CHRONIC IDIOPATHIC CONSTIPATION IN CHILDREN GUIDELINE

Appendix J - EVIDENCE TABLES

Key Components of the History Taking and the Physical Examination in Children with chronic constipation

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Borowitz et al. Precipitants of constipation during early childhood. 2003. Journal of the American Board of Family Practice 16[3], 213-218United States. Borowitz, 2003	Study type: Case-control Evidence level: III Study aim: To determine the precipitants to constipation in early childhood	220 children Inclusion criteria: Aged 2y 0m to 6y 11m, at least average intelligence - patients: First time presentation to physician with constipation - controls: no history of constipation Exclusion criteria: Underlying medical condition, medication that could account for constipation	220 children -Patients n=125 mean age (months): 44±13 49% male -Controls n=95 mean age (months): 46±18 54% male Country: USA Setting: 26 primary care facilities (15 paediatricians, 11 family medicine centres)	Test History of events occurring in the 3 months prior to onset of constipation: -large/painful bowel movement -toilet training -started day care -travelling -liquid to solid foods -breast to bottle -family move -vomiting /dehydration -new medication -parental separation -birth of a sibling -tent camping -high fever -surgery -extended bed rest -trauma in	Degree of difficulty with toilet training (mean ± SD) (0=none, 4=extreme) Patients: 2.1±1.3 Controls: 1.4±1.1 p<0.001 Degree of difficulty passing some bowel movements (% children) None: patients 3 , controls 49 Mild: patients 86, controls 49 Moderate: patients 80, controls 10 Extreme: patients 76, controls 5 p<0.001 (patients as compared to controls in each category) Degree of pain passing some bowel movements (% children) None: patients 5, controls 56 Mild: patients 82, controls 40	Additional information from study Constipation defined as passage of < 3 bowel movements each week for at least 2 consecutive weeks 22 non-patient siblings matched as controls, an additional 73 non-sibling controls recruited from advertisements Likert scale: 0 to 4. 0 being not at all difficult and 4 being extremely difficult Questionnaire for parents to fill out describing children's bowel habits. - indication of how difficult toilet training had been for bowel movements using Likert scale - parents to indicate if any of 18 different events occurred in the 3 months preceding the onset of constipation, and which of these they believed contributed to the onset of constipation Both groups comparable regarding age and sex

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				bathroom -sexual abuse -family death <u>Reference Standard</u> None	Moderate: patients 69, controls 8 Severe: patients 67, controls 6 p<0.001 (patients as compared to controls in each category) <u>Children expressing worry about passing bowel movements (% children)</u> Patients: 75 Controls: 8 p<.001 -Family history of constipation and initial age of toilet training no significantly different between the 2 groups -Subgroup analysis: children grouped according to whether they became constipated before or after their second birthday. The events parents reported having occurred in the 3 months before the onset of constipation were similar in the two groups, with the exception of toilet training having occurred more often before constipation in the older children (40% vs. 20%), and making the dietary transition from breast to bottle and from liquid to solid diets having occurred more often before	<u>Reviewer comments</u> Potential recall bias <u>Source of funding:</u> NIH grant RO1HD 28160

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					constipation in the younger children (30% vs. 0). Large or painful bowel movements were seen by far the most frequent precipitating event for both age groups. Toilet training was seen as more of a precipitant for older onset children (20% vs. 10%), whereas transition from breast to bottle and from liquid to solid foods was seen to be more of a problem for younger-onset children (25% vs. 0)	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Freedman et al. The crying infant: Diagnostic testing and frequency of serious underlying disease. 2009. Pediatrics 123[3], 841-848United States. Freedman, 2009	Study type: Retrospective case series Evidence level: III Study aim: To determine the proportion of children evaluated in an emergency department because of crying who have a serious underlying aetiology	238 patients Inclusion criteria: - less than 12 months age - afebrile - presenting to ED during 9 month eligibility period with chief complaint of crying Exclusion criteria: Not stated	238 patients Males 124 (52%) Median age 2.3 months (range 1.0 to 5.4) Country: Canada Setting: Tertiary care referral hospital	Tests Abdominal radiograph Abdominal ultrasound Reference Standard History taking and physical examination	-Positive findings on history and/or physical examination alone suggested the final diagnosis in 66.4% (158 of 238) of the crying children -11 cases of constipation were diagnosed, all diagnosed by category 1 data source – positive history and physical examination only Constipation defined as history of difficult, infrequent, hard stools, palpation of small pellets on abdominal examination Abdominal radiograph – performed 14 times with 0 positive findings Abdominal ultrasound – performed 16 times with positive findings 2 times (12.5%) contributing only to the diagnosis of intussusception and acute cholecystitis, but not constipation -History and examination were found to be the most important aspect in the evaluation of the crying infant. Investigations only helpful in 3% of sample in this study	Additional information from study Patients presenting with chief complaint of crying identified retrospectively by searching electronic database using a chief complaint family word root search for: “cry”, “irritable”, “fuss”, “scream” and “colic”. Afebrile defined as < 38°C 37,549 ED visits during 9 month eligibility period, of which 238 children met inclusion criteria Patients and their final diagnoses grouped into 1 - 4 categories according to the sources of data that contributed the diagnosis Data source categories: 1) Diagnosis was based on the history (Hx) and/or physical examination (PE) alone 2) Diagnosis was based on positive test results obtained after the Hx and PE failed to suggest a cause 3) Diagnosis was based on tests ordered to investigate positive findings from the Hx and/or PE that suggested a cause 4) Neither Hx, PE nor investigations were diagnostic Required sample size calculated to yield stable estimates (±5%) of the primary outcome measure (proportion of infants who had potentially serious underlying aetiology). Estimated that 10% sample would have underlying serious aetiologies. Minimum sample of 138 subjects required. Anticipated

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						follow-up telephone call response rate of only 75%. Final size after adjustment:: 245 <u>Reviewer comments</u> No data on follow up care of accuracy of constipation cases Minimum sample size required not achieved <u>Source of funding:</u> Not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Lewis et al. Diagnosing Hirschsprung's disease: increasing the odds of a positive rectal biopsy result. 2003. Journal of Pediatric Surgery 38[3], 412-416 Lewis et al., 2003	Study type: Retrospective cohort Evidence level: III Study aim: To test the hypothesis that key features in the history, physical examination and radiographic evaluation would allow to avoid unnecessary rectal biopsies	315 children Inclusion criteria: -Cohort 1: Children presenting with constipation to diagnose Hirschsprung's disease (HD) -Cohort 2: idiopathic constipation Exclusion criteria: Patients undergoing re-evaluation fro constipation after pull-through procedure for HD	315 children: -265 children who hade undergone rectal biopsy -50 children, concurrent selected cohort (cohort 2) Country: USA	Tests: Rectal biopsy	Clinical features in children with Hirschsprung's disease and idiopathic constipation (IC, n=40) -Onset of constipation <1 year old Delayed passage of meconium (%) HD: 65 IC: 13 P< 0.05 Abdominal distension (%) HD: 80 IC: 42 P< 0.05 Vomiting (%) HD: 72 IC: 21 P< 0.05 Faecal impaction requiring manual evacuation (%) HD: 6 IC: 30 P< 0.05 Enterocolitis (%) HD: 13 IC: 15 NS -Onset of constipation >1 year old Delayed passage of meconium (%)	Additional information from study Questionnaires, telephone interviews and patients visits used to compile long-term data. In reporting features listed in the questionnaire only patients with definite information were included: the number of patients in each analysis varies to exclude those with missing data Delayed passage of meconium defined as failure to pass meconium in the first 48h of life. These data were available in 59% of cases Abdominal distension determined from parental response to questionnaire or data noted during patients visits Enterocolitis defined as diarrhoea associated with fever Reviewer comments: Data on clinical features not available for all children Unclear what kind of rectal biopsy was performed and how the diagnosis of HD was made Source of funding: Not stated

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					HD: 81 IC: 1 P< 0.05 Abdominal distension (%) HD: 53 IC: 7 P< 0.05 Vomiting (%) HD: 23 IC: 0 P< 0.05 Faecal impaction requiring manual evacuation (%) HD: 46 IC: 30 NS Enterocolitis (%) HD: 13 IC: 14 NS <u>Age at onset of symptoms</u> -Hirschsprung's (HD) (n=46) Mean: 8 months (range 1 day to 9 years) 1rst week of life: 60 % 1rst month of life: 70% 1rst year of life: 87% after 1 year of life: 13% -Idiopathic constipation (IC) (n=40) Mean: 15 months (range 7 days to 16 years)	

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					1rst week of life: 15% 1rst month of life: 55% 1rst year of life: 68% after 1 year of life: 32% At least 34% of HD patients had the classic triad (delayed passage of meconium + vomiting + abdominal distension). At least 1 feature of the triad noted in 98% of patients with HD. Only 60% of patients with IC had a history of delayed passage of meconium, vomiting or abdominal distension. 100 % HD patients vs. 64% IC patients had 1 or more of the following: delayed passage of meconium, vomiting, abdominal distension and a transition zone on contrast enema. 36% of IC patients had none of these features.	

Diagnostic Value of the Digital Rectal Examination (DRE) Children with Chronic Idiopathic Constipation

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Beckmann et al. Accuracy of clinical variables in the identification of radiographically proven constipation in children. 2001. Wisconsin Medical Journal 100[1], 33-36United States.	Study type: Prospective case series Evidence level: III Study aim: to determine whether clinical variables accurately identify children with radiologically proven constipation	251 children Inclusion criteria: Children aged 2-12 years old who presented to the Emergency Department (ED) of Children's Hospital of Wisconsin with abdominal pain and underwent radiographic evaluation. Exclusion criteria: previous abdominal surgery, known abdominal pathology, menarche or sickle cell disease Setting: hospital	Group 1: 141 children with radiologically proven constipation Age: 7.9 +-3.1 years 63 (25%) male Group 2: 110 children with no radiographic evidence of constipation Age: 7.4 +-3.0 years 57 (23%) male Country: USA	Test: Clinical variables -History of gastrointestinal problems -Duration of abdominal pain -Stool habits -Straining on defecation -Faecal consistency (normal/hard stools) -Medication -Physical exam: rebound, rigidity, guarding, tympanic/distended -Physical exam-tenderness: diffuse, each of four quadrants, flank, epigastric, periumbilical -Physical exam: bowel sounds, rectal exam Clinical examination (including rectal exam) performed by	Clinical variables (as a model) Sensitivity: 77% (+) Specificity: 35% (-) PPV 60% NPV: 55% Only the following clinical variables were significantly different between the two groups: History of normal/hard stool consistency: Group 1: 74% (100/135) Group 2: 61% (61/99) p: 0.016 Absence of rebound tenderness Group 1: 98% (138/141) Group 2: 90% (99/110) p: 0.007 Presence of left lower quadrant tenderness:	Abdominal radiograph was either a single flatplate or a flatplate with upright view, ordered by the ED attending physician based on customary practices. The ED physicians ordering the radiographs were blinded to study objectives 32% of the enrolled subjects did not undergo rectal exam A clinical diagnose previous to radiology was made and reported. However it was not clear how many of the clinical variables needed to be present to diagnose constipation. Furthermore, the physical exam was completed by one of several paediatric ED physicians and no assessment of inter-rater reliability was performed. Official radiologic diagnosis was provided by a single board certified paediatric radiologist blinded to the study. This was compared with the ED physician interpretation of the radiograph and the patients were divided into the two groups, but it is not clear on the basis of what this decision was made. A data sheet with demographic-clinical

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		Emergency Department		the ED physician <u>Reference test:</u> Abdominal radiograph <u>Radiological diagnose of constipation (based on faecal loading score originated and validated by Barr et al and later revised by Blethyn et al)</u> -Normal, grade 0: faeces in rectum and cecum only -Grade 1, mild constipation: faeces in rectum, cecum and discontinuous elsewhere -Grade 2, moderate constipation: faeces in rectum, cecum with continuous faeces affecting all segments but allowing for gas -Grade 3, severe constipation: continuous faeces with dilated colon and rectal impaction	Group 1: 20% (19/96) Group 2: 9% (6/69) p: 0.0499 <u>Stool present in rectal vault as per rectal exam:</u> Group 1: 69% (70/102) Group 2: 43% (29/68) p: 0.008	data was required before an abdominal radiograph was ordered, but in 159 patients no data-sheet was submitted for various reasons. These patients were excluded from the study and the lack of data makes impossible to tell whether they differed from the group of included patients <u>Source of funding:</u> Not reported

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Rockney et al. The plain abdominal roentgenogram in the management of encopresis. 1995. Archives of Pediatrics and Adolescent Medicine 149[6], 623-627	Study type: Retrospective case series Evidence level: III Study aim: to determine whether faecal retention in encopretic children can be assessed objectively using the plain abdominal roentgenogram and whether roentgenographic evidence of faecal retention is associated with clinical findings on presentation in encopretic children	60 encopretic children Inclusion/ exclusion criteria Encopresis as defined by the DSM Revised Third Edition: "repeated involuntary (or, much more rarely, intentional) passage of faeces into places not appropriate for that purpose (e.g., clothing or floor)…the event must occur at least once a month for at least 6 months, the chronological and mental age of the child must be at least 4 years, and physical disorders that can cause faecal incontinence, such as	Age: 4-11 years old Group 1 47 encopretic children with faecal retention by roentgenogram criteria on presentation Male sex: 74.5% Group 2 13 encopretic children without faecal retention by roentgenogram criteria on presentation Male sex: 61.5 % Country: USA	Test: Rectal examination Reference test: Plain abdominal roentgenogram Three radiologists, two paediatric and one general, at three separate institutions, blind to the identity of the subjects evaluated the plain abdominal Rx twice: a "subjective" reading assessed faecal content as markedly excessive, moderately excessive or normal and a "systematic" reading where a stool retention rating record was completed and a score assigned (0-25) reflecting the severity of faecal retention (score of 10 or greater indicates faecal retention, scale validated by Barr et al.) Final results were taken from the systematic reading	Values for rectal examination: a) When the diagnosis of retention by abdominal RX, systematic reading was agreed by at least two radiologists: (%) Sensitivity: 88.6 Specificity: 41.6 Positive predictive value: 84.8 Negative predictive value: 50 b) When the diagnosis of retention by abdominal RX, systematic reading was agreed by the three radiologists: (%) Sensitivity: 91.7 Specificity: 71.4 Positive predictive value: 94.3 Negative predictive value: 62.5 Not all data were available for every subject	78 encopretic children originally enrolled but only 60 children for whom Rx could be retrieved were included in analysis. There were no significant differences between encopretic children whose abdominal Rx were reviewed for the study and those who did not have a Rx or whose Rx could not be retrieved. There were no significant differences in patients' characteristics at the two sites. Not all data were available for every subject Children with retention (as per Rx) were significantly more likely to have stool in the rectum on presentation (p 0.015) and were significantly less likely to have parents report a difficult toilet training (p 0.018). There were no other significant differences between the two groups regarding the rest of the variables measured. Each patient's medical record was reviewed separately by one of the authors and a research assistant. When discrepancies existed charts were reviewed again conjointly and discrepancies resolved for both reviewers' satisfaction. The reliability of the radiologists' assessments was tested by two different procedures. Overall agreement among the three radiologists was 77.8% for the subjective assessment, k=0.53 (z=7.04,

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		aganglionic megacolon, must be ruled out" Children younger than 4 years old and children who had a soiling frequency of less than once a month or who had recently stopped soiling were excluded <u>Setting:</u> two paediatric incontinence clinics, one located in the ambulatory care facility of a tertiary care hospital and the other at a community hospital		only. At least two radiologists had to agree in order to classify roentgenograms either as in the retention or nonretention category Presence of stool in rectal examination was recorded in the patient records as "none", "small", "moderate" or "large" amount. Patients with moderate or large amounts of stool on rectal examination were classified as having stool in the rectum for subsequent analysis. The specific professional qualification of the person who performed the rectal examination was not reported		p<0.0001). Agreement using the systematic assessment was 87.4%, k=0.65 (z=7.2, p<0.0001). There were no differences in interrater reliabilities between pairs of radiologists. The study from which the systematic scoring system was derived has not been replicated, and the cut-off point of 10, might not be valid for all populations <u>Source of funding:</u> Primary Care Faculty Development Fellowship Programme at Michigan State University, East Lansing.

