic manometry may predict outcome after the performance of an antegrade continence enema (ACE) procedure, identifies patients with an ACE who may be able to be weaned from the irrigations, and can identify specific segments of colonic dysfunction that may be amenable for surgery (47–49).

The search identified 165 studies. None of them fulfilled our inclusion criteria.

5.2 Magnetic Resonance Imaging (MRI) of the Spine (Fig. 2, Box 29)

The search identified 77 studies. One study fulfilled the inclusion criteria (50). A total of 130 children with intractable constipation and 28 with nonretentive fecal incontinence (see question 3.3) underwent MRI that revealed that 3% had lumbosacral spine abnormalities and the neurologic examination revealed no abnormalities in these patients. The therapeutic response was similar in the children without and with lumbosacral spine abnormalities, although the follow-up was short.

In conclusion, evidence does not support the use of MRI of the spine in patients with intractable constipation without other neurologic abnormalities.

Comment: Limited retrospective data have shown that spinal cord abnormalities may be present in children with intractable constipation even when the neurologic examination is normal. Improvement in constipation after the spinal cord abnormalities are surgically corrected (51).

5.3 Colonic Full-Thickness Biopsies

Preliminary evidence suggests that children with intractable constipation may have abnormalities in the colonic neuromuscular layers (52–54). Alterations in both histology and neurotransmitters have been described, but the exact clinical significance of those abnormalities is not clear. There is also no association between

specific histologic abnormalities and the type of colonic dysfunction (52–54).

The search identified 50 studies. None of them fulfilled our inclusion criteria.

Comment: Although we do not recommend surgery just to obtain full-thickness colonic biopsies, a full-thickness biopsy may be appropriate in the context of the child receiving another intra-abdominal surgical procedure.

5.4 Colonic Scintigraphy

Nuclear scintigraphy provides information on colonic transit and may provide data also on gastric emptying and small bowel transit. It is considered to be useful in measuring colonic motility in children with slow transit constipation (55).

The search identified 263 studies. None fulfilled our inclusion criteria. No studies have assessed the diagnostic value of scintigraphy in children with functional constipation.

- | | |
|------|---|
| (17) | Based on expert opinion, colonic manometry may be indicated in patients with intractable constipation before considering surgical intervention.
Voting: 7, 7, 8, 9, 9, 9, 9 |
| (18) | The routine use of MRI of the spine is not recommended in patients with intractable constipation without other neurologic abnormalities.
Voting: 7, 7, 9, 9, 9, 9, 9 |
| (19) | Based on expert opinion, we do not recommend obtaining full-thickness colonic biopsies to diagnose colonic neuromuscular disorders in children with intractable constipation.
Voting: 7, 8, 8, 8, 8, 9, 9 |
| (20) | Based on expert opinion we do not recommend routine use of colonic scintigraphy studies in children with intractable constipation.
Voting: 9, 9, 9, 9, 9, 9, 9 |

Question 6: What Is the Additional Effect of the Following Nonpharmacologic Treatments in Children With Functional Constipation?

For the role of CMP-free diet: see question 4.1 (Fig. 1, Box 24; Fig. 2, Box 21).

6.1 Fiber (Fig. 1, Box 8; Fig. 2, Box 9 “Education”)

The search identified 111 studies including 3 systematic reviews (9,56,57). Tabbers et al (9) performed a Clinical Evidence GRADE evaluation for most of the interventions. They, however, used different inclusion criteria and outcome measures compared with the present review. They found limited evidence that additional fiber improves constipation compared with placebo and that increased fiber intake is not as effective as lactulose. Pijpers et al (56) included 2 studies concerning fiber and concluded that the pooled weighted standardized mean difference was 0.35 bowel movements per week in favor of fiber (95% CI –0.04 to 0.74), which is neither statistically significant nor clinically relevant. The third and most recent systematic review concluded that studies were highly diverse with regard to the participants, interventions, and outcome measures; therefore, a meta-analysis could not be performed (57). Based on these 3 reviews, 3 studies

fulfilled our inclusion criteria (58–60). After these reviews, 2 more RCTs were published that also fulfilled our inclusion criteria (61,62). Consequently, we included 5 studies concerning fiber according to our outcome measures: see GRADE evidence profiles in Appendix, question 6, <http://links.lww.com/MPG/A295>.

In conclusion, evidence does not support the use of fiber supplements in the treatment of functional constipation.

6.2 Fluid (Fig. 1, Box 8; Fig. 2, Box 9 “Education”)

The search identified 166 studies including 2 systematic reviews (9,57). Both reviews concluded that based on 1 study, increasing oral fluid intake has not been shown to be beneficial (63). Young et al (63) investigated 108 children, 2 to 12 years with an unclear definition of constipation, comparing 3 groups: 50% increase in water intake, hyperosmolar (>600 mOsm/L) supplemental fluid, and normal fluid intake. This study has a high risk of bias: no information was provided about randomization, blinding, or the rate of loss-to-follow-up monitoring. No statistical assessment was conducted. The RCT found similar stool frequency at 3 weeks for the 3 groups. Because of the missing data such as means with SD, a GRADE evidence profile could not be performed.

In conclusion, evidence does not support the use of extra fluid intake in the treatment of functional constipation.

6.3 Physical Activity (Fig. 2, Box 9 “Education”)

There are no randomized studies that evaluate the effect of increased physical activity in childhood constipation.