Prevalence of Coeliac Disease and Hypothyroidism in children with Chronic Idiopathic Constipation

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comment
Bonamico et al. Prevalence and clinical picture of celiac disease in Italian down syndrome patients: A multicenter study. 2001. Journal of Pediatric Gastroenterology and Nutrition 33[2], 139-143United States.	Study type: Prospective cohort Evidence level: 2+ Study aim: To estimate the prevalence of coeliac disease (CD) in patients with Down syndrome and to define the clinical characteristics of CD among Down Syndrome patients	1202 patients Inclusion criteria: Down's syndrome Exclusion criteria: IgA deficiency Setting: Community	1202 patients 609 males 1110 children age range: 15 months to 18 years 92 adults age range 18 to 46 years Country: Italy -Group 1: 55 CD patients diagnosed by ESPGHAN Criteria (36 males, aged 4 to 46 years) -Group 2: 55 IgA AGA-positive EMA negative DS patients (33 males, aged 3 to 40 years) -Group 3: 57 IgA AGA-negative EMA-negative DS patients (34 males,	Tests: -Coeliac disease: Revised European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria Patients selected for intestinal biopsy on the basis of EMA positivity, AGA IgA positivity, or both in children < 2 years of age (AGA: antigliadin antibodies; EMA: antiendomysium antibodies; IgA: immunoglobulin A) -Down syndrome: confirmed by cariotype in all cases	Signs/symptoms (%): -Group 1 (n=55): Growth failure 52.7 Diarrhoea 41.8 Vomiting 20 Anorexia 18.2 Constipation 29.1 Distended abdomen 23.6 -Group 2 (n=55): Growth failure 10.9 Diarrhoea 1.8 Vomiting 1.8 Anorexia 1.8 Constipation 14.5 Distended abdomen 14.5 -Group 3 (n=57): Growth failure 7 $P < 0.001$ Diarrhoea 6.9 $P < 0.001$ Vomiting 1.7 $P < 0.001$ Anorexia 3.4 $P < 0.01$ Constipation 8.8 $P < 0.05$	Additional information from study Levels of IgA AGA were measured by enzymelinked immunosorbent assay by the Alfa-gliatest (Eurospital, Trieste, Italy). Levels of EMA IgA were evaluated by an indirect immunofluorescence method (Eurospital, Trieste, Italy). Sections from the distal portion of monkey oesophagus were used as a substrate, and fluorescein-labeled goat antihuman IgA antibody was used as the second antibody. The patients' serum was diluted 1:5 in phosphate buffer at pH 7.2. The presence of a brilliant green network pattern under a fluorescence microscope was taken as a positive result. Intestinal biopsies performed by Watson capsule or by paediatric or adult endoscopes Patients selected for intestinal biopsy on the basis of both EMA positivity and AGA IgA positivity in children < 2 years of age, because in this age group, EMA positivity may have a false-negative result A detailed questionnaire was completed to obtain information about familial gastroenterologic history with special attention to feeding habits (breast milk

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comment
			aged 4 to 38 years)		Distended abdomen 15.5 NS P values are the results of comparing group 1 vs. group 2 and group 3	or formula, age of introduction of gluten-containing foods); gastrointestinal function, particularly the features of CD, such as chronic diarrhoea, vomiting, failure to thrive, and anorexia; presence of autoimmune or neoplastic conditions All patients were receiving a gluten-containing diet. Weight and height were evaluated using Down syndrome percentile charts (DSPC) The clinical features of 55 CD patients diagnosed by ESPGHAN Criteria (group 1) were compared with those observed in 55 IgA AGA-positive EMA negative DS patients (group 2) and in 57 IgA AGA-negative EMA-negative DS patients (group 3). Group 2 and group 3 patients were selected randomly from among the screened patients to be age and gender matched to group 1. 18 symptomatic patients belonging to group 2 underwent intestinal biopsy and showed normal small bowel mucosa Parents of 8 EMA positive children and 2 EMA-positive adults did not give permission for intestinal biopsy to be performed and were not included among the 55 CD patients <u>Reviewer comments:</u> It is unclear whether some patients had EMA and others had AGA IgA measured alternatively, or whether all patients had both EMA and AGA IgA

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						measured at the same. This considered it is also unclear why only IgA AGA-positive EMA-negative patients and IgA AGA-negative EMA-negative patients were chosen as control groups and there is no mention of the EMA-positive IgA AGA-negative group <u>Source of funding:</u> Not stated

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comment
Bingley et al. Undiagnosed coeliac disease at age seven: Population based prospective birth cohort study. 2004. British Medical Journal 328[7435], 322-323United Kingdom.	Study type: Prospective cohort Evidence level: 2+ Study aim: to establish the prevalence of undiagnosed coeliac disease in the general population at age seven and to look for any associated clinical features	5470 children Inclusion criteria: Children aged 7.5 years participating In the Avon Longitudinal Study of Parents and Children (ALPASC), a population based birth cohort study established in 1990 Exclusion criteria: Not stated Setting: Community	5470 children age: 7.5 years gender not reported Country: UK	Tests: -Coeliac disease: Two stage screening: 1. Sensitive initial radioimmunoassay for antibodies to tissue transglutaminase (endomysial antigen) (tTG antibodies) 2. If positive to previous, serum IgA antiendomysial antibodies (IgA-EMA) by indirect inmunofluorescence -Constipation: Clinical variables	Any constipation reported at age 6.75 years (No, %): -tTG antibody negative controls (n=4285 questionnaires): 435 (10) -IgA-EMA positive (n=42 questionnaires): 6 (14) odds ratio (95% CI): 1.48 (0.62 to 3.52) Other symptoms reported at age 6.75 years (No, %): -tTG antibody negative controls (n=4285 questionnaires): any diarrhoea: 1450 (34) any vomiting: 1933 (45) any stomach pains: 2557 (60) ≥3 GI symptoms: 931 (22) -IgA-EMA positive (n=42 questionnaires): any diarrhoea: 21 (50) odds ratio (95% CI): 1.96 (1.06 to 3.59) any vomiting: 23 (55) odds ratio (95% CI): 1.47 (0.80 to 2.71) any stomach pains: 28 (66)	Additional information from study Children with tTG antibodies < 97.5th centile were defined as antibody negative Details of gastrointestinal symptoms and special diets collected by routine questionnaire at age 6.75 years Total tTG antibody negative controls (n=5333 children). Total IgA-EMA positive children (n=54) (1.0%; 95% confidence interval 0.8 to 1.4) 4324 children (79%) returned questionnaires An additional 137 children were tTG antibody positive, but Ig-EMA negative IgA-EMA were more common in girls (OR 2.12; 1.20 to 3.75). IgA-EMA positive children were shorter and weighted less than those who tested negative fro tTG antibody (p<0.0001 for all comparisons) Since ALPASC is an observational study based on analysis of anonymous samples, confirmatory biopsy was not possible Reviewer comments: Unclear how the symptom “constipation” was defined in the first place No data regarding clinical symptoms at

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					odds ratio (95% CI): 1.35 (0.71 to 2.57) ≥3 GI symptoms: 17 (40) odds ratio (95% CI): 2.45 (1.33 to 4.5)	6.75 years for 21% of the total sample <u>Sources of funding:</u> Coeliac UK, Medical Research Council, Wellcome Trust, UK government departments, and various charitable organisations and commercial companies, ALSPAC is part of the WHO initiated European Longitudinal Study on Pregnancy and Childhood

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comment
Cataldo et al. Epidemiological and clinical features in immigrant children with coeliac disease: An Italian multicentre study. 2004. Digestive and Liver Disease 36[11], 722-729United States.	Study type: Retrospective case series Evidence level: 3 Study aim: To evaluate the prevalence of immigrant children with coeliac disease (CD) in Italy, the clinical findings in these patients and the possible relationship between immigration, dietary habits and CD in childhood	1917 children Inclusion criteria: Italian and immigrant children consecutively diagnosed as having CD between January 1999 to December 2001 Exclusion criteria: Not stated Setting: Hospital (multicentre)	Total: 1917 children with CD 36 immigrant children with CD 15 males age range 6 months to 15 years (mean 7.3) 1881 Italian children 891 males age range 6 months to 16 years (mean 7.9) Country: Italy	Test: -coeliac disease: diagnosis based on the revised criteria of the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN): 1. Finding of a flat small intestinal mucosa with the features of hyperplastic villous atrophy on histological examination of a biopsy specimen, while the patient is eating adequate amounts of gluten 2. Clear cut clinical remission on a strict gluten free diet with relief of all symptoms of the disease. This response should be reasonably rapid occurring within a matter of weeks rather than many months	Clinical pattern and presenting symptoms at diagnosis (n=36) -Classical forms (25/36) (69.4%): No child with constipation reported -Atypical forms (9/36) (25%): Abdominal pain with constipation : 2/9 -Silent forms (2/36) (5.5%): No child with constipation reported	Additional information from study Classical forms not clearly defined, but included the following symptoms: chronic diarrhoea, weight loss, abdominal distension and vomit Atypical forms included: iron-deficiency anaemia, short stature, delayed puberty, recurrent oral aphtae Silent forms included: serological screening of first degree relative, loss of Kerckring folds at endoscopy Clinical patterns in Italian children were similar to those of immigrant children Reviewer comments: Unclear how the symptom “constipation” was defined in the first place Presenting symptoms at diagnosis were not reported for Italian children Source of funding: Study supported by grants of Ministero dell’Universita e della Ricerca Scientifica e Tecnologica (MURST) 60% di F.C.

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comment
				3. The finding of circulating antibodies (IgA gliadin, antireticulin, and antiendomysiun) at time of diagnosis and their disappearance when the patient is taking a gluten free diet add weight to the diagnosis		

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comment
Egan-Mitchell et al. Constipation in childhood coeliac disease. 1972. Archives of Disease in Childhood 47[252], 238-240	Study type: Retrospective case series Evidence level: 3 Study aim: To assess the incidence of constipation in coeliac disease	112 children Inclusion criteria: Coeliac disease Exclusion criteria: Not stated Setting: Regional and university hospitals	112 children 12 children with constipation: 6 males, age range 6 to 102 months Country: Ireland	Tests: -Coeliac disease 1. Clinical variables: undernutrition and retarded growth. 2. Jejunal biopsy: Grade 2/3 or grade 3 jejunal mucosal damage -Constipation: Clinical variables: passage of stools of harder consistency than normal, or the clinical observation of impaction of abnormal amounts of hard (usually pale) faeces in colon and rectum	Incidence of constipation: 12 children constipated at some stage before diagnoses: -9 of those children presented with constipation and faecal impaction, of these 5 had intermittent diarrhoea and constipation but 4 never had diarrhoea. Of these 4, 3 children presented at around 1 year of age with anorexia, failure to thrive and faecal impaction -the 3 children who did not have faecal impaction when investigated had histories of constipation alternating with mild diarrhoea and all had been given laxatives frequently for their constipation	Additional information from study Growth retardation assessed on the graphs of Tanner and Whitehouse (1959) and subsequently confirmed by catch-up growth following treatment with gluten-free diet Mucosal damage according to authors' classification (normal mucosa grade 0; mild non-specific change grade 1; grade 2 and 3 correspond to moderate and severe villous atrophy) Reviewer comments: Unclear whether authors' classification system for jejunal mucosa damage has been validated Source of funding: The main author was receiving a grant from the Medical Research Council of Ireland