6.4 Prebiotics

6.5 Probiotics

The present search identified 153 studies, including 4 systematic reviews (9,56,57,64). Tabbers et al (9) performed a GRADE assessment for most of the interventions. In the latter assessment, different inclusion criteria and outcome measures were used compared with the present review. No evidence was found supporting the use of prebiotics and probiotics (9). The other reviews included the same 2 RCTs concerning probiotics (56,57,64). Two systematic reviews included the same study concerning prebiotics but did not perform a GRADE evaluation (56,57). After these reviews, 3 more RCTs, fulfilling our inclusion criteria, evaluating the effect of probiotics, were published (65–67). It was, however, only possible to perform a GRADE evidence profile of 1 study owing to missing data in the other 2 studies (67). Therefore, we discuss these 2 studies. Guerra et al (65) carried out a crossover double-blind trial in 59 Brazilian children with functional constipation according to Rome III criteria. This study has a low risk of bias. The patients were randomized in 2 groups to receive either a goat yogurt supplemented with 10^9 colony-forming unit/mL *Bifidobacterium longum* daily or only the yogurt for a period of 5 weeks. The results were only graphically presented without reporting absolute numbers.

Coccorullo et al (66) performed a double-blind randomized placebo-controlled study in 44 formula-fed infants with a diagnosis of functional chronic constipation according to Rome III criteria. This study has a low risk of bias. One group received supplementation with the probiotic *Lactobacillus reuteri* (DSM 17938) and the other group received a placebo. *L reuteri* was administered at a dose of 10^8 colony-forming units in 5 drops of oil suspension once per day for 8 weeks. Infants treated with *L reuteri* had a significantly higher defecation frequency than placebo after 2, 4, and 8 weeks of

treatment. The results were graphically presented without reporting absolute numbers with means and SDs, and there was no mean difference for outcome measures between the 2 groups.

In summary, 1 study reporting the effect of prebiotics and 5 studies reporting the effect of probiotics fulfilled our inclusion criteria. It was possible to perform a GRADE evidence profile concerning the prebiotic study and 3 concerning probiotic studies.

In conclusion, evidence does not support the use of pre- or probiotics in the treatment of childhood constipation.

6.6 Behavioral Therapy (Fig. 2, Boxes 11, 27, and 35) and 6.7 Biofeedback (Fig. 2, Box 35)

The search identified 194 studies including 3 systematic reviews (9,57,68). All of the reviews concluded that behavioral therapy in addition to laxatives is not more effective than laxatives alone. Only 1 study (69) fulfilled our inclusion criteria: see Appendix, question 6, <http://links.lww.com/MPG/A295>. Concerning biofeedback therapy, 2 systematic reviews included the same studies with the same outcome measures (57,68). See GRADE evidence profiles in Appendix, question 7, <http://links.lww.com/MPG/A295>.

In conclusion, evidence does not support the use of behavioral therapy or biofeedback in the treatment of childhood constipation.

Comment: There may be benefit to refer children with constipation and behavioral abnormalities to a mental health provider (Fig. 2, boxes 11, 27, and 35).

6.8 Multidisciplinary Treatment (Pediatrician or Pediatric Gastroenterologist, Dietician, Psychologist, and Physical Therapist)

No RCTs were found.

6.9 Alternative Medicine (Including Acupuncture, Homeopathy, Mind-Body Therapy, Musculoskeletal Manipulations Such As Osteopathic and Chiropractic and Yoga)

No RCTs were found.

Quality of evidence: very low.

(21) A normal fiber intake is recommended in children with constipation.
Voting: 6, 8, 9, 9, 9, 9, 9

Quality of evidence: low.

(22) Based on expert opinion, we recommend a normal fluid intake in children with constipation.
Voting: 9, 9, 9, 9, 9, 9, 9

Quality of evidence: low.

(23) Based on expert opinion, we recommend a normal physical activity in children with constipation.
Voting: 9, 9, 9, 9, 9, 9, 9

Quality of evidence: very low.

(24) The routine use of prebiotics is not recommended in the treatment of childhood constipation.
Voting: 9, 9, 9, 9, 9, 9, 9

Quality of evidence: low.

(25) The routine use of probiotics is not recommended in the treatment of childhood constipation.
Voting: 7, 8, 8, 9, 9, 9, 9

Quality of evidence: low.

(26) The routine use of an intensive behavioral protocolized therapy program in addition to conventional treatment is not recommended in childhood constipation.
Voting: 9, 9, 9, 9, 9, 9, 9

(27) Based on expert opinion, we recommend demystification, explanation, and guidance for toilet training (in children with a developmental age of at least 4 years) in the treatment of childhood constipation.
Voting: 7, 8, 8, 8, 9, 9, 9

Quality of evidence: low.

(28) The use of biofeedback as additional treatment is not recommended in childhood constipation.
Voting: 7, 8, 8, 9, 9, 9, 9

Quality of evidence: low.

(29) Based on expert opinion, we do not recommend the routine use of multidisciplinary treatment in childhood constipation.
Voting: 9, 9, 9, 9, 9, 9, 9

Quality of evidence: low.

(30) Based on expert opinion, we do not recommend the use of alternative treatments in childhood constipation.
Voting: 9, 9, 9, 9, 9, 9, 9

Question 7: What Is the Most Effective and Safest Pharmacologic Treatment in Children With Functional Constipation?

The search identified 252 studies including 5 systematic reviews (9,56,70–72). Among the 5 systematic reviews, the review of Price et al (70) did not include any drug trial. Lee-Robichaud et al (71) performed a review to determine whether lactulose or polyethylene glycol (PEG) was more effective in treating chronic constipation and fecal impaction in adults and children. We included the 5 pediatric studies from that review in this guideline:

see GRADE evidence profiles for pooled outcome measures in Appendix, question 7, <http://links.lww.com/MPG/A295> (73–77). Tabbers et al (9) investigated the effectiveness of most of the pharmacologic interventions but used different inclusion criteria and outcome measures compared with our guidelines. In separate reviews, both Candy et al (72) and Pijpers et al (56) concluded that because of the heterogeneity of the included studies with regard to participants, interventions, and outcome measures, statistical pooling of the results was not possible for most of the interventions. Nine studies fulfilled our inclusion criteria and were not already included by Lee-Robichaud et al (see GRADE evidence profiles in Appendix, question 7, <http://links.lww.com/MPG/A295>) (78–86). No RCTs were found about the optimal dosages of the different medications (see Table 6 for recommended dosages of most frequently used oral and rectal laxatives).

7.1 Which Pharmacologic Treatment Should Be Given for Disimpaction? (Fig. 2, Boxes 6 and 11)

No placebo-controlled studies have evaluated the effect of oral laxatives or enemas on disimpaction. One study compared the effect of PEG to enemas but could not detect a difference in effect (85).

In conclusion, evidence shows that PEG and enemas are equally effective for fecal disimpaction.

Comment: High-dose PEG given orally is associated with a higher frequency of fecal incontinence during treatment of the fecal impaction compared with enema use; however, based on the argument that PEG can be administered orally, the working group decided to prefer PEG.

7.2 Which Pharmacologic Treatment Should Be Given for Maintenance Therapy? (Fig. 1, Boxes 10 and 14; Fig. 2, Box 13)

In conclusion, evidence shows that PEG is more effective compared with lactulose, milk of magnesia, mineral oil, or placebo. More studies have been performed evaluating the effectiveness of lactulose than studies evaluating the effect of milk of magnesia and mineral oil in children with constipation. More important, lactulose is considered to be safe for all ages. For these reasons, lactulose is recommended in case PEG is not available. Furthermore, evidence does not support the addition of enemas to the chronic use of PEG in children with constipation.

7.3 How Long Should Children Receive Medical Therapy? (Fig. 1, Box 14; Fig. 2, Box 13)

No RCTs have investigated the optimal duration of medical treatment in children with functional constipation.

Quality of evidence: very low.

- | | |
|------|--|
| (31) | The use of PEG with or without electrolytes orally 1 to 1.5 g · kg ⁻¹ · day ⁻¹ for 3 to 6 days is recommended as the first-line treatment for children presenting with fecal impaction.
Voting: 6, 7, 7, 8, 8, 9, 9, 9 |
| (32) | An enema once per day for 3 to 6 days is recommended for children with fecal impaction, if PEG is not available. |

TABLE 6. Dosages of most frequently used oral and rectal laxatives

Oral laxatives	Dosages
Osmotic laxatives	
Lactulose	1–2 g/kg, once or twice/day
PEG 3350	Maintenance: 0.2–0.8 g · kg ⁻¹ · day ⁻¹
PEG 4000	Fecal disimpaction: 1–1.5 g · kg ⁻¹ · day ⁻¹ (with a maximum of 6 consecutive days)
Milk of magnesia (magnesium hydroxide)	2–5 y: 0.4–1.2 g/day, once or divided 6–11 y: 1.2–2.4 g/day, once or divided 12–18 y: 2.4–4.8 g/day, once or divided
Fecal softeners	
Mineral oil	1–18 y: 1–3 mL · kg ⁻¹ · day ⁻¹ , once or divided, max 90 mL/day
Stimulant laxatives	
Bisacodyl	3–10 y: 5 mg/day >10 y: 5–10 mg/day
Senna	2–6 y: 2.5–5 mg once or twice/day 6–12 y: 7.5–10 mg/day >12 y: 15–20 mg /day
Sodium picosulfate	1 mo–4 y: 2.5–10 mg once/day 4–18 y: 2.5–20 mg once/day
Rectal laxatives/enemas	
Bisacodyl	2–10 y: 5 mg once /day >10 y: 5–10 mg once /day
Sodium docusate	<6 y: 60 mL >6 y: 120 mL
Sodium phosphate	1–18 y: 2.5 mL/kg, max 133 mL/dose
NaCl	Neonate <1 kg: 5 mL, >1 kg: 10 mL >1 y: 6 mL/kg once or twice/day
Mineral oil	2–11 y: 30–60 mL once/day >11 y: 60–150 mL once/day

PEG = polyethylene glycol.

Quality of evidence: very low.

- (33) The use of PEG with or without electrolytes is recommended as the first-line maintenance treatment. A starting dose of $0.4 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ is recommended and the dose should be adjusted according to the clinical response.
Voting: 7, 7, 8, 8, 9, 9. Two members (who had disclosed a COI with industry manufacturing PEG) did not participate in the discussion and did not vote.
- (34) The addition of enemas to the chronic use of PEG is not recommended in children with constipation.
Voting: 7, 8, 8, 8, 8, 9, 9, 9
- (35) The use of lactulose as the first-line maintenance treatment is recommended, if PEG is not available.
Voting: 7, 7, 8, 8, 8, 9, 9, 9
- (36) Based on expert opinion, the use of milk of magnesia, mineral oil, and stimulant laxatives may be considered as an additional or second-line treatment.
Voting: 7, 7, 7, 7, 9, 9, 9, 9

Quality of evidence: low.

- (37) Based on expert opinion, maintenance treatment should continue for at least 2 months. All symptoms of constipation symptoms should be resolved for at least 1 month before discontinuation of treatment. Treatment should be decreased gradually.
Voting: 7,7,8,8,8,8,9,9
- (38) Based on expert opinion, in the developmental stage of toilet training, medication should only be stopped once toilet training is achieved.
Voting: 7,7,7,8,8,8,9,9,9

Question 8: What Is the Efficacy and Safety of Novel Therapies for Children With Intractable Constipation?**8.1 Lubiprostone, Linaclotide, and Prucalopride**

Lubiprostone, linaclotide, and prucalopride are drugs that have been found to be effective in constipated adults. To date, no randomized studies have been published in children.

8.2 Surgery (Fig. 2, Boxes 34 and 35)

The use of ACE has been reported as a successful therapeutic option for patients with long-lasting constipation when maximal conventional therapy is not successful. The antegrade delivery of cleansing solutions enables the patient to evacuate the colon at regular intervals, avoiding impaction of feces and reducing fecal incontinence.

No randomized studies were found.