Diagnostic Value of the Anorectal Manometry in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comments
Jarvi et al. Anorectal manometry with reference to operative rectal biopsy for the diagnosis/exclusion of Hirschprung's disease in children under 1 year of age. 2009. International Journal of Colorectal Disease 24[4], 451-454Germany.	Study type: Retrospective case series Evidence level: III Study aim: To report on the value of anorectal manometry (ARM) with reference to operative rectal biopsy in the diagnosis/exclusion of Hirschsprung's disease in children under 1 year of age and on the prognostic significance of a normal	81 patients Inclusion criteria: Patients under 1 year of age who presented with delayed passage of meconium, abdominal distension and vomiting or constipation who underwent ARM Exclusion criteria: Other congenital gastrointestinal malformations such as anorectal anomaly, funnel anus or gastroschisis	81 patients 49 male median age at time of ARM and biopsy: 2 months (range 0.1 to 11 months) Country: Finland	Tests: -Anorectal manometry: Performed using a 4-cm long rectal balloon inflated incrementally with 5 to 50 mL of air -Operative rectal biopsy: Taken 3 cm above the dentate in the posterior midline, consisting of a generous, longitudinal specimen extending to the submucosa	Rectoanal inhibitory reflex (RAIR) and histology results -RAIR present (N=40) HD: no children Normal histology: 39 children Hypoganglionosis: 1 child -RAIR absent (N=41) HD: 33 children Normal histology: 8 children Diagnostic variables for ARM and operative rectal biopsy in HD (%): -Biopsy: Sensitivity: 100 Specificity: 100 Positive predictive value: 100 Negative predictive value: 100 -ARM: Sensitivity: 100 Specificity: 83 Positive predictive value: 80	Additional information from study Records of all patients who met the inclusion criteria were reviewed In each case ARM was performed under ketamine anaesthesia by a consultant paediatric surgeon, and operative rectal biopsy was taken simultaneously RAIR defined as greater than 25% drop in the anal sphincter pressure for at least 5 seconds Patients who had HD were significantly younger at the time of investigation than those who did not In the case of patients diagnosed with HD histology from bowel resected at pull-through operation was consistent with pre-operative diagnosis in all cases Operative rectal biopsy was adequate and diagnostic in all cases. There was one case of rectal bleeding following biopsy which required suturing in theatre Reviewer comments:

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	RAIR in these patients				Negative predictive value: 100	Unclear how the reviewing process was conducted Unclear how the biopsy specimens were processed and analysed <u>Source of funding:</u> Not stated

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Lee et al. Allergic proctitis and abdominal distention mimicking Hirschsprung's disease in infants. 2007. Acta Paediatrica, International Journal of Paediatrics 96[12], 1784-1789United Kingdom.	Study type: Retrospective case series Evidence level: III Study aim: To evaluate the incidence and clinical aspects of allergic proctitis (AP) in patients with symptoms that mimic Hirschsprung's disease (HD). In addition authors determined the sensitivity and specificity of anorectal manometry and suction rectal biopsy used for evaluation of	105 children Inclusion criteria: Infants < 6 months of age with severe abdominal distension that mimicked HD referred to department of paediatrics and division of paediatric surgery and underwent all triple tests including barium enema, anorectal manometry and rectal suction biopsy. Some patients had associated symptoms like constipation, poor oral intake, vomiting, poor weight gain and diarrhoea Exclusion criteria: Coeliac disease and cystic fibrosis not	105 children 61 boys Mean age: 2.1 ± 0.9 months Country: Korea	Tests: -Anorectal manometry: Performed by paediatricians using a silicon rubber catheter with an array of 8 channels of sensors. Sedation with chloral hydrate for the procedure was used -Suction rectal biopsy: Taken from 4 different sites using a rectal suction biopsy tube. Biopsy sites were 3cm and 5 cm for anal verge. When ganglion cells were observed to be present with normal appearance on haematoxylin-eosin staining HD was excluded. HD was finally diagnosed with full thickness	Rectoanal inhibitory reflex (RAIR) and histology results -RAIR absent (N=48) HD: 34 Normal histology: 10 AP: 2 IND: 2 -RAIR present (N=57) HD: 5 Normal histology: 43 AP: 5 IND: 4 Diagnostic variables for ARM and rectal suction biopsy in HD (%): -Biopsy: Sensitivity: 92.31% (CI: 76.68 to 97.35) Specificity: 100 % (94.50 to 100.00) Positive predictive value 100% Negative predictive value: 95.65% -ARM: Sensitivity: 87.18% (CI: 73.29 to 94.90) Specificity: 78.79% (CI: 67.49 to 86.92)	Additional information from study Severe abdominal distension defined as an abdominal wall that protruded, was shiny and tense upon palpation Reviewer comments: Unclear how the reviewing process was conducted Unclear what was the order in which investigations were carried out Source of funding: Not stated

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	HD	considered in the differential diagnosis because are extremely rare in Korea		biopsy	Positive predictive value: 70.83% Negative predictive value: 91.23%	

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Low et al. Accuracy of anorectal manometry in the diagnosis of Hirschsprung's disease. 1989. Journal of Pediatric Gastroenterology and Nutrition 9[3], 342-346	Study type: Prospective case series Evidence level: III Study aim: To asses the accuracy of anorectal manometry in the diagnosis of Hirschsprung's disease (HD) using histological aganglionosis as the reference point for final diagnosis	50 children Inclusion criteria: Children referred consecutively to one of the authors for anorectal manometric studies Exclusion criteria: Not stated	50 children (data available for 45 children) 31 male 14 female Age range birth to 11 months Country: Singapore	Tests: -Anorectal manometry Performed as a side-room procedure. All children under 4 years of age who were unable to cooperate were tested after oral sedation with chloral hydrate -Suction rectal biopsy Suction rectal biopsies obtained without anaesthesia by paediatric surgeon on outpatient basis. Biopsies taken at 4 cms from the anal verge with a Noblet or Quinton biopsy set.	Rectoanal inhibitory reflex (RAIR) and histology results -RAIR absent (N=16) HD: 15 Normal histology: 1 -RAIR present (N= 34) HD: 4 Normal histology: 30 Diagnostic variables for ARM, total sample N=50 (%): Accuracy: 90 Sensitivity: 79 Specificity: 97 Positive predictive value: 94 Negative predictive value: 88 Diagnostic variables for ARM, neonates N=10 (%): Accuracy: 90 Sensitivity: 86 Specificity: 100 Positive predictive value: 100 Negative predictive value: 75 Diagnostic variables for ARM, infants N=18 (%): Accuracy: 94.4 Sensitivity: 90 Specificity: 100 Positive predictive value: 100	Additional information from study 5 children (10%) required repeat full-thickness biopsy for inadequate sampling All children underwent both manometry and biopsy. Biopsy specimens prepared in paraffin sections and stained with haematoxylin and eosin. Up to 60 6-µm-thick serial sections of each specimen were examined histologically by pathologist for ganglion cells and hypertrophied nerve bundles. Specimens not including the submucosal layer were considered inadequate and repeat full-thickness operative rectal biopsies were taken A normal reflex was present when rythmicity of internal sphincter contractility was totally inhibited by rectal distension accompanied by simultaneous drop in internal sphincteric pressure. Rythmicity and tone recovered when rectal distension was removed. When rythmicity and internal sphincter pressure remained virtually unchanged after rectal distension a negative response was recorded No complications encountered with manometry in all 50 children studied Reviewer comments: No definition of constipation/idiopathic constipation given

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					Negative predictive value: 89	Unclear what “infant” meant for authors <u>Source of funding:</u> Research grant (RP53/81) from the National University of Singapore, Singapore

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Kong et al. Screening Hirschsprung's disease by anorectal manometry. 1993. Chinese Journal of Gastroenterology 10[1], 29-32Taiwan, Province of China.	Study type: Retrospective case series Evidence level: III Study aim: To evaluate the possibility of using anorectal manometry (ARM) for screening Hirschsprung's disease (HD)	39 patients Inclusion criteria: Children with constipation or suspected HD Exclusion criteria: Systemic diseases like hypothyroidism or neurologic disorders	39 patients age range: 3 days to 9 years (no other details provided) Country: Taiwan	Tests: -Anorectal manometry: Double lumen stainless steel manometric probes with internal diameter of 6 mm used. Entire system closed and water filled. Multiple-channel recorder used for recording results. No previous bowel preparation. Stimulus balloon placed from 3 to 5 cm from anal verge, depending on size of patients. For uncooperative patients intramuscular injection with mixture of chlorpromazine, promethazine and meperidine with or without intravenous diazepam was given	Rectoanal inhibitory reflex (RAIR) and histology results -RAIR absent (N=18) HD: 15 Normal histology: 3 -RAIR present (N=18) HD: 0 Normal histology: 18 -RAIR inconclusive (N=3) HD: 0 Normal histology: 3 Diagnosis variables ARM (%): Accuracy: 90 Sensitivity: 100 Specificity: 86 PPV: 83 NPV: 100	Additional information from study A normal reflex (RAIR) was present when rythmicity of internal sphincter contractility was totally inhibited by rectal distension accompanied by a simultaneous drop of internal sphincteric pressure fro 5mmHg or more. A positive rectoanal response consisted of 3 successive pressure falls, each immediately following upon rectal distension by balloon. When rythmicity and internal sphincter pressure remained unchanged following rectal distension, the amount of air was increased gradually to 10 cc fro neonates and 50 cc for children. If RAIR was absent, a negative response was recorded The final diagnosis of HD was made by patient's clinical history, barium enema and rectal suction biopsy Inconclusive results with manometry due to poor tracing of internal sphincter contraction as a result of oversedation (n=2) and to anal stenosis (n=1) Reviewer comments: No definition of constipation given Insufficient details on how HD was diagnosed It is not completely clear whether or not all patients underwent rectal biopsy but it looks as this was probably the case

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				- Rectal suction biopsy (no other details provided)		The 3 children in whom manometry was inconclusive were not included in the calculation of the diagnostic variables and this introduces bias <u>Source of funding:</u> Not stated

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comments
Penninckx et al. Pitfalls and limitations of testing the rectoanal inhibitory reflex in screening for hirschsprung's disease. 1990. Pediatric Surgery International 5[4], 260-265Germany.	Study type: Prospective case series Evidence level: III Study aim: To better ascertain the traps and limitations of testing the rectoanal inhibitory reflex (RAIR), how frequently they occur and the possible explanations fro equivocal or false results	261 patients Inclusion criteria: Patients referred for anorectal manometry in order to confirm or exclude Hirschsprung's disease. All patients had presented with constipation varying from slight to intractable, with highly differing durations ranging from neonatal ileus to chronic constipation in adults Exclusion criteria: Not stated	261 patients -gender not reported for all patients -Age: < 6 months: 94 (36%) 6 month to 6 years: 106 (41%) 6 to 15 years: 47 (18%) 2 adolescents and 12 adults (5%) Country: Belgium	Tests: -Anorectal manometry No special bowel preparation given. if a considerable amount of faecal impaction was found, patients were sent back for evacuating enema (s) and reexamination planned for the next day. Children not sedated. Entire system filled with degassed water. Multiple-channel recorder used for recording results - Superficial biopsy of rectal mucosa and submucosa taken with a laryngeal biopsy forceps. Frozen section biopsies stained for acetylcholinesterase and nicotinamide adenine dinucleotide-	Rectoanal inhibitory reflex (RAIR) and histology results -RAIR equivocal result (absent?): 9 children HD: 4 Normal histology: 5 -RAIR equivocal result (present?): 8 children HD: 2 Normal histology: 6 -RAIR confident interpretation: 232 children RAIR+: 207 RAIR-: 25 Of the previous 54 children underwent either biopsy or repeated manometry. Only false results reported: -RAIR present and HD: 2 children -RAIR absent and normal histology: 4 children Incidence of false results and age of patients at first manometry	Additional information from study In no case the result of a rectal biopsy was known at the time of manometry RAIR considered to be present if the anal pressure decreased on rectal distension followed by recovery of the basal tone. RAIR was also considered to be present if the typical anal pressure waves were clearly abolished Confident interpretation of the RAIR was made in 232/261 patients (89%): RAIR present in 207 cases and absent in 25. The result of this first manometric evaluation was verified either by biopsy or by repeated manometry in 54 cases. In other cases the clinical evolution did not warrant further investigation. Manometrically the following factors prevented examiners from reaching a definite conclusion: low anal tone (n=8), restlessness of patient (n=7), reflex external sphincter contraction partially or completely masking possible RAIR (n=4), presence of megarectum (n=3), artifacts (n=1), unstable RAIR (n=6) Reviewer comments: Not all children underwent both manometry and biopsy: 261 patients underwent manometry and only 24 underwent biopsy Details of both the manometry and biopsy results were reported only in cases where the RAIR was equivocal in

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				reduced diaphorase. Aganglionosis with hypertrophic bundles was diagnostic for HD	-In <1 month old: 5/22 (22.7.8%) -In > 1 month old: 4/239 (1.7%) <u>Incidence of equivocal results and age of patients at first manometry</u> -In <1 month old: 4/22 (18.2%) -In > 1 month old: 25/239 (10.4%)	the first manometry and in those children where the result proved to be false (either negative or positive). Considering this it is not possible to calculate the sensitivity, specificity, positive and negative predictive values of the anorectal manometry The incidence of false results in manometry performed by different examiners is reported in the paper, but there are missing data not accounted for and therefore we do not report it here <u>Source of funding:</u> Not stated

Diagnostic Value of the Plain Abdominal Radiography in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Reuchlin-Vroklage et al. Diagnostic value of abdominal radiography in constipated children: a systematic review. 2005. Archives of Pediatrics and Adolescent Medicine 159[7], 671-678	Study type: Systematic Review Evidence level: 1+ Study aim: to evaluate the additional diagnostic value of the plain abdominal radiography in the diagnosis of constipation in children	6 studies (3 case series, 2 case-control studies, 1retrospective re-examination of abdominal radiographs Inclusion criteria: Controlled, observational studies investigating the relationship between faecal loading on plain abdominal radiography and symptoms and signs related to constipation in otherwise healthy children aged from 1 to 18 years old Exclusion criteria:	Otherwise healthy children aged from 1 to 18 years old with signs and symptoms related to constipation. Some studies included children with soiling or encopresis, while others exclude this group Country: The Netherlands	Test and Reference Standard (studies could treat either test as the reference standard) -Faecal loading on plain abdominal radiography according to a predefined scoring system (reference test in 3 studies) -Clinical diagnosis of constipation according to the presence or absence of predefined symptoms and signs (reference test in 3 studies) In the 6 studies	Diagnostic value: (LR: Likelihood ratio) -Ability of the abdominal radiography to discriminate between clinically constipated and non constipated children (4 studies): 1. Sensitivity: 76 (95% CI: 58 to 89) Specificity: 75 (95% CI: 63 to 85) LR: 3.0 (95% CI: 1.6 to 4.3) 2. Sensitivity: 60 (95% CI: 46 to 72) Specificity: 43 (95% CI: 18 to 71) LR: 1.0 (95% CI: 0.5 to 1.6) 3. Sensitivity: 80 (95% CI: 65 to 90) Specificity: 90 (95% CI: 74 to 98) LR: 8.0 (95% CI: 0.7 to 17.1)	MEDLINE searched from inception to April 2004, search terms reported and comprehensive. Results of this search combined with search strategy specific to identify diagnostic studies. References lists of reviews articles and included studies checked for further relevant articles. Experts in the field contacted and asked to identify published and unpublished studies. No language restrictions applied Two reviewers independently screened the titles and abstracts f studies identified by the searches for eligibility. All potentially relevant studies were retrieved as full papers and independently screened by two reviewers. Any disagreements were resolved through consensus or by arbitration of a third reviewer Methodological quality of studies assessed using the QUADAS tool. An overall methodological quality value was assigned to studies by calculating the number of positive scores (maximum value 14). Studies with scores of 9 or higher >60%) were arbitrarily regarded as being of “high”

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		Lack of control group, no data on diagnostic value presented, symptoms of constipation not related to the outcomes of a plain abdominal radiography <u>Setting:</u> all 6 studies hospital based		included, 3 different scoring systems for assessing impaction on abdominal radiography were used: 3 studies: Barr-score 2 studies: revised Barr-score 1 study: authors' own scoring system	4.Accuracy 80% (95% CI: 50 to 100) Ability of the clinical examination to discriminate between radiographically constipated and non constipated children (1 study): Sensitivity: 77 (95% CI: 70 to 84) Specificity: 35 (95% CI: 27 to 44) LR: 1.2 (95% CI: 1.0 to 1.4) -Association between a history of hard stool and faecal impaction on radiography: LR: 1.2 (95% CI, 1.0 to 1.4) -Association between a finding of absence of rebound tenderness and faecal impaction on radiography: LR: 1.1 (95% CI, 1.0 to 1.2) -Association between stool present on rectal examination and faecal impaction on abdominal radiography: LR: 1.6 (95% CI, 1.2 to 2.0) LR: 1.5 (95% CI, 0.8 to 2.3)	methodological quality. Two reviewers independently assessed the methodological quality of the independent studies. Any disagreements were resolved by consensus or through consultation with third reviewer. Reviewers scored 84 items and agreed on 65 item (77.4%, k=0.54) Structured data extraction performed independently by two reviewers and any disagreement resolved by consensus <u>Source of funding:</u> Not reported

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					<u>Interobserver reliability:</u> 5 studies: moderate to excellent (k range, 0.63 to 0.95) 1 study: poor to moderate (k=0.28 to 0.060) <u>Intraobserver reliability</u>: Evaluated in 3 studies, ranged from moderate (k=0.52) to excellent (k≥0.85)	

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de Lorijn et al. The Leech method for diagnosing constipation: intra- and interobserver variability and accuracy. 2006. Pediatric Radiology 36[1], 43-49	Study type: Diagnostic. Case control Evidence level: III Study aim: to assess intra- and interobserver variability and determine diagnostic accuracy of the Leech method in identifying children with functional constipation	89 non selected consecutive children Inclusion criteria: patients referred for the evaluation of abdominal pain, constipation or faecal incontinence. Diagnosis of constipation: at least two of the following was present: -defecation frequency less than 3 times/week -2/more episodes of faecal incontinence per week -production of large amounts of stool once over a period of 7-30 days -presence of palpable abdominal or rectal mass (control children fulfilled criteria	89 children Median age: 9.8 years Group 1 (constipation): n=52 (28 boys) Group 2 (controls): N=37 (24 boys) 31: FNRFI 6: FAP Diagnosis of functional non-retentive faecal incontinence (FNRFI) based on: 1) two/more faecal incontinence episodes/week with no signs of constipation 2) defecation frequency 3/more times/week 3) no periodic passage of very large amounts of stool at least once during a period of 7-30 days 4) no palpable abdominal or rectal mass on physical examination fro a	Test: Leech method to diagnose constipation in plain abdominal radiography Reference test: Colonic Transit Time (CTT) Leech scoring method: Colon divided into three segments: right, left and recto sigmoid Each segment provided with a score from 0-5 0:no faeces visible 1:scanty faeces visible 2: mild faecal loading 3: moderate faecal loading 4: severe faecal loading 5: severe faecal loading with bowel dilatation Colonic transit	Mean Leech score (using the first score): -Group 1 (constipation): 10.1 -Group 2 (controls): 8.5 p=0.002 Mean CTT: -Group 1 (constipation): 92 h -Group 2 (controls): 37 h p<0.0001 Diagnostic accuracy of Leech method vs. CTT method: -Leech method: (cut-off point as per study comparable to 9 as per literature) Sensitivity: 75% Specificity : 59% (cut-off point 9 as per literature) Positive Predictive Value: 72% Negative Predictive Value: 63% -CCT: (cut-off point 54h as per study) Sensitivity: 79% Specificity: 92% (cut-off point 62h as per literature) Sensitivity: 71%	Children with clinical characteristics of FAP and FNRFI were classified as the control group, because according the authors they have “little or no faecal loading on an abdominal radiograph” Treatment with oral/rectal laxatives was discontinued in each patient for at least 4 days. Thereafter the patient ingested one capsule with 10 small radiograph opaque markers on 6 consecutive days, in order to determine the CTT. Subsequently, a plain abdominal radiograph was taken on day 7. this radiograph was both used in the Leech method and for CTT measurement Three scorers independently scored the same radiography twice (4 weeks apart) using the Leech method, which was discussed amongst the three scorers previous to both readings Scorers were three experienced doctors (a 5th year radiology resident, a paediatric radiologist and a senior paediatric gastroenterologist). No clinical information was about the patients was made available to them. A Leech score of 9 or more was considered as suggestive of constipation. CTT were assessed once by a single scorer. It was assumed that the counting of radiopaque markers would not lead to intra- or interobserver

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		for functional abdominal pain (FAP) and for functional non-retentive faecal incontinence (FNRFI)) Exclusion criteria: not reported Setting: tertiary gastroenterology outpatients clinic	period of at least 1 week during the preceding 12 weeks. Faecal incontinence defined as the voluntary/involuntary loss of loose stools in the underwear after the age of 4 years Functional abdominal pain (FAP) defined as abdominal pain of at least 12 weeks duration 1)that was continuous or nearly discontinuous in a school-aged child or adolescent 2) that had no or only an occasional relationship with physiological events 3) that was accompanied by some loss of daily functioning 4) that was not feigned and) for which there were insufficient criteria to indicate the presence of another functional gastrointestinal	time: Determined by the method of Bouchoucha. Radiography on day 7 used to count the number of markers in the colon. Number of markers x 2 produced total CTT in hours. Localization of markers and CTT calculated according to previously described formula. Normal range fro total transit time based on the upper limits (mean ± 2xSD) from a study in healthy children. Based on this study a CTT > 62 h was considered delayed.	Specificity: 95% Positive Predictive Value: 69% Negative Predictive Value: 97% ROC analysis -AUC (Leech method): 0.68 (95% CI 0.58-0.80) -AUC (CTT method): 0.90 (95% CI 0.83-0.96) p=0.00015 AUC=Area Under the ROC curve ROC=Receiving Operator Characteristic Intraobserver variability (Leech score) a. Systematic difference (Mean, 95% CI): -Scorer 1 0.7 (0.2-1.2) P=0.89 -Scorer 2 0.03 (-0.4-0.5) P=0.0005 -Scorer 3 -1.6 (-2.0-1.3) P<0.0001 b. Variability (SD) -Scorer 1: 2.2	variability In 5% of cases the Leech scores of the same patient produced by different scorers could differ by 4 points or more Source of funding: not stated

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			disorder <u>Country:</u> The Netherlands		Limits of agreement: -6.0-5.0 -Scorer 2 : 2.2 Limits of agreement: -7.0-7.0 -Scorer 3: 1.5 Limits of agreement: -5.0-3.0 <u>Interobserver variability (using the first score):</u> -Scorer 3 vs. scorer 1: Mean of differences 2.7 p<0.0001 -Scorer 3 vs. scorer 2: Mean of differences 2.9 p<0.0001 - Scorer 2 vs. scorer 1: no systematic differences found	

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van den Bosch et al. Systematic assessment of constipation on plain abdominal radiographs in children. 2006. Pediatric Radiology 36[3], 224-226	Study type: Diagnostic retrospective case series Evidence level: III Study aim: To assess the reproducibility of there scoring systems (Barr, Leech and Blethyn) for plain abdominal radiography, in order to determine which one is most useful in clinical practice	40 patients Inclusion criteria: consecutive patients referred to hospital for assessment of constipation. Patients complained of infrequent defection, soiling, encopresis, or abdominal pain Exclusion criteria: None reported Setting: hospital	40 patients Mean age 7 years (range 3-12) 55% boys Country: The Netherlands	Test and Reference Standard (all tests compared to each other) -Barr scoring system -Leech scoring system -Blethyn scoring system Barr scoring system: Quantifies the amount of faeces in four different bowel segments (ascending colon, transverse colon, descending colon and rectum) and also the consistency of the faces i.e. granular or rocky stools Constipation defined as Barr score>10 Blethyn system: Rough scoring system used to assess amount of faeces in large bowel -Normal, grade 0:	Intraobserver variability (k values) -Observer 1: Barr: 0.75 Blethyn: 0.61 Leech: 0.88 -Observer 2: Barr: 0.66 Blethyn: 0.65 Leech: 1.00 Interobserver variability (k values) -Period 1 Barr: 0.45 Blethyn: 0.43 Leech: 0.91 -Period 2 Barr:0.71 Blethyn: 0.31 Leech: 0.84 All k values are statistically significant ($p<0.05$) Kappa (k) coefficients (level of agreement): <0.20: poor 021-0.40: fair 0.41-0.60: moderate 0.61-0.80: good 0.81-1.00: very good	Masked abdominal radiographs of the children were independently evaluated by two observers, both experienced paediatric radiologists. Observers assessed each radiograph on two separate occasions, 6 weeks apart. Each abdominal radiograph was scored according to the three different scoring systems Intraobserver variability was determined for each scoring system by comparing data from the same observer at two different reading sessions. Interobserver reproducibility was determined by comparing data from the two observers on one occasion. Thus two intraobserver and two interobserver variabilities could be derived for each parameter. Kappa coefficients were calculated as indicators of intra- and interobserver variability.

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				faeces in rectum and cecum only -Grade 1, mild constipation: faeces in rectum, cecum and discontinuous elsewhere -Grade 2, moderate constipation: faeces in rectum, cecum with continuous faeces affecting all segments -Grade 3, severe constipation: faeces in rectum and caecum, continuous elsewhere with dilated colon and rectal impaction <u>Leech method:</u> The colon is divided into there segments: 1.ascending and proximal transverse colon 2.distal transverse and descending colon 3. rectosigmoid Amount of faces in each segment		

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				scored from 0 to 5. O indicates no faeces and 5 severe faecal loading and bowel dilatation. With a possible score of 0-15, > 8 considered to indicate constipation		

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Giramonti et al. The association of constipation with childhood urinary tract infections. 2005. Journal of Pediatric Urology 1[4], 273-278United Kingdom.	Study type: Diagnostic case control Evidence level: III Study aim: To evaluate the relationship between a history of constipation, faecal loading on X-rays and a history of UTIs in an office practice	133 children Inclusion criteria: Cases: Children with a history of UTIs who were already undergoing a VCUG(voiding cystourethrogram), who were on medications for the treatment of constipation Controls: Children undergoing a plain film of the abdomen for reasons that did not include constipation/ UTIs (e.g. renal calculi, gastroesophageal reflux) Exclusion criteria: Neurological bowel and/or bladder dysfunction or lower gastrointestinal problems.	133 children 35 males Mean age: 5.6 years (range: from newborn to 14 years) Group 1 (history of UTI n=100 Group 2 (no history of UTI) n= 33 Country: USA	Test and Reference Standard (not clear which one was what) -Abdominal radiograph (KUB) -Clinical variables: Number of bowel movements/week Stools consistency	Correlation between symptoms of constipation and faecal load on abdominal X-ray: Correlation coefficient=0.08	Authors defined constipation in the past as “at least 2 weeks of hard, rock-like stools passed less than 3 times/week without evidence of structural, endocrine or metabolic disease, other useful association include: abnormally large stools, and difficult or painful defecation, associated with stools accidents or faecal smearing in undergarments Abdominal X-rays reviewed blindly by three physicians: two paediatric radiologists an one paediatric urologist and score for faecal loading based on a previously validated scoring system (Leech) Data collected prospectively on several historical questions about constipation shortly after the X-ray was performed, but before they were reviewed with the family. An interviewer filled out the history questionnaire using consensus of the child’s and parents’ responses. Data were also obtained regarding a history of UTI. No data on the interviewer are reported Constipation history responses were scored from 1 to 3 and a total history score was obtained scored were grouped as: 1-none or mild, 2-moderate, 3-severe Data derived from scores on faecal loading were averaged for each patient and the scores then grouped in the

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		Children with no history of UTI who were undergoing a plain film of the abdomen for constipation or encopresis Setting: office practice				same way as previous. Questionnaire not piloted previous to the study As it was thought that children beyond toilet-training age would be more likely to have developed constipation related to overall elimination dysfunction and therefore UTIs as well, the data for children > 3 years were analysed separately

Diagnostic Value of the Rectal Biopsy in children with Chronic Idiopathic Constipation

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comments
Lewis et al. Diagnosing Hirschsprung's disease: increasing the odds of a positive rectal biopsy result. 2003. Journal of Pediatric Surgery 38[3], 412-416	Study type: Retrospective cohort Evidence level: 2+ Study aim: To test the hypothesis that key features in the history, physical examination and radiographic evaluation would allow to avoid unnecessary rectal biopsies	315 children Inclusion criteria: -Cohort 1: Children presenting with constipation to diagnose Hirschsprung's disease (HD) -Cohort 2: idiopathic constipation Exclusion criteria: Patients undergoing re-evaluation fro constipation after pull-through procedure for HD	315 children: -265 children who hade undergone rectal biopsy -50 children, concurrent selected cohort (cohort 2) Country: USA	Tests: Rectal biopsy	Clinical features in children with Hirschsprung's disease and idiopathic constipation (IC, n=40) -Onset of constipation <1 year old Delayed passage of meconium (%) HD: 65 IC: 13 P< 0.05 Abdominal distension (%) HD: 80 IC: 42 P< 0.05 Vomiting (%) HD: 72 IC: 21 P< 0.05 Faecal impaction requiring manual evacuation (%) HD: 6 IC: 30 P< 0.05 Enterocolitis (%) HD: 13 IC: 15	Additional information from study Questionnaires, telephone interviews and patients visits used to compile long-term data. In reporting features listed in the questionnaire only patients with definite information were included: the number of patients in each analysis varies to exclude those with missing data Delayed passage of meconium defined as failure to pass meconium in the first 48h of life. These data were available in 59% of cases Abdominal distension determined from parental response to questionnaire or data noted during patients visits Enterocolitis defined as diarrhoea associated with fever Reviewer comments: Data on clinical features not available for all children Unclear what kind of rectal biopsy was performed and how the diagnosis of HD was made Source of funding: Not stated

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					NS -Onset of constipation >1 year old Delayed passage of meconium (%) HD: 81 IC: 1 P< 0.05 Abdominal distension (%) HD: 53 IC: 7 P< 0.05 Vomiting (%) HD: 23 IC: 0 P< 0.05 Faecal impaction requiring manual evacuation (%) HD: 46 IC: 30 NS Enterocolitis (%) HD: 13 IC: 14 NS <u>Age at onset of symptoms</u> -Hirschsprung's (HD) (n=46) Mean: 8 months (range 1 day to 9 years) 1rst week of life: 60 % 1rst month of life: 70% 1rst year of life: 87%	

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					after 1 year of life: 13% -Idiopathic constipation (IC) (n=40) Mean: 15 months (range 7 days to 16 years) 1rst week of life: 15% 1rst month of life: 55% 1rst year of life: 68% after 1 year of life: 32% At least 34% of HD patients had the classic triad (delayed passage of meconium + vomiting + abdominal distension). At least 1 feature of the triad noted in 98% of patients with HD. Only 60% of patients with IC had a history of delayed passage of meconium, vomiting or abdominal distension. 100 % HD patients vs. 64% IC patients had 1 or more of the following: delayed passage of meconium, vomiting, abdominal distension and a transition zone on contrast enema. 36% of IC patients had none of these features.	