Comment: Six open retrospective studies are available in children suggesting that ACE may be an option in children with intractable constipation (87–92). Potential complications (development of granulation tissue, leakage around the tube, tube displacement, skin infection, and stoma stenosis) should be thoroughly considered and discussed with parents and children. No data

comparing different types of surgical procedures for the administration of antegrade enemas have been published.

8.3 Transcutaneous Nerve Stimulation (TNS) (Fig. 2, Boxes 34 and 35)

Transcutaneous electrical stimulation is a noninvasive and painless form of interferential therapy in which 4 surface electrodes are applied to the skin (2 abdominal, just below the costal margin; 2 paraspinal, over muscles between T9 and L2 spinal segments), which produce 2 sinusoidal currents that cross within the body (93).

See the GRADE evidence profile of 1 study in Appendix, question 8, <http://links.lww.com/MPG/A295> (94). In this RCT, investigators report a significant improvement of quality of life in children treated with TNS; however, the basal scores of quality of life in the 2 groups were not similar, thus precluding any valuable conclusion. In addition, in another report, TNS decreased transit time in treated patients but no data on stool pattern and frequency were reported (95).

In conclusion, evidence does not support the use of TNS in children with intractable constipation.

Quality of evidence: low.

- (39) Based on expert opinion, we do not recommend the routine use of lubiprostone, linaclotide, and prucalopride in children with intractable constipation.
Voting: 9, 9, 9, 9, 9, 9, 9, 9

Quality of evidence: low.

- (40) Based on expert opinion, we recommend antegrade enemas in the treatment of selected children with intractable constipation.
Voting: 7, 7, 8, 8, 8, 9, 9 (General practitioner did not vote because of lack of experience.)

Quality of evidence: very low.

- (41) The routine use of TNS in children with intractable constipation is not recommended.
Voting: 9, 9, 9, 9, 9, 9, 9, 9

Question 9: What Is the Prognosis and What Are Prognostic Factors in Children With Functional Constipation?

One systematic review was included (96). In addition to the systematic review, 2 studies were added (97,98). In total, 15 prospective studies were included, of which 7 were performed in tertiary care hospitals, 6 in general pediatric practices, and 1 in primary care; in 1 study the location was not specified (97–111). Borowitz et al (98) reported that primary care physicians tend to undertreat childhood constipation. This is in line with the results of Bongers et al (97) that delay in treatment, defined as time between age at onset and first presentation at the department of pediatric gastroenterology, is negatively related to recovery (OR 0.81, 95% CI 0.71–0.91). Moreover, it also agrees with the results of van den Berg et al (109), who

found that duration of symptoms <3 months before presentation had a positive effect on recovery.

Approximately 80% of the children adequately treated early in their course recovered without using laxatives at 6-month follow-up, compared with only 32% of the children with a delay in treatment. These data indicated that early adequate therapeutic intervention was more likely to be beneficial and contributed to successful outcome of constipation. Both high- and low-quality studies showed approximately 50% to 60% recovery rate after 1 year of intensive treatment. Prognostic factors could not be identified.

Data from tertiary care centers showed similar recovery rates of 50% after 5 years of follow-up (101,111). Approximately 50% of children with constipation had at least 1 relapse within the first 5 years after initial recovery (105). This finding may explain similar success percentages between 1 and 5 years of follow-up. Thus, it seems of great importance to follow constipated children closely and restart medication promptly, if necessary. Furthermore, emphasis on recommended regimens for maintenance and how to reduce medication will help to improve the long-term outcome.

9.1 What Is the Prognosis of Functional Constipation in Children?

Among patients referred to pediatric gastroenterologists 50% will recover (≥ 3 bowel movements per week without fecal incontinence) and be without laxatives after 6 to 12 months. Approximately an additional 10% are well while taking laxatives, and 40% will still be symptomatic despite use of laxatives. A total of 50% and 80% of the children are recovered after 5 and 10 years, respectively, with the vast majority of patients no longer taking laxatives. In patients referred to pediatric gastroenterologists, a delay in initial medical treatment for >3 months from symptom onset correlates with longer duration of symptoms.

9.2 What Are Prognostic Factors in Children With Functional Constipation?

See Table 7.

TABLE 7. Summary of evidence for any of the following factors being related to the prognosis of functional constipation (see Appendix for more details, <http://links.lww.com/MPG/A295>)

There is limited /insufficient evidence relative to the prognostic value of functional constipation of the following factors

Demographics/history: age at presentation, age at onset, duration of symptoms <3 mo before presentation, treatment duration <2 mo before presentation, premature birth, delayed passage of meconium, history of constipation in the first year of life
Clinical symptoms: defecation frequency, presence of fecal incontinence, abdominal pain at presentation/history of abdominal pain, large stools, urinary tract infection, nighttime urinary incontinence, stool withholding
Physical examination: absence of a rectal or abdominal mass
Additional examination: balloon defecation, relaxation of external sphincter, megarectum and/or megacolon at diagnosis

There is limited evidence for a negative prognostic value for

Additional examination: prolonged CTT

There is strong evidence that the following factors have no prognostic value

Demographics: sex, positive family history

CTT = colonic transit time.