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Pini-Prato et al. Rectal suction biopsy in the workup of childhood chronic constipation: indications and diagnostic value. 2007. Pediatric Surgery International 23[2], 117-122	Study type: Retrospective cohort Evidence level: 2+ Study aim: To describe the clinical features of a group patients with intestinal dysganglinoses (ID) (Hirschsprung's disease (HD) and intestinal neuronal dysplasia (IND)) along with a group of consecutive patients with functional constipation (FC), to compare them and to find out if the clinical criteria to indicate rectal	141 patients Inclusion criteria: Patients with intestinal dysganglinonoses (ID) (Hirschsprung's disease (HD) and intestinal neuronal dysplasia (IND)) who were diagnosed in the period between February 2000 and July 2005 Exclusion criteria: Not stated	141 patients median age: 20 months mean 44 months ± 67 Country: Italy	Tests: -Rectal suction biopsy -Clinical variables: a. Meconium passage b. Symptoms onset c. Intestinal obstruction d. Abdominal distension e. Reported enterocolitis f. Failure to thrive g. Palpable faecal masses h. Soiling	Clinical variables a. Meconium passage (%) -Failure/delay FC (n=45): 7 HD (n=47): 87 IND (49): 22.5 FC vs. HD p<0.001 -Normal FC (n=45): 93 HD (n=47): 13 IND (49): 77.5 FC vs. HD p<0.001 b. Symptoms onset (%) - at < 1year old FC (n=45): 80 HD (n=47): 96 IND (49): 94 FC vs. HD p<0.02 - at > 1 year old FC (n=45): 20 HD (n=47): 4 IND (49): 6 FC vs. HD p<0.02 c. Intestinal obstruction (%) FC (n=45): 0 HD (n=47): 49 IND (49): 26.5 FC vs. HD p<0.001	Additional information from study Total number of biopsies: 1118 performed on 429 patients (mean of 2.6 each). In 63 patients (14.7%) biopsies inadequate for a reliable diagnosis absence of submucosal layer) 143 patients (33.3%) received a diagnosis of ID. 96/143 fulfilled inclusion criteria, being 49 IND and 47 HD. 45 consecutive patients with a diagnosis of FC (out of the remaining 286 patients) fulfilled inclusion criteria and were consequently included, for a total sample of 141 Rectal suction biopsies (RSB) performed with the instrument Solo-RBT ©. Each patient underwent 2 to 4 biopsies 2 to 10 cms from the pectinate line. Various histochemical staining (AChE, LDH, ANE, NADPH-diaphorase and Toluidine Blue) were used to diagnose HD and IND. All biopsies were evaluated by a single, senior and experienced pathologist. HD diagnosed by demonstrating: - a dramatic increased in AChE-positive nerve fibres in the lamina propia and muscularis mucosae - -thick nerve trunks - absent ganglion cells in submucosal In case on negative RSB functional constipation diagnosed according to

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	suction biopsy in constipated children do exist				d. Abdominal distension (%) FC (n=45): 20 HD (n=47): 85 IND (49): 26.5 FC vs. HD p<0.001 e. Reported enterocolitis (%) FC (n=45): 9 HD (n=47): 10.5 IND (49): 20.5 FC vs. HD, NS f. Failure to thrive (%) FC (n=45): 11 HD (n=47): 27.5 IND (49): 22.5 FC vs. HD p<0.045 g. Palpable faecal masses (%) FC (n=45): 22 HD (n=47): 17 IND (49): 20.5 FC vs. HD, NS h. Soiling (%) FC (n=45): 46.5 HD (n=47): 4 IND (49): 4 FC vs. HD p<0.001	Rome II criteria: At least 2 weeks of: -scybalous, pebble like, hard stools fro a majority of stools -firm stools 2 o less times/week absence of any organic cause of constipation (IND, HD, anorectal malformations, spinal dysraphism, metabolic disorders) Clinical variables retrospectively extracted from patients' notes <u>Reviewer comments:</u> Unclear how the reviewing process was conducted <u>Source of funding:</u> Not stated

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comments
Ghosh et al. Rectal biopsy in the investigation of constipation. 1998. Archives of Disease in Childhood 79[3], 266-268	Study type: Retrospective case series Evidence level: 3 Study aim: To develop criteria that would reliably and consistently identify children with Hirschsprung's disease (HD) and thereby avoid the trauma and expense of unnecessary rectal biopsies in the others	141 children Inclusion criteria: All children who had rectal biopsy to exclude Hirschsprung's disease between January 1, 1993 and December 31, 1995 at Southampton General Hospital Exclusion criteria: Not stated	141 children age at biopsy: 1 day to 13 years gender not reported Country: UK	Tests: -Rectal biopsy: Noblett suction biopsy in children younger than 1 year Open transanal rectal biopsy under general anaesthesia performed at least 1cm above pectinate line, in older children or following repeated failure of Nobblet biopsy - Clinical variables: extracted from case notes	Features in history and examination -Hirschsprung's (n=17): age at diagnosis: 1 day to 3 years 14 children: < 4 weeks 1 child: 4 to 12 weeks 1 child: 12 weeks to 1 year 1 child: > 1 year history of delayed passage of meconium (>48h after birth): 10 (58.8%) age of onset of constipation: all 17 children: < 4 weeks bleeding per rectum: 0 anal fissures:0 sever behavioural/emotional problems: 0 soiling: 0 enterocolitis: 8 (47%) -No Hirschsprung's (n=124) age at biopsy: 1 day to 13 years 20 children: < 4 weeks 12 children: 4 to 12 weeks 14 children: 12 weeks to 1 year 78 children: > 1 year history of delayed passage of meconium (>48h after birth): 17 (13.7%)	Additional information from study Histological diagnosis usually made on haematoxylin and eosin staining with at least 100 serial sections looked at in detail. Acetylcholinesterase used occasionally but not as the main method of diagnosis Constipation defined as a decreased frequency of bowel movements(<3/week), or a difficulty in defection which is perceived by the parents as a problem, requiring medication (oral or rectal) or manual intervention by the parents. This included anal stimulation with cotton bud, holding the buttocks apart and manual evacuation History of onset of constipation was available in 136 of the 141 children (96%). The 5 children in whom this history could not be obtained from the notes were all older than 1 year (3 teenagers) and none had HD A total of 186 biopsies performed, with 22% failures. (Suction: total 74, 35% failures; Open: total 100, 14% failures, operative total 12 , no failures) Reviewer comments: Unclear how the reviewing process was conducted Source of funding: Not stated

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comments
					age of onset of constipation: 40 children: < 4 weeks 32 children: 4 to 12 weeks 22 children: 12 weeks to 1 year 25 children: > 1 year bleeding per rectum: 37 (30%) anal fissures: 14 (11%) sever behavioural/emotional problems: 10 (8%) soiling: 16 (13%) enterocolitis: 0	

Bibliographic Information	Study type & Evidence level	Number of patients	Population Characteristics	Type of test (s)	Follow-up & Outcome Measures Effect Size	Reviewer comments
Khan et al. The constipated child: how likely is Hirschsprung's disease? 2003. Pediatric Surgery International 19[6], 439-442	Study type: Retrospective case series Evidence level: 3 Study aim: To review author's experience of rectal biopsy to exclude Hirschsprung's disease (HD) by haematoxylin-eosin (HE) staining and acetylcholinesterase (AChE) stains, and author's clinical criteria to perform rectal biopsy in these children	182 patients Inclusion criteria: Patients who presented with chronic constipation or intestinal obstruction and had rectal biopsy to exclude HD in the University Hospital of Wales, Cardiff Exclusion criteria: Not stated	182 patients 118 males Mean age 2.9 years (range 2 days to 16 years) Country: UK	Tests: -Suction rectal biopsy (SRB) and full-thickness rectal biopsy -Clinical variables: a. Meconium passage b. Constipation since birth c. Intestinal obstruction d. Failure to thrive e. Chronic abdominal distension	-Total number of patients diagnosed with HD: 25 (14%) -mean age of patients diagnosed with HD: 3.64 months (range 2 days to 4 years) Clinical symptoms in children with HD (number of children): Meconium passed> 48 h: -In total sample: < 1 year old: 35 >1 year old: 6 -In HD children: 16 % of clinical feature to HD: 39 Meconium passed< 24 h: -In total sample: < 1 year old: 40 >1 year old: 74 -In HD children: 6 % of clinical feature to HD: 5 Passage of meconium unknown: -In total sample: < 1 year old: 29 >1 year old: 17 -In HD children: 3 % of clinical feature to HD: 11 Constipation since birth: -In total sample: < 1 year old: 33 >1 year old: 20 -In HD children: 17	Additional information from study Clinical details, laboratory investigations and histopathological reports reviewed retrospectively The Great Ormond Street (GOS) suction instrument (modified Nobblet) was used. 2 of 4 specimens were obtained at 2, 3 and 4 cm above the dentate line, in the ward or theatre without anaesthesias. All suction biopsy specimens were examined by routine fixation with HE staining and AChE histochemistry. All full thickness biopsies were done under general anaesthesia and examined by routine fixation with HE staining. The histochemical criteria used for the diagnosis of HD were those of Meier-Ruge in 1972 i.e. the combination of an absence of submucosal ganglion cells and an increased AChE activity with parasympathetic fibres of the muscularis mucosae and lamina propia mucosae. At least 60 sections were examined from each block to find the submucosal ganglion cells Suction biopsy accepted as adequate even if only 1 out of 2 to 4 specimens contained mucosa and sub-mucosa 182 patents who had rectal biopsies provided355 specimens in which 79% of suctions biopsies and 97% of full-thickness biopsies were adequate. Adequate biopsies include rectal mucosa and submucosal according to

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					% of clinical feature to HD: 32 Intestinal obstruction: -In total sample: < 1 year old: 12 >1 year old: 1 -In HD children: 9 % of clinical feature to HD: 69 Failure to thrive: -In total sample: < 1 year old: 10 >1 year old: 8 -In HD children: 4 % of clinical feature to HD: 22 Chronic abdominal distension: -In total sample: < 1 year old: 6 >1 year old: 7 -In HD children: 3 % of clinical feature to HD: 23	Noblett. In 20 children with HD the diagnosis was made at the first attempt by suction rectal biopsy. Repeat biopsies performed on 14 (8%) of 182 patients because of inadequate initial biopsy, clarification of atypical inervation and confirmation of false negative results. 19/104 patients who underwent SRB were > 1 year old. Because 5 children (12 specimens) who were older than 1 year had inadequate suction biopsies at beginning of series, it was decided that SRB was not suitable fro children >1 year old. 3 patients with HD (aged 6 days, 12 days and 6 weeks) has false negative AChE staining. In these the diagnosis were later established from repeated biopsies: 1 full thickness biopsy, 1 laparotomy and 1 suction biopsy <u>Reviewer comments:</u> Unclear how the reviewing process was conducted No definition of constipation or other clinical symptoms given Authors explained that patients may have had more than one symptom, but these figures were not reported in the paper <u>Source of funding:</u> Not stated

Diagnostic Value of the Abdominal Ultrasound in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Klijn et al. The diameter of the rectum on ultrasonography as a diagnostic tool for constipation in children with dysfunctional voiding. 2004. Journal of Urology 172[5 Pt 1], 1986-1988	Study type: Diagnostic. Case control Evidence level: III Study aim: to prove the accuracy of the transverse diameter of the rectum on ultrasonography as an additional parameter for diagnosing constipation in children with lower urinary tract dysfunction	49 patients Inclusion criteria: Positive diagnosis of constipation, made by patient history and physical examination when the patient had at least 2 positive signs, including: -2 or fewer bowel movements weekly without laxative therapy -2 or more episodes of faecal soiling weekly -periodic passage of a large amount of stool once every 7 to 30 days -palpable abdominal and/or rectal mass Exclusion criteria: laxative therapy,	49 patients aged between 5-13 years Group 1: 23 patient s with positive history of voiding dysfunction and constipation Group 2: 26 urological patients without lower urinary tract dysfunction and a normal defecation pattern, diagnosed with undescended testicle, periodic control for upper urinary tract dilatation, etc. Country: UK	Test: lower abdominal ultrasound of rectum Reference Standard : None reported	Rectal diameter (cm) (Mean, standard deviation, 95% CI) -Group 1 (constipated, n=23): 4.9 (1.01; 4.4 to 5.3) -Group 2 (control, n=26) 2.1 (0.64; 1.8 to 2.4) p<0.001	Ultrasound done with the patient supine. 7.5 MHz probe applied on abdominal skin approximately 2cm above the symphysis. Measurement performed with moderate (30-70 % capacity of for age) filled bladder at an angle of about 15 degrees downward from the transverse plane. The diameter of the rectum, behind the bladder was measured twice. If stools had been passed in the last two hours or patients had an urge to defecate during the investigation the were not included in the study, but this situation did not occur In all patients it was possible to obtain a reliable and repeatable measurement of the rectum if at least some bladder filling was present It was not reported who performed the ultrasound, or whether this person was blinded No significant difference in age between the two groups (p=0.20) or in period between the last time a stool was passed prior to the rectal measurement (p=0.16) In all patients with voiding dysfunction and faecal constipation (Group 1) rectal examination confirmed stool in the rectum, but there are no data reported on this variable for the control group, probably for ethical reasons