Diagnostic Recommendations

- (1) The Rome III criteria are recommended for the definition of functional constipation for all age groups.
- (2) The diagnosis of functional constipation is based on history and physical examination.
- (3) We recommend using alarm signs and symptoms and diagnostic clues to identify an underlying disease responsible for the constipation.
- (4) If only 1 of the Rome III criteria is present and the diagnosis of functional constipation is uncertain, a digital examination of the anorectum is recommended.
- (5) In the presence of alarm signs or symptoms or in children with intractable constipation, a digital examination of the anorectum is recommended to exclude underlying medical conditions.
- (6) The routine use of an abdominal radiograph has no role to diagnose functional constipation.
- (7) A plain abdominal radiography may be used in a child in whom fecal impaction is suspected but in whom physical examination is unreliable/not possible.
- (8) Colonic transit studies are not recommended to diagnose functional constipation.
- (9) A colonic transit study may be useful to discriminate between functional constipation and functional nonretentive fecal incontinence and in situations in which the diagnosis is not clear.
- (10) Rectal ultrasound is not recommended to diagnose functional constipation.
- (11) Routine allergy testing to diagnose cow's-milk allergy is not recommended in children with constipation in the absence of alarm symptoms.
- (12) Based on expert opinion, a 2- to 4-week trial of avoidance of CMP may be indicated in the child with intractable constipation.
- (13) Routine laboratory testing to screen for hypothyroidism, celiac disease, and hypercalcemia is not recommended in children with constipation in the absence of alarm symptoms.
- (14) Based on expert opinion, the main indication to perform ARM in the evaluation of intractable constipation is to assess the presence of the RAIR.
- (15) Rectal biopsy is the gold standard for diagnosing HD.
- (16) We do not recommend performing barium enema as an initial diagnostic tool for the evaluation of children with constipation.
- (17) Colonic manometry may be indicated in patients with intractable constipation before considering surgical intervention.
- (18) The routine use of MRI of the spine is not recommended in patients with intractable constipation without other neurologic abnormalities.
- (19) We do not recommend obtaining full-thickness colonic biopsies to diagnose colonic neuromuscular disorders in children with intractable constipation.
- (20) We do not recommend the routine use of colonic scintigraphy studies in children with intractable constipation.

Therapeutic Recommendations

- (21) A normal fiber intake is recommended.
- (22) A normal fluid intake is recommended.

- (23) We recommend a normal physical activity in children with constipation.
- (24) The routine use of prebiotics is not recommended in the treatment of childhood constipation.
- (25) The routine use of probiotics is not recommended in the treatment of childhood constipation.
- (26) The routine use of an intensive behavioral protocolized therapy program in addition to conventional treatment is not recommended in childhood constipation.
- (27) Based on expert opinion, we recommend demystification, explanation, and guidance for toilet training (in children with a developmental age of at least 4 years) in the treatment of childhood constipation.
- (28) The use of biofeedback as additional treatment is not recommended in childhood constipation.
- (29) We do not recommend the routine use of multidisciplinary treatment in childhood constipation.
- (30) We do not recommend the use of alternative treatments in childhood constipation.
- (31) PEG with or without electrolytes orally 1 to 1.5 g · kg⁻¹ · day⁻¹ for 3 to 6 days is recommended as the first-line treatment for children presenting with fecal impaction.
- (32) An enema once per day for 3 to 6 days is recommended for children with fecal impaction, if PEG is not available.
- (33) PEG with or without electrolytes is recommended as the first-line maintenance treatment. A starting dose of 0.4 g · kg⁻¹ · day⁻¹ is recommended and the dose should be adjusted according to the clinical response.
- (34) Addition of enemas to the chronic use of PEG is not recommended.
- (35) Lactulose is recommended as the first-line maintenance treatment, if PEG is not available.
- (36) Based on expert opinion, the use of milk of magnesia, mineral oil, and stimulant laxatives may be considered as an additional or second-line treatment.
- (37) Maintenance treatment should continue for at least 2 months. All symptoms of constipation symptoms should be resolved for at least 1 month before discontinuation of treatment. Treatment should be decreased gradually.
- (38) In the developmental stage of toilet training, medication should only be stopped once toilet training is achieved.
- (39) The routine use of lubiprostone, linaclotide, and prucalopride in children with intractable constipation is not recommended.
- (40) Antegrade enemas are recommended in the treatment of selected children with intractable constipation.
- (41) The routine use of TNS is not recommended in children with intractable constipation

REFERENCES

1. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *Am J Gastroenterol* 2006;101:2401–9.
2. Loening-Baucke V. Constipation in early childhood: patient characteristics, treatment, and long-term follow up. *Gut* 1993;34:1400–4.
3. Liem O, Harman J, Benninga M, et al. Health utilization and cost impact of childhood constipation in the United States. *J Pediatr* 2009;154:258–62.
4. Baker SS, Liptak GS, Colletti RB, et al. Constipation in infants and children: evaluation and treatment. A medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1999;29:612–26.
5. Bardisa-Ezcurra L, Ullman R, Gordon J. Guideline Development Group. Diagnosis and management of idiopathic childhood constipation: summary of NICE guidance. *BMJ* 2010;340:c2585.
6. Tabbers MM, Boluyt N, Berger MY, et al. Clinical practice: diagnosis and treatment of functional constipation. *Eur J Pediatr* 2011;170:955–63.
7. Evaluation and treatment of constipation in children: summary of updated recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2006;43:405–7.
8. Felt B, Wise CG, Olson A, et al. Guideline for the management of pediatric idiopathic constipation and soiling. Multidisciplinary team from the University of Michigan Medical Center in Ann Arbor. *Arch Pediatr Adolesc Med* 1999;153:380–5.
9. Tabbers MM, Boluyt N, Berger MY, et al. Constipation in children. *Clin Evid (Online)* 2010;2010:ii:0303.
10. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
11. McMurray AR. Three decision-making aids: brainstorming, nominal group, and Delphi technique. *J Nurs Staff Dev* 1994;10:62–5.
12. Hyman PE, Milla PJ, Benninga MA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;130:1519–26.
13. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006;130:1527–37.
14. Boccia G, Manguso F, Coccorullo P, et al. Functional defecation disorders in children: PACCT criteria versus Rome II criteria. *J Pediatr* 2007;151:394–8.
15. Devanarayana NM, Adhikari C, Pannala W, et al. Prevalence of functional gastrointestinal diseases in a cohort of Sri Lankan adolescents: comparison between Rome II and Rome III criteria. *J Trop Pediatr* 2011;57:34–9.
16. Burgers R, Levin AD, Di Lorenzo C, et al. Functional defecation disorders in children: comparing the Rome II with the Rome III criteria. *J Pediatr* 2012;161:615–20.
17. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130:1480–91.
18. Bekkali N, Hamers SL, Reitsma JB, et al. Infant stool form scale: development and results. *J Pediatr* 2009;154:521–6.
19. Lane MM, Czyzewski DI, Chumpitazi BP, et al. Reliability and validity of a modified Bristol Stool Form Scale for children. *J Pediatr* 2011;159:437–41.
20. Chumpitazi BP, Lane MM, Czyzewski DI, et al. Creation and initial evaluation of a Stool Form Scale for children. *J Pediatr* 2010;157:594–7.
21. Ghosh A, Griffiths DM. Rectal biopsy in the investigation of constipation. *Arch Dis Child* 1998;79:266–8.
22. Metaj M, Laroia N, Lawrence RA, et al. Comparison of breast- and formula-fed normal newborns in time to first stool and urine. *J Perinatol* 2003;23:624–8.
23. Jung PM. Hirschsprung's disease: one surgeon's experience in one institution. *J Pediatr Surg* 1995;30:646–51.
24. Beckmann KR, Hennes H, Sty JR, et al. Accuracy of clinical variables in the identification of radiographically proven constipation in children. *Wis Med J* 2001;100:33–6.
25. Reuchlin-Vroklage L, Bierma-Zeinstra SMA, Benninga MA, et al. Diagnostic value of abdominal radiography in constipated children: a systematic review. *Arch Pediatr Adolesc Med* 2005;159:671–8.
26. Barr RG, Levine MD, Wilkinson RH, et al. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. *Clin Pediatr (Phila)* 1979;18:676–9.
27. Benninga MA, Büller HA, Staalman CR, et al. Defaecation disorders in children, colonic transit time versus the Barr-score. *Eur J Pediatr* 1995;154:277–84.

28. Leech SC, McHugh K, Sullivan PB. Evaluation of a method of assessing faecal loading on plain abdominal radiographs in children. *Pediatr Radiol* 1999;29:255–8.
29. de Lorijn F, van Rijn RR, Heijmans J, et al. The Leech method for diagnosing constipation: intra- and interobserver variability and accuracy. *Pediatr Radiol* 2006;36:43–9.
30. Çayan S, Doruk E, Bozlu M, et al. The assessment of constipation in monosymptomatic primary nocturnal enuresis. *Int Urol Nephrol* 2001;33:513–6.
31. Blethyn AJ, Verrier Jones K, Newcombe R, et al. Radiological assessment of constipation. *Arch Dis Child* 1995;73:532–3.
32. Jackson CR, Lee RE, Wylie AB, et al. Diagnostic accuracy of the Barr and Blethyn radiological scoring systems for childhood constipation assessed using colonic transit time as the gold standard. *Pediatr Radiol* 2009;39:664–7.
33. Gutiérrez C, Marco A, Nogales A, et al. Total and segmental colonic transit time and anorectal manometry in children with chronic idiopathic constipation. *J Pediatr Gastroenterol Nutr* 2002;35:31–8.
34. Zaslavsky C, da Silveira TR, Maguilnik J. Total and segmental colonic transit time with radio-opaque markers in adolescents with functional constipation. *J Pediatr Gastroenterol Nutr* 1998;27:138–42.
35. Bijoš A, Czerwionka-Szafarska M, Mazur A, et al. The usefulness of ultrasound examination of the bowel as a method of assessment of functional chronic constipation in children. *Pediatr Radiol* 2007;37:1247–52.
36. Singh SJ, Gibbons NJ, Vincenta MV, et al. Use of pelvic ultrasound in the diagnosis of megarectum in children with constipation. *J Pediatr Surg* 2005;40:1941–4.
37. Joensson IM, Siggaard C, Rittig S, et al. Transabdominal ultrasound of rectum as a diagnostic tool in childhood constipation. *J Urol* 2008;179:1997–2002.
38. Klijn AJ, Asselman M, Vijverberg MA, et al. The diameter of the rectum on ultrasonography as a diagnostic tool for constipation in children with dysfunctional voiding. *J Urol* 2004;172:1986–8.
39. Iacono G, Carroccio A, Cavataio FA, et al. Chronic constipation as a symptom of cow milk allergy. *J Pediatr* 1995;126:34–9.
40. Iacono G, Cavataio F, Montalto G, et al. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med* 1998;339:1100–4.
41. Simeone D, Miele E, Boccia G, et al. Prevalence of atopy in children with chronic constipation. *Arch Dis Child* 2008;93:1044–7.
42. El-Hodhod MA, Younis NT, Zaitoun YA, et al. Cow's milk allergy related pediatric constipation: appropriate time of milk tolerance. *Pediatr Allergy Immunol* 2010;21:e407–12.
43. Irastorza I, Ibañez B, Delgado-Sanzonetti L, et al. Cow's-milk-free diet as a therapeutic option in childhood chronic constipation. *J Pediatr Gastroenterol Nutr* 2010;51:171–6.
44. Ciamarra P, Nurko S, Barksdale E, et al. Internal anal sphincter achalasia in children: clinical characteristics and treatment with *Clostridium botulinum* toxin. *J Pediatr Gastroenterol Nutr* 2003;37:315–9.
45. Chumpitazi BP, Fishman SJ, Nurko S. Long-term clinical outcome after botulinum toxin injection in children with nonrelaxing internal anal sphincter. *Am J Gastroenterol* 2009;104:976–83.
46. Reid JR, Buonomo C, Moreira C, et al. The barium enema in constipation: comparison with rectal manometry and biopsy to exclude Hirschsprung's disease after the neonatal period. *Pediatr Radiol* 2000;30:681–4.
47. Rodriguez L, Nurko S, Flores A. Factors associated with successful decrease and discontinuation of antegrade continence enemas (ACE) in children with defecation disorders: a study evaluating the effect of ACE on colon motility. *Neurogastroenterol Motil* 2013;25:140–81.
48. van den Berg MM, Hogan M, Caniano DA, et al. Colonic manometry as predictor of cecostomy success in children with defecation disorders. *J Pediatr Surg* 2006;41:730–6.
49. Pensabene L, Youssef NN, Griffiths JM, et al. Colonic manometry in children with defecatory disorders. role in diagnosis and management. *Am J Gastroenterol* 2003;98:1052–7.