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		constipation due to neurological disease, disease of the gastrointestinal tract based on endocrinological, metabolic, genetic or toxic disease, or connective tissue disease Setting: hospital				Source of funding: Not stated

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Singh et al. Use of pelvic ultrasound in the diagnosis of megarectum in children with constipation. 2005. Journal of Pediatric Surgery 40[12], 1941-1944	Study type: Diagnostic. Case control Evidence level: III Study aim: to establish normal values for the rectal crescent in healthy children, compare them with the rectal crescent in children with constipation and explore whether pelvic ultrasound can hep in establishing a diagnosis of megarectum	177 children Inclusion criteria: Children referred after failing to respond to medical treatment. Diagnosis of constipation made once the child had 2 or more of the following: -less than 3 bowel movements/week -periodic passage of a large stool with discomfort or pain -a palpable abdominal mass on physical examination -faecal soiling in the presence of any of the above Exclusion criteria: Previous	177 children Group 1: 82 children (median age 5.5 years, range 0.30-15.30) with no history of constipation or other anorectal or gastrointestinal problems and no previous anorectal surgery Group 2: 95 children (median age 6.5 years, range 0.40-16.40) with a history of constipation of at least 6 months duration, referred to a tertiary referral centre Country: UK	Test: Pelvic ultrasound Reference test: none reported	Median rectal crescent (cm) Group 1 (healthy children): 2.4 (range 1.3 to 4.2; IQR 0.72) Group 2 (children with constipation): 3.4 (range 2.10 to 7.0; IQR 1.0) p<0.001 IQR= interquartile range Receiver operating characteristic analysis: -Area under the curve: 0.847 95% CI: 0.791 to 0.904 Cut-off point for establishing the diagnosis of megarectum: 3.0 cm	A portable US machine with a 5-MHz probe (falcon 2101 Ultrasound scanner with a transducer type 8803 [3.0-5.0 MHz], B-K Medical, Copenhagen, Denmark) was used. The same individual performed all the US scans, but not other data on this were reported (as blinding, individual's experience in radiology, etc) All children had a full or partially full bladder at the time of measurement. In cases where the child was initially scanned and the bladder was noted to be empty, the US was abandoned and the child was offered liberal fluids orally. The scan was repeated within an hour and in all cases, by then, the child had a full or partially full bladder The US probe was applied on the anterior abdominal wall in the midline, approximately 1-2 cm above the symphysis at a 90 degrees angle to the abdominal wall. This showed the impression of the rectum behind the urinary bladder as a crescent which was measured in centimetres There were no significant differences between the two groups in terms of age, weight and height (p values 0.114, 0.198 and 0.131 respectively) Results were adjusted for confounders (age, height and weight)

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		anorectal surgery (e.g. pull-through procedures for Hirschsprung's disease or anorectal myectomy) Setting: tertiary referral centre				Age and rectal diameter were significantly related ($p<0.0001$): the older the child the bigger the rectal diameter Time to last evacuation was not ascertained and authors acknowledged this may influence the size of the rectal crescent Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Bijos et al. The usefulness of ultrasound examination of the bowel as a method of assessment of functional chronic constipation in children. 2007. Pediatric Radiology 37[12], 1247-1252	Study type: Diagnostic Case control Evidence level: III Study aim: to determine whether a new method of ultrasound (US) assessment of stool retention could be used as a method of identifying children with functional chronic constipation, and to determine whether children with an enlarged rectum and colon (as seen on US) should be referred for further procedures such as	225 children Inclusion criteria: Referred because of chronic constipation, based on history and physical examination: defecation disorders persisting longer than 6 months, all patients fulfilled Rome II criteria for defecation disorders (frequency of bowel movements less than twice a week, consistency and size of stool caused pain during defecation, withholding behaviour) Exclusion criteria: anatomic abnormality	225 children Group 1: 120 children with chronic constipation (72 boys, mean age 6.25 years, range 1.6 to 17.9) Group 2: 105 children with normal defecation pattern (mean age 8.25 years) Country: Poland	Test: Abdominal ultrasound Reference tests: Proctoscopy (for diagnosing faecal impaction) Transit times (hours, upper limit of 66 based on literature) ≤66: normal-transit constipation 66-100: slow-transit constipation >100: very delayed slow-transit constipation	Diameters of rectal ampulla by US (mm, mean ± SD) Age (years) -Group 1 (constipated): All ages: 43. 06 ± 9.68 (range 30 to 82) ≤3: 38.35 ± 8.65 3.1 to 6: 41.16 ± 8.72 6.1 to 12: 46.15 ± 9.56 >12 years: 49.09 ± 10.19 -Group 2 (control): All ages: 31. 83 ± 8.24 (range not given) ≤3: 27.07 ± 8.00 3.1 to 6: 29.25 ± 6.86 6.1 to 12: 32.85 ± 8.73 >12 years: 35.15 ± 7.18 p<0.001 for every age group Mean rectopelvic ratios for all ages (mean ± SD) (Cut-off value to diagnose megarectum: 0.189) -Group 1 (constipated): All ages: 0. 22 ± 0.05 ≤3: 0.24 ± 0.060 3.1 to 6: 0.23 ± 0.05 6.1 to 12: 0.22 ± 0.05 >12 years: 0.19 ± 0.04	US assessment of stool retention and colonic enlargement involved measurement of the transverse diameter of the rectal ampulla (by US) and pelvic width (externally using a measuring tape) Pelvic width was defined as the distance between the external margins of the anterior superior iliac spines. The ratio between the transverse diameter of the rectal ampulla and transverse diameter of the pelvis was calculated to give the rectopelvic ratio. US was performed using a Philips HDI 4000 US unit (Philips, Best, The Netherlands) equipped with three electronic transducers with various frequencies from 2-14 MHz. children were examined before food and had a slightly filled bladder. Patients who passed stool on the day of the examination were temporarily excluded from the study until they became constipated again. Rectal ampulla width was measured with the probe applied to the anterior abdomen above the symphysis. Measurement was performed on oblique transaxial scanning plane to obtain transverse diameter of the ampulla. Measurement was taken several times and the highest one recorded taken as the final measurement Total and segmental colonic transit

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	proctoscopy and assessment of colonic transit time.	(Hirschsprung's disease, congenital abnormalities of the anorectal region) neurological and psychiatric conditions (cerebral palsy, spina bifida, mental retardation, anorexia nervosa) ,metabolic conditions (diabetes mellitus/insipidus) endocrine disorders (hypothyroidism), previous thoracic or abdominal surgery (control patients: normal defecation patterns, treated for various symptoms like chronic abdominal pain, food allergies)			-Group 2 (control): All ages: 0.15 ± 0.04 ≤3: 0.17 ± 0.05 3.1 to 6: 0.16 ± 0.04 1 to 12: 0.15 ± 0.05 >12 years: 0.14 ± 0.03 p<0.001 for age groups (years): ≤3; 3.1 to 6; 6.1 to 12 p=0.002 for >12 years <u>US vs. proctoscopy in the diagnosis of faecal impaction</u> -Sensitivity: 88.3% <u>Mean colonic transit times:</u> Children with faecal impaction (as per US) had significantly longer average segmental transit time for the rectum, sigmoid and left colon (p<0.001, p=0.0015 and p=0.0104 respectively) there was not statistically significant difference for the right side of the colon. Children with an overfilled splenic flexure on US had a significantly longer transit time in the left side of the colon (p=0.0029) <u>Definitions of:</u> -Faecal impaction (as per US in	time measured by the modified sixth day Hinton method. Total and segmental time obtained by multiplying the number of radiopaque markers seen on the radiograph by 1.2 (time in hours/number of markers swallowed by the patient) The same individual performed all the US scans, but not other data on this were reported (as blinding, individual's experience in radiology, etc) It is not clear what number of children underwent each of the tests It is not clear how the authors calculated the sensitivity of the US vs., proctoscopy to diagnose faecal impaction, as the results of proctoscopy are not reported It is difficult to know exactly how many children were diagnosed with faecal impaction by US, as these data are reported only in the form of a bar graph. Data on number of children diagnosed with "overfilled colon" are not reported at all. It is not clear whether "enlarged" and "overfilled" colon mean the same for the authors, as no measurements of "enlarged" colon are reported. Children apparently underwent DRE but no results are reported

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		Setting: gastroenterology outpatient clinic			sagital plane): when pelvic structures were covered by stool masses and were not even partially visible. -Overfilled colon (as per US): Overfilled bowel at the splenic flexure: when it was impossible to visualise the entire length of the left kidney due to the lack of visibility of the lower pole of the kidney because of bowel contents. Probe applied to the long axis of the spleen. Overfilling of the transverse colon: when the superior mesenteric artery was not visible with the probe applied in the sagital plane over the aorta	Control group did not differ from patients regarding gender, the comparison regarding age is not clearly reported Source of funding: Not stated

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Joensson et al. Transabdominal ultrasound of rectum as a diagnostic tool in childhood constipation. 2008. Journal of Urology 179[5], 1997-2002	Study type: Diagnostic. Case control Evidence level: III Study aim: To look into a possible correlation between a dilated rectum measured by ultrasound and a faecal mass detected by digital rectal examination. To evaluate whether this method could diagnose constipation according to Rome III criteria	51 children Inclusion: Children referred to outpatient clinic with either constipation or faecal incontinence, with or without urinary incontinence and a history of UTI. Patients fulfilled Rome III criteria, had at least 2 of the following characteristics: -fewer than 3 bowel movements/week -more than 1 episode of faecal incontinence weekly -large stools in rectum by DRE or palpable on abdominal palpation -occasional passage of large stools -display of	51 children, aged 4-12 years Group 1: 27 children (mean age 7.0±1.8 years) diagnosed with chronic constipation by Rome III criteria Group 2: 24 healthy children (mean age 9.1±2.7 years) Country: the Netherlands	Test: Transabdominal ultrasound of rectum Reference test: Digital rectal examination (DRE)	Rectal diameter (mm) (mean ± 2SD) -Children with rectal impaction as per DRE (n=22, 20 constipated, 2 healthy): 40.5 ± 7.9 -Children without rectal impaction as per DRE (n=26, 7 constipated, 19 healthy): 21.0 ± 4.2 p<0.001 Cut-off value for the presence of rectal impaction (average rectal diameter of children without impaction plus 2SD): 29.4 mm Rectal diameter (mm) (mean ± 2SD) *Before treatment:* -Group 1 (Constipated, n=27): 39.6 ± 8.2 -Group 2 (Healthy): 21.4 ± 6.00 p<0.001	For transabdominal measurements of rectal diameter: a 7.5 MHz probe applied to the abdomen approximately 2cm above the symphysis at 10 to15-degree downward angle. Diameter of the rectum measured in traverse plane. At each session (n=3) diameters were measured three times and mean value was calculated. All children had a partially full bladder range (28 to 450 ml) corresponding to 20-155% of expected bladder capacity for age at the time of the measurement. In case of empty bladder fluid was offered orally and scanning was repeated. If the child had a bowel movement within 3 hours before the investigation or had an urge to defecate, the result was excluded. All investigations were performed by the same observer (a paediatric intern, who had no prior radiological experience) This observer was not reported blinded to the study objectives and patient's characteristics There was no significant difference in height and weight distribution between the 2 groups, but the healthy children were significantly older than the constipated children Constipated children received 3 days of disimpaction followed by 4 weeks of laxative treatment with polyethylene glycol and behavioural therapy. No other details reported No significant correlation between

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		retentive posturing and withholding behaviour painful defecation (healthy control children were recruited form employees of the Paediatrics Department at the hospital) <u>Exclusion criteria:</u> known organic causes of constipation, including Hirschsprung's disease, spinal and anal congenital abnormalities, previous surgery on the colon, inflammatory bowel disease, allergy, metabolic and endocrine diseases, children receiving drugs know to affect bowel function			*After treatment* -Group 1 (Constipated, responded to treatment, n=15): 26.9 ± 5.6 p<0.01 (as compared to same group before) p<0.05 (as compared to group 2) 11 children did not respond to treatment and no significant differences were observed in their rectal diameter as compared to pre-treatment <u>Intraobserver variability:</u> -coefficient of variation of the 3 consecutive measurements: 5.8% ± 4.3% 7 of the constipated children (26%) had a rectal diameter smaller than the established cut-off point for rectal impaction, despite the fact that they fulfilled the Rome III criteria for constipation. 2 healthy children with rectal impaction had a markedly larger rectal diameter (38 and 31 mm) than the other healthy controls.	bladder volume at the time of measurement and rectal diameter (r=0.04) There are missing data not accounted for Apparently healthy children diagnosed with faecal impaction did not receive any laxative treatment, which is worrying from an ethical point of view Authors acknowledged the abdominal ultrasound technique might bear technical limitations related to artefacts like: acoustic enhancement, speed error, and refraction artefacts although their possible influence on their results is unclear No correlation was found between the rectal diameter and age or sex of the children in either group <u>Source of funding:</u> Supported by Karen Elise Jensen Foundation

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		during a 2-mont period before initiation (not specified which) <u>Setting:</u> outpatient clinic				