50. Bekkali NL, Hagebeuk EE, Bongers ME, et al. Magnetic resonance imaging of the lumbosacral spine in children with chronic constipation or non-retentive fecal incontinence: a prospective study. *J Pediatr* 2010;156:461–5.
51. Rosen R, Buonomo C, Andrade R, et al. Incidence of spinal cord lesions in patients with intractable constipation. *J Pediatr* 2004;145:409–11.
52. King SK, Sutcliffe JR, Ong SY, et al. Substance P and vasoactive intestinal peptide are reduced in right transverse colon in pediatric slow-transit constipation. *Neurogastroenterol Motil* 2010;22:883–92.
53. van den Berg MM, Di Lorenzo C, Mousa HM, et al. Morphological changes of the enteric nervous system, interstitial cells of cajal, and smooth muscle in children with colonic motility disorders. *J Pediatr Gastroenterol Nutr* 2009;48:22–9.
54. Giorgio V, Borrelli O, Smith VV, et al. High-resolution colonic manometry accurately predicts colonic neuromuscular pathological phenotype in pediatric slow transit constipation. *Neurogastroenterol Motil* 2013;25:70–9.
55. Southwell BR, Clarke MC, Sutcliffe J, et al. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. *Pediatr Surg Int* 2009;25:559–72.
56. Pijpers MA, Tabbers MM, Benninga MA, et al. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. *Arch Dis Child* 2009;94:117–31.
57. Tabbers MM, Boluyt N, Berger MY, et al. Nonpharmacologic treatments for childhood constipation: systematic review. *Pediatrics* 2011;128:753–61.
58. Loening-Baucke V, Miele E, Staiano A. Fiber (glucomannan) is beneficial in the treatment of childhood constipation. *Pediatrics* 2004;113:e259–64.
59. Castillejo G, Bullo M, Anguera A, et al. A controlled, randomized, double-blind trial to evaluate the effect of a supplement of cocoa husk that is rich in dietary fiber on colonic transit in constipated pediatric patients. *Pediatrics* 2006;118:e641–8.
60. Kokke FT, Scholtens PA, Alles MS, et al. A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial. *J Pediatr Gastroenterol Nutr* 2008;47:592–7.
61. Chmielewska A, Horvath A, Dziechciarz P, et al. Glucomannan is not effective for the treatment of functional constipation in children: a double-blind, placebo-controlled, randomized trial. *Clin Nutr* 2011;30:462–8.
62. Üstündağ G, Kuloğlu Z, Kirbaş N, et al. Can partially hydrolyzed guar gum be an alternative to lactulose in treatment of childhood constipation? *Turk J Gastroenterol* 2010;21:360–4.
63. Young RJ, Beerman LE, Vanderhoof JA. Increasing oral fluid in chronic constipation in children. *Gastroenterol Nurs* 1998;21:156–61.
64. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. *World J Gastroenterol* 2010;16:69–75.
65. Guerra PV, Lima LN, Souza TC, et al. Pediatric functional constipation treatment with Bifidobacterium-containing yogurt: a crossover, double-blind, controlled trial. *World J Gastroenterol* 2011;17:3916–21.
66. Coccorullo P, Strisciuglio C, Martinelli M, et al. *Lactobacillus reuteri* (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized placebo-controlled study. *J Pediatr* 2010;157:598–602.
67. Tabbers MM, Chmielewska A, Roseboom MG, et al. Fermented milk containing Bifidobacterium lactis DN-173 010 in childhood constipation: a randomized, double-blind, controlled trial. *Pediatrics* 2011;127:e1392–9.
68. Brazzelli M, Griffiths PV, Cody JD, et al. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev* 2011; CD002240.
69. van Dijk M, Bongers ME, de Vries GJ, et al. Behavioral therapy for childhood constipation: a randomized, controlled trial. *Pediatrics* 2008;121:e1334–41.
70. Price KJ, Elliott TM. What is the role of stimulant laxatives in the management of childhood constipation and soiling? *Cochrane Database Syst Rev* 2001; CD002040.
71. Lee-Robichaud H, Thomas K, Morgan J, et al. Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database Syst Rev* 2010; CD007570.

72. Candy D, Belsey J. Macrogol (polyethylene glycol) laxatives in children with functional constipation and faecal impaction: a systematic review. *Arch Dis Child* 2009;94:156–60.
73. Dupont C, Leluyer B, Maamri N, et al. Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. *J Pediatr Gastroenterol Nutr* 2005;41:625–33.
74. Wang BX, Wang MG, Jiang MZ, et al. Forlax in the treatment of childhood constipation: a randomized, controlled, multicenter clinical study. *Zhongguo Dang Dai Er Ke Za Zhi* 2007;9:429–32.
75. Candy D, Edwards D, Geraint M. Treatment of faecal impaction with polyethylene glycol plus electrolytes (PGE+E) followed by a double-blind comparison of PEG+E versus lactulose as maintenance therapy. *J Pediatr Gastroenterol Nutr* 2006;43:65–70.
76. Gremse DA, Hixon J, Crutchfield A. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. *Clin Pediatr* 2002;41:225–9.
77. Voskuijl W, de LF, Verwijs W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut* 2004;53:1590–4.
78. Thomson MA, Jenkins HR, Bisset WM, et al. Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study. *Arch Dis Child* 2007;92:96–1000.
79. Nurko S, Youssef NN, Sabri M, et al. PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial. *J Pediatr* 2008;153:254–61.
80. Urganci N, Akyildiz B, Polat TB. A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation. *Pediatr Int* 2005;47:15–9.
81. Tolia V, Lin CH, Elitsur Y. A prospective randomized study with mineral oil and oral lavage solution for treatment of fecal impaction in children. *Aliment Pharmacol Ther* 1993;7:523–9.
82. Rafati M, Karami H, Salehifar E, et al. Clinical efficacy and safety of polyethylene glycol 3350 versus liquid paraffin in the treatment of pediatric functional constipation. *Daru* 2011;19:154–8.
83. Loening-Baucke V, Pashankar DS. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. *Pediatrics* 2006;118:528–35.
84. Ratanamongkol P, Lertmaharit S, Jongpiputvanich S. Polyethylene glycol without electrolytes versus milk of magnesia for the treatment of functional constipation in infants and young children: a randomized controlled trial. *Asian Biomedicine* 2009;4:391–9.
85. Bekkali NL, van den Berg MM, Dijkgraaf MG, et al. Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics* 2009;124:e1108–15.
86. Bongers ME, van den Berg MM, Reitsma JB, et al. A randomized controlled trial of enemas in combination with oral laxative therapy for children with chronic constipation. *Clin Gastroenterol Hepatol* 2009;7:1069–74.
87. Mugie SM, Machado RS, Mousa HM, et al. Ten-year experience using antegrade enemas in children. *J Pediatr* 2012;161:700–4.
88. Siddiqui AA, Fishman SJ, Bauer SB, et al. Long-term follow-up of patients after antegrade continence enema procedure. *J Pediatr Gastroenterol Nutr* 2011;52:574–80.
89. Ok J-h, Kurzrock EA. Objective measurement of quality of life changes after ACE Malone using the FICQOL survey. *J Pediatr Urol* 2011;7:389–93.
90. Hoekstra LT, Kuijper CF, Bakx R, et al. The Malone antegrade continence enema procedure: the Amsterdam experience. *J Pediatr Surg* 2011;46:1603–8.
91. King SK, Sutcliffe JR, Southwell BR, et al. The antegrade continence enema successfully treats idiopathic slow-transit constipation. *J Pediatr Surg* 2005;40:1935–40.
92. Cascio S, Flett ME, De la Hunt M, et al. MACE or caecostomy button for idiopathic constipation in children: a comparison of complications and outcomes. *Pediatr Surg Int* 2004;20:484–7.
93. van Wunnik BP, Baeten CG, Southwell BR. Neuromodulation for constipation: sacral and transcutaneous stimulation. *Best Pract Res Clin Gastroenterol* 2011;25:181–91.
94. Clarke MC, Chase JW, Gibb S, et al. Improvement of quality of life in children with slow transit constipation after treatment with transcutaneous electrical stimulation. *J Pediatr Surg* 2009;44:1268–72.
95. Clarke MC, Chase JW, Gibb S, et al. Decreased colonic transit time after transcutaneous interferential electrical stimulation in children with slow transit constipation. *J Pediatr Surg* 2009;44:408–12.
96. Pijpers M, Bongers M, Benninga M, et al. Functional constipation in children: a systematic review on prognosis and predictive factors. *J Pediatr Gastroenterol Nutr* 2010;50:256–68.
97. Bongers MEJ, van Wijk MP, Reitsma JB, et al. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. *Pediatrics* 2010;126:e156–62.
98. Borowitz SM, Cox DJ, Kovatchev B, et al. Treatment of childhood constipation by primary care physicians: efficacy and predictors of outcome. *Pediatrics* 2005;115:873–7.
99. Loening-Baucke VA. Factors responsible for persistence of childhood constipation. *J Pediatr Gastroenterol Nutr* 1987;6:915–22.
100. Loening-Baucke V. Factors determining outcome in children with chronic constipation and fecal soiling. *Gut* 1989;30:999–1006.
101. Loening-Baucke V. Constipation in early childhood: patient characteristics, treatment and longterm follow-up. *Gut* 1993;34:1400–4.
102. Staiano A, Andreotti MR, Greco L, et al. Long term follow up of children with chronic idiopathic constipation. *Dig Dis Sci* 1994;39:561–4.
103. Loening-Baucke V. Balloon defecation as a predictor of outcome in children with functional constipation and encopresis. *J Pediatr* 1996;128:336–40.
104. Elshimy N, Gallagher B, West D, et al. Outcome in children under 5 years of age with constipation: a prospective follow-up study. *Int J Clin Pract* 2000;54:25–7.
105. Van Ginkel R, Reitsma JB, Büller HA, et al. Childhood constipation: longitudinal follow up beyond puberty. *Gastroenterology* 2003;125:357–63.
106. de Lorijn F, van Wijk MP, Reitsma JB, et al. Prognosis of constipation: clinical factors and colonic transit time. *Arch Dis Child* 2004;89:723–7.
107. Polanco I, Abarca L, García-Sicilia J, et al. Longitudinal study of constipation symptoms and dietetic habits in children. FREI study. *Pediatr* 2004;24:9–16.
108. Miele E, Simeone D, Marino A, et al. Functional gastrointestinal disorders in children: an Italian prospective survey. *Pediatrics* 2004;114:73–8.
109. van den Berg MM, van Rossum CH, de Lorijn F, et al. Functional constipation in infants: a follow-up study. *J Pediatr* 2005;147:700–4.
110. Martinez-Costa C, Palao-Ortuño MJ, Alfaro Ponce B, et al. Functional constipation: prospective study and treatment response. *An Pediatr* 2005;63:418–25.
111. Banaszkiewicz A, Bibik A, Szajewska H. Functional constipation in children: a follow up study. *Pediatr Wspol* 2006;8:21–3.