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Lakshminarayanan et al. A new ultrasound scoring system for assessing the severity of constipation in children. 2008. Pediatric Surgery International 24[12], 1379-1384	Study type: Diagnostic prospective case series Evidence level: III Study aim: To asses the correlation between severity of constipation and ultrasound (US) findings, the correlation between clinical examination and US findings and the correlation between findings at serial out-patient follow-up visits to assess clinical improvements and US findings	500 children Inclusion: All children, both new referrals and follow-up, attending a constipation outpatient clinic Exclusion criteria: Children not compliant to have assessment done by US, cases when the US machine was not available Setting: Constipation outpatient clinic	500 children 317 male median age: 8 years (age range 8 months to 18 years) Country: UK	Test: Pelvic ultrasound Both transverse and longitudinal planes All scans done by same clinician after very brief training Reference test: Clinical assessment: Standard symptoms severity scoring sheet (SSS), completed by parent or child if old enough Clinical assessment done by detailed history taking and abdominal examination	Correlation between SSS and US score -first visit (n=500) Mean SSS: 23.5 (SD 11.6) Mean US total score: 4.02 (SD 2.8) Pearson's correlation: 0.39 P<0.001 -second visit (n=226) Mean SSS: 19.9 (SD 12.6) Mean US total score: 3.49 (SD 2.6) Pearson's correlation: 0.49 P<0.001 -third visit (n=62) Mean SSS: 23.02 (SD 13.7) Mean US total score: 3.66 (SD 2.6) Pearson's correlation: 0.26 P=0.04 -fourth visit (n=12) Mean SSS: 28.5 (SD 16.8) Mean US total score: 4.9 (SD	Additional information from study -US scoring sheet (this score can be used even with an empty bladder) Stool height (x): (bladder effect (y)): No stool: 1 (empty bladder: 0 Retro bladder: 2 (n compression: 0) Just above bladder: 3 Nearly umbilicus: 4 (indented bladder: 1) To umbilicus: 5 (Flattened bladder: 2) Beyond umbilicus: 6 (displaced bladder: 3) Can't see upper edge: 7 Uncooperative: 99 Not available: 0 total =x+y -Symptom severity scoring sheet: Filled in by parent, or child if old enough. Q1 About the soiling problem (faecal incontinence/mess in underclothes) : - none (0) - rarely (1) - occasionally (2) - only is bowel loaded (5) - continuous day only (8) - continuous day and night (10) Q2 About the delay from passing one complete stool to the next: - daily stool (0) - every 2 or 3 days (1) - every 3-5 days (2)

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					3.2) Pearson's correlation: 0.70 P=0.01 <u>Pearson's correlation between US score and clinical examination of palpable faeces per abdomen</u> -first visit (n=500) Mean palpable faeces score: 1.42 (SD 1.6) Mean US total score: 4.02 (SD 2.8) Pearson's correlation: 0.89 P<0.001 -second visit (n=226) Mean palpable faeces score: 1.10 (SD 1.6) Mean US total score: 3.49 (SD 2.6) Pearson's correlation: 0.845 P<0.001 -third visit (n=62) Mean palpable faeces score: 1.10 (SD 1.6) Mean US total score: 3.66 (SD	- every 5-10 days (5), - greater than 10 (8) - never (10) Q3 About pain and difficulty with passing stools: - none (0) - occasionally (1) - often (2) - with most stools (4) - with every stool (5) Q4 About the amount and types of medicine needed regularly over the last month: - none (0) - softeners only e.g.: lactulose or Docusate or daily Movicol or methyl cellulose (1) - softeners and daily stimulants e.g.: Senokot or picosulphate (2) - softeners and daily stimulants and weekend extra picosulphate or Movicol (4) - medicines as well as extra weekend klenprep or high dose Movicol (8) - medicines as well as regular enemas or suppositories (10) Q5 About how your child's general health has been affected by the bowel problem over the last month: - well (0) - occasionally ill (2) - often ill (3) - ill most days (4) - never well (5)

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					2.6) Pearson's correlation: 0.77 P<0.001 -fourth visit (n=12) Mean palpable faeces score: 1.92 (SD 1.7) Mean US total score: 4.9 (3.2) Pearson's correlation: 0.91 P<0.001	Q6 About behavior related to the bowel problem: - cooperative OK (0) - needs reminding to use the lavatory/pot (2) - refuses the lavatory or pot (3) - also refuses medicines (4) - also generally difficult behavior (5) Q7 overall, which best describes how the problems are now compared with the last time seen at hospital: - nearly completely OK (0) - much better (1) - some improvement (4) - still as difficult (8) - getting worse (12) Filled in by practitioner Amount of stool detected on clinical examination of abdomen score: - None palpable: 0 - Little: 1 - Suprapubic only: 2 - To umbilicus: 3 - Beyond umbilicus: 5 - Reaching ribs: 8 <u>Reviewers comments</u> No control/comparison group Very small sample size at the fourth visit <u>Source of funding:</u> Not stated

Diagnostic Value of Transit Studies in Children with Chronic Idiopathic Constipation

Radiopaque Markers

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
de Lorijn et al. Prognosis of constipation: clinical factors and colonic transit time. 2004. Archives of Disease in Childhood 89[8], 723-727	Study type: Diagnostic prospective case series Evidence level: III Study aim: To investigate the relation between symptoms of chronic constipation and colonic transit time (CTT). To evaluate the possible relation between symptoms and CTT and the outcome after one year of follow up	169 consecutive patients Inclusion criteria: All referred patients ≥ 5 years old, at least two of the following: 1) defecation <3/week 2) encopresis episodes >1/week 3) passing of very large stools every7-30 days 4)a palpable abdominal or rectal faecal mass Exclusion criteria: Hirschsprung's disease, spinal and anal abnormalities, mental retardation, use	169 consecutive patients 65% boys Median age 8.4 years Country: the Netherlands	Test: Colonic transit time (CTT) with radiopaque markers Reference: Clinical variables: -defecation frequency -encopresis frequency -night-time encopresis -rectal mass	Total and segmental transit times (hours) , (median, 25 to75th centiles) a. Boys (n=109) -total colon: 60 (38 to 103) -delayed >62 h: 49% -ascending colon: 10 (5 to 16) -delayed >18 h: 23% -descending colon: 11 (4 to 18) -delayed >20 h: 21% -rectosigmoid: 37 (19 to 68) -delayed >34h: 53% b. Girls (n=60) -total colon: 53 (37 to 74) -delayed >62 h: 43% -ascending colon: 11 (5 to 15) -delayed >18 h: 18% -descending colon : 8 (5 to 18) -delayed >20 h: 23% -rectosigmoid: 31 (17 to 47) -delayed >34h: 38% c. Total group (n=169) -total colon: 58 (37 to 92) -delayed >62 h: 47% -ascending colon: 10 (5 to 16) -delayed >18 h: 21% -descending colon: 10 (5 to 18) -delayed >20 h: 22%	Additional information from study: Significant baseline differences between boys and girls: median defecation frequency at intake lower in girls than boys (1.0 vs. 2.0 times/week; p=0.03); encopresis frequency more than twice weekly reported more often in boys (94% vs. 73%; p=0.0002). More girls than boys reported no encopresis at all (20% vs. 6% p<0.05) At entry all children underwent CCT. Treatment with oral/rectal laxatives discontinued for at least 4 days before the test; during this period they took one sachet of fibre (Volcolon, 6g) each day. Then they ingested a capsule containing 20 radiopaque markers on 3 consecutive mornings. Abdominal X ray performed on days 4 and 7 in morning. Additional abdominal x ray performed on days 10, 13 and 16 if more than 20% of markers remained on previous film. X ray localisation of markers based identification of bony landmarks and gaseous outlines. Markers counted in right, left and rectosigmoid region and mean segmental transit time calculated according to previously described formula.

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		of drugs other than laxatives <u>Setting:</u> gastrointestinal outpatient clinic			-rectosigmoid: 32 (18 to 63) -delayed >34h: 48% (no significant differences between boys and girls in the CTT and rectosigmoid transit time) <u>Correlation between clinical parameters and transit time (hours)</u> <u>(RSTT: rectosigmoid transit time)</u> 1. Defection frequency: <u>a. 0 to1/week (n=79)</u> CTT (median): 74 RSTT (median): 38 <u>b. >1 to 3/week (n=55)</u> CTT (median): 50 RSTT (median): 30 <u>c. ≥ 3/week (n=35)</u> CTT (median): 49 RSTT (median): 28 CTT: p=0.001 a. vs. b and a vs. c RSTT: p= 0.009 a. vs. b and a vs. c 2. Encopresis frequency (day and night) <u>a. no encopresis (n=18)</u> CTT (median): 49 RSTT (median): 24	Normal ranges for total and segmental transit times based on upper limits (mean ± 2 SD) from a study in healthy children: CTT > 62 h considered delayed. Upper limits for right colon, left colon ad rectosigmoid transit time were 18, 20 and 34 hours respectively <u>Reviewers' comments:</u> Researchers not blinded No definition of encopresis given No control group <u>Source of funding:</u> not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					b. <1/day (n=24) CTT (median): 52 RSTT (median): 31 c. 1 to 2/day (n=48) CTT (median): 50 RSTT (median): 30 d. ≥2/day (n=79) CTT (median): 70 RSTT (median): 38 CTT: p= 0.003 d vs. c, d vs. b, and d vs. a RSTT: p= 0.03 d vs. c, d vs. b, and d vs. a 3. Night time encopresis: a. not present (n=106) CTT (median): 47 RSTT (median): 28 b. present (n=63) CTT (median): 74 RSTT (median): 46 CTT: p< 0.0001 RSTT: p< 0.0001 4. Rectal mass: a. not present (n=118) CTT (median): 48 RSTT (median): 28 b. present (n=51) CTT (median): 86 RSTT (median): 64 CTT: p< 0.0001	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					RSTT: p< 0.0001	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Yang et al. Determination of gastrointestinal transit time in functional constipation in children. 2005. Chinese Journal of Clinical Rehabilitation 9[7], 236-237China.	Study type: Diagnostic case control Evidence level: III Study aim: to investigate the difference of gastrointestinal transit time (GTT) between constipated and normal healthy controls to elicit its significance in assessing the dynamics of the whole gastro-intestine and each segment	96 children Inclusion criteria: -Patients: confirmed functional constipation (FC). Two of the following for more than 3 months: Evacuation less 3 times/week, evacuating pains, faecal soiling every week or incontinence more 2 times/week in over 5 years old, touchable stool by abdominal or anal examination, excessive defecation at interval of 7 to 30 days. No administration of gastrointestinal dynamic and evacuation drugs for 2 weeks	96 children -Patients (n=28): 38 boys Mean age: 6 years (range 3 to 14) -Controls (n=68) 38 boys Mean age: 6 years (range 3 to 13) Country: China	Tests: Colonic transit time (CTT) with radiopaque markers Reference: none	Total transit time (hours, mean ± SD) -Patients (n=28) 59.9 ± 2.3 -Controls (n=68) 14.8 ± 0.8 p<0.01 Segmental transit time (hours, mean ± SD) Right colon: -Patients (n=28) 20.3 ± 1.2 -Controls (n=68) 7.3 ± 1.1 p<0.01 Left colon: -Patients (n=28) 12.8 ± 1.7 -Controls (n=68) 3.4 ± 0.8 p<0.01 Rectosigmoid: -Patients (n=28) 26.8 ± 1.4 -Controls (n=68) 4.1 ± 1.2	Reviewers' comments: Researchers not blinded No data available on diet, use of laxatives previous to the measurement of CTT Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		-Controls: normal height and weight, normal frequency and character of evacuation fro 3 months without administration of any gastrointestinal dynamic and evacuation drugs Exclusion criteria: organic ailment in alimentary tract and other organs ailment that would affect gastrointestinal function Setting: general hospital			p<0.01	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
de Lorijn et al. The Leech method for diagnosing constipation: intra- and interobserver variability and accuracy. 2006. Pediatric Radiology 36[1], 43-49	Study type: Diagnostic. Case control Evidence level: III Study aim: to assess intra- and interobserver variability and determine diagnostic accuracy of the Leech method in identifying children with functional constipation	89 non selected consecutive children Inclusion criteria: patients referred for the evaluation of abdominal pain, constipation or faecal incontinence. Diagnosis of constipation: at least two of the following was present: -defecation frequency less than 3 times/week -2/more episodes of faecal incontinence per week -production of large amounts of stool once over a period of 7-30 days -presence of palpable abdominal or rectal mass (control children fulfilled criteria	89 children Median age: 9.8 years Group 1 (constipation): n=52 (28 boys) Group 2 (controls): N=37 (24 boys) 31: FNRFI 6: FAP Country: the Netherlands	Test: Plain abdominal radiography (read using the Leech method) Reference test: Colonic transit time (CTT) with radiopaque markers	Mean Leech score (using the first score): -Group 1 (constipation): 10.1 -Group 2 (controls): 8.5 p=0.002 Mean CTT: -Group 1 (constipation): 92 h -Group 2 (controls): 37 h p<0.0001 Diagnostic accuracy of Leech method vs. CTT method: -Leech method: (cut-off point as per study comparable to 9 as per literature) Sensitivity: 75% Specificity : 59% (cut-off point 9 as per literature) Positive Predictive Value: 72% Negative Predictive Value: 63% -CCT: (cut-off point 54h as per study) Sensitivity: 79% Specificity: 92% (cut-off point 62h as per literature) Sensitivity: 71%	Additional information from study Diagnosis of functional non-retentive faecal incontinence (FNRFI) based on: 1) two/more faecal incontinence episodes/week with no signs of constipation 2) defecation frequency 3/more times/week 3) no periodic passage of very large amounts of stool at least once during a period of 7-30 days 4) no palpable abdominal or rectal mass on physical examination fro a period of at least 1 week during the preceding 12 weeks. Faecal incontinence defined as the voluntary/involuntary loss of loose stools in the underwear after the age of 4 years Functional abdominal pain (FAP) defined as abdominal pain of at least 12 weeks duration 1)that was continuous or nearly discontinuous in a school-aged child or adolescent 2) that had no or only an occasional relationship with physiological events 3) that was accompanied by some loss of daily functioning 4) that was not feigned and) for which there were insufficient criteria to indicate the presence of another functional gastrointestinal disorder Children with clinical characteristics of FAP and FNRFI classified as the control group: according to authors they have “little or no faecal loading on an abdominal radiograph” Treatment with oral/rectal laxatives discontinued in each patient for at least

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		for functional abdominal pain (FAP) and for functional non-retentive faecal incontinence (FNRFI)) <u>Exclusion criteria:</u> not reported <u>Setting:</u> tertiary gastroenterology outpatients clinic			Specificity: 95% Positive Predictive Value: 69% Negative Predictive Value: 97% <u>ROC analysis</u> -AUC (Leech method): 0.68 (95% CI 0.58-0.80) -AUC (CTT method): 0.90 (95% CI 0.83-0.96) p=0.00015 AUC=Area Under the ROC curve ROC=Receiving Operator Characteristic	4 days. Thereafter the patient ingested one capsule with 10 small radiograph opaque markers on 6 consecutive days, in order to determine the CTT. Subsequently, a plain abdominal radiograph was taken on day 7. this radiograph was both used in the Leech method and for CTT measurement CTT determined by the method of Bouchoucha. Radiography on day 7 used to count the number of markers in the colon. Number of markers x 2 produced total CTT in hours. Localization of markers and CTT calculated according to previously described formula. Normal range for total transit time based on the upper limits (mean ± 2xSD) from a study in healthy children. Based on this study a CTT > 62 h was considered delayed 3 scorers independently scored the same radiography twice (4 weeks apart) using the Leech method, discussed amongst the 3 scorers previous to both readings CTT assessed once by single scorer. Assumed the counting of radiopaque markers would not lead to intra- or interobserver variability <u>Leech scoring method:</u> Colon divided into three segments: right, left and recto sigmoid Each segment provided with a score from 0-5 0:no faeces visible

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						1:scanty faeces visible 2: mild faecal loading 3: moderate faecal loading 4: severe faecal loading 5: severe faecal loading with bowel dilatation Leech score of 9 or more: suggestive of constipation Scorers: 3 experienced doctors (a 5th year radiology resident, a paediatric radiologist and a senior paediatric gastroenterologist). No clinical information about the patients was made available to them. In 5% of cases the Leech scores of the same patient produced by different scorers could differ by 4 points or more Reviewer's comments: No data reported on type of diet given prior to the measurement of CTT Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Zaslavsky et al. Chronic functional constipation in adolescents: clinical findings and motility studies. 2004. Journal of Adolescent Health 34[6], 517-522	Study type: Diagnostic case control Evidence level: III Study aim: to evaluate symptoms and clinical findings in a prospective series of adolescents with functional constipation and to identify colonic disorders by measuring total and segmental colonic transit times with radiopaque markers	61 adolescents Inclusion criteria: -patients: aged 12 to 18 years, both sexes, normal sexual maturation and growth (Tanner staging), <3 evacuations/week, excessive straining, complaints for 1 year or longer -controls: no digestive complaints, more than 3 bowel movements/week (participated in previous study by authors) Exclusion criteria: neurologic/metabolic diseases, Hirschsprung's disease (barium enema), spinal disease, anorectal anomalies, surgery of the	61 adolescents -Patients (n=48) Mean age: 14 years (range 12 to 18) 13 boys -Controls (n=13) 9 boys age not reported Country: Brazil	Test: Colonic transit time (CTT) with radiopaque markers Reference: Clinical variables	Colonic transit times patterns (N, %): Normal colonic transit: 8 (17) Slow colonic transit: 29 (60) Pelvic floor dysfunction: 6 (13) Slow colonic transit and pelvic floor dysfunction: 5 (10) Total transit time (hours, mean ± SD, median and range) Constipated: 62.9 ± 12.6 69 (62.9 to 12.6) Non constipated: 30.2 ± 13.2 27.5 (10.8 to 50.4) p<0.001 Segmental transit time (hours, mean ± SD, range) -Right colon: Constipated: 18.6 ± 15 13.2 (12 to 54) Non constipated: 6.7 ± 3.9 4.8 (1.2 to 12) P=0.001 -Left colon: Constipated: 24.3 ± 13.7 22.8 (2.4 to 51.6)	Additional information from study: Radiographs interpreted by 2 of the authors (no further data provided) Adolescents told to keep their usual diet during examination and to discontinue use of laxatives 7 days before examination Patients underwent plain abdominal radiography as per Metcalf method -Slow CTT: delay of total CTT and delay of markers in the right and/or left colon -Pelvic floor dysfunction: delay in the rectosigmoid -Slow CTT associated with pelvic floor dysfunction: delay in the colon and rectosigmoid together with delay in the total CTT Cut-off points for measurements: mean value plus two SDs. Right colon (>14 h); left colon (>24h), rectosigmoid (>>36 h) and total (>51 h) Reviewers' comments: Researchers not blinded Cut-off points for total and segmental transit times apparently taken from previous 1998 study by the authors Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		colon, mental retardation, use of drugs that act on digestive motility, no clinical evidence of bowel /systemic disease that could cause constipation <u>Setting:</u> hospital gastroenterology outpatients clinic			Non constipated: 7.9 ± 7.8 7.2 (0-28.8) P<0.001 -Rectosigmoid: Constipated: 20 ± 15.7 18 (0 to 54) Non constipated: 15.6 ± 10.7 12 (3.6 to 36) NS <u>Interval between evacuations:</u> -Slow colonic transit (n=29): 7.7 ± 6.6 days -Pelvic floor dysfunction (n=6): 3.7 ± 2.4 days p<0.003 Faecal mass palpable at initial examination statistically associated with slow colonic transit (p=0.03) Other clinical variables not statistically associated with delay in colon or rectosigmoid transit: onset of constipation, scybalous faeces, large volume, faecaloma, anal bleeding, soiling, previous use of	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					laxative/suppositories/enemas, history of constipation in family, anal fissure, daily ingestion of fibre, sex, age, skin colour	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Gutierrez et al. Total and segmental colonic transit time and anorectal manometry in children with chronic idiopathic constipation. 2002. Journal of Pediatric Gastroenterology and Nutrition 35[1], 31-38	Study type: Diagnostic case control Evidence level: III Study aim: to evaluate the use of a colonic motility study easily applied in daily clinical practice to more clearly define patients with this disorder and to improve therapy and follow-up	68 children Inclusion criteria: Patients: history of chronic idiopathic constipation > 6 months, with/without secondary encopresis, refractory to conventional treatment of disimpaction, re-education of defecatory habits, measures to increase dietary fibre content and administration of mineral oil or osmotic-type laxatives (lactulose or Lactinol). Encopresis defined as non-voluntary defecation with a frequency of more than twice weekly in children older than 4 years in	68 children aged 2 to 14 years Patients (n=38) Controls (n=30) Country: Spain	Test: Colonic transit time (CTT) with radiopaque markers Reference: Frequency of defecation	Total transit time (hours) (mean ± SD, ranges) Patients (n=38) 49.57 ± 25.38 (15.6 to 122.4) Controls (n=30) 29.08 ± 8.30 (14.4 to 50) p<0.001 Segmental transit time (hours) (mean ± SD, ranges) -RC: Patients (n=38) 9.53 ± 9.07 (2.4 to 36) Controls (n=30) 7.52 ± 5.75 (2.4 to 15.6) p value NS -LC: Patients (n=38) 15.41 ± 13.13 (2.4 to 32) Controls (n=30) 6.60 ± 6.20 (2.4 to 24) p=0.01 -RS: Patients (n=38) 24.20 ± 16.77 (4.8 to 69.6) Controls (n=30) 14.96 ± 8.70 (2.4 to 19.2)	Additional information from study: Two children from patients group did not complete study: one refused to swallow the capsules; one did not comply (not clear exactly with what) No significant differences observed in mean daily fibre intake and calorie consumption between the 2 groups Measurements made while children maintained their usual diets. Laxative treatment discontinued 1 week before the test and a cleansing enema administered on the day before the test No differences observed in CTT in relation to either se or age. Statistically significant inverse correlation observed between total CTT and number of weekly defecations (correlation coefficient, r=0.68, p<0.001) Reviewer comments: Researchers not blinded Source of funding: Janssen Pharmaceutical contributed the material required to determine the colonic transit time. No further details provided

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		the absence of any underlying organic cause Controls: normal bowel habits (between 3 defecations daily and 3 weekly, without staring at stool, and faces of normal consistency for at least 12 months before the study, no history of previous abdominal/major extra-abdominal surgery, not on medication with effects on digestive tract, normal diet, and underwent abdominal radiography as part of clinical study with normal results <u>Exclusion criteria:</u> Hirschsprung's disease, spinal/ anal			p=0.01 <u>Clinical characteristic of the patients' group as a function of colonic transit time:</u> a) Age at onset of constipation (y, mean, SD): -Total CTT within reference values (n=19): 2.54 (1.18) -Prolonged total CTT (n=19): 1.77 (0.88) p<0.05 b) Family history of constipation: -Total CTT within reference values (n=19): 21% -Prolonged total CTT (n=19): 79% p<0.01 c) Abdominal mass -Total CTT within reference values (n=19): 60% -Prolonged total CTT (n=19): 93.8% p<0.05 d) Encopresis episodes/night (mean, SD) -Total CTT within reference values (n=19): 0.10 (0.44) -Prolonged total CTT (n=19): 0.60 (0.91) p<0.05	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		malformations, prior surgery of colon, metabolic diseases, mental retardation <u>Setting:</u> gastroenterology outpatients clinic			No significant differences found for age at diagnosis, sex, defecations/week, pain at defecation, enuresis, anal fissure, rectal mass or encopresis episodes/day	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Zaslavsky et al. Total and segmental colonic transit time with radio-opaque markers in adolescents with functional constipation. 1998. Journal of Pediatric Gastroenterology and Nutrition 27[2], 138-142	Study type: Diagnostic case control Evidence level: III Study aim: To measure total and segmental colonic transit time in constipated adolescents and compared the results with those in non constipated children	26 adolescents Inclusion criteria: -patients: hard stools, difficulty in evacuating, less than 3 bowel movements/week, no evidence of palpable rectal mass, history of constipation of at least one year of duration -controls: no digestive complaints, more than 3 bowel movements/week Exclusion criteria: neurologic/metabolic diseases, Hirschsprung's disease, spinal/anal anomalies, surgery of the colon, mental retardation, history of drug abuse	26 adolescents aged 12-18 years Constipated (n=13) Nonconstipated (n=13) 9 boys in each group Country: Brazil	Test: Colonic transit time (CTT) with radiopaque markers Reference: Clinical variables	Total transit time (hours, mean ± SD, range) -Constipated 58.25 ± 17.46 68.4 (27.6 to 72) -Non constipated 30.18 ± 13.15 27.5 (10.8 to 50.4) P<0.001 Segmental transit time (hours, mean ± SD, range) -Right colon: Constipated 15.97 ± 12.48 13.7 (2.4 to 43.2) Non constipated 6.74 ± 3.91 7.2 (1.2 to 12) P=0.03 -Left colon: Constipated 24.74 ± 13.39 25.7 (7.2 to 51.6) Non constipated 7.94 ± 7.82 7.2 (0 to 28.8) P<0.001 -Rectosigmoid: Constipated 17.60 ± 16.25	Additional information from study: No significant statistical differences between two groups regarding age, weight and height Total and segmental CTT measured using Metcalf technique On the days the measurements were performed adolescents were advised not to alter their diets and not to ingest food that might alter bowel motility. Fibre intake standardised at 15g/day but due to poor compliance, test was performed on their normal diet. Any treatment with laxatives discontinued at least 7 days before test All radiographs interpreted by the same radiologist who did not know whether the patient was constipated Patients with constipation considered to have slow colonic transit when delay in transit through the right colon, the left colon or both. They were considered to have distal obstruction when the delay occurred in the rectosigmoid. Normal values for total and segmental transit times taken from the 95th percentile of adolescents without constipation Reviewers' comments: Small sample size Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		Setting: hospital			16.6 (0 to 49.2) Non constipated 15.58 ± 10.69 12 (3.6 to 36) NS Interval between stools: -Constipated: 5.8 ± 2.3 days -Nonconstipated: Daily P<0.01 No significant differences between the 2 groups regarding: bulky or small stools, encopresis, rectal mass, intense use of laxatives, bowel movements/week and mean daily intake of fibres	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Bijos et al. The usefulness of ultrasound examination of the bowel as a method of assessment of functional chronic constipation in children. 2007. Pediatric Radiology 37[12], 1247-1252	Study type: Diagnostic Case control Evidence level: III Study aim: to determine whether a new method of ultrasound (US) assessment of stool retention could be used as a method of identifying children with functional chronic constipation, and to determine whether children with an enlarged rectum and colon (as seen on US) should be referred for further procedures such as	225 children Inclusion criteria: Referred because of chronic constipation, based on history and physical examination: defecation disorders persisting longer than 6 months, all patients fulfilled Rome II criteria for defecation disorders (frequency of bowel movements less than twice a week, consistency and size of stool caused pain during defecation, withholding behaviour) Exclusion criteria: anatomic abnormality	225 children Group 1: 120 children with chronic constipation (72 boys, mean age 6.25 years, range 1.6 to 17.9) Group 2: 105 children with normal defecation pattern (mean age 8.25 years) Country: Poland	Test: Abdominal ultrasound Reference: Colonic transit time (CTT) with radiopaque markers Transit times (hours, upper limit of 66 based on literature) ≤66: normal-transit constipation 66-100: slow-transit constipation >100: very delayed slow-transit constipation	Mean colonic transit times: Children with faecal impaction (as per US) had significantly longer average segmental transit time for the rectum, sigmoid and left colon ($p<0.001$, $p=0.0015$ and $p=0.0104$ respectively) there was not statistically significant difference for the right side of the colon. Children with an overfilled splenic flexure on US had a significantly longer transit time in the left side of the colon ($p=0.0029$) Total CTT (mean values are estimates taken from a bar chart): -Patients with faecal impaction on US: 67 -Patients without faecal impaction on US: 42 $p<0.001$ Segmental CTT (mean values are estimates taken from a bar chart) 1. Right colon -Patients with faecal impaction on US: 9	Additional information from study: Faecal impaction (as per US in sagital plane): when pelvic structures were covered by stool masses and were not even partially visible. -Overfilled colon (as per US): Overfilled bowel at the splenic flexure: when it was impossible to visualise the entire length of the left kidney due to the lack of visibility of the lower pole of the kidney because of bowel contents. Probe applied to the long axis of the spleen. Overfilling of the transverse colon: when the superior mesenteric artery was not visible with the probe applied in the sagital plane over the aorta US: children examined before food and had a slightly filled bladder. Patients who passed stool on the day of the examination were temporarily excluded from the study until they became constipated again. Measurement was taken several times and the highest one recorded taken as the final measurement Total and segmental colonic transit time measured by the modified sixth day Hinton method. Total and segmental time obtained by multiplying the number of radiopaque markers seen on the radiograph by 1.2 (time in hours/number of markers swallowed by

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	proctoscopy and assessment of colonic transit time.	(Hirschsprung's disease, congenital abnormalities of the anorectal region) neurological and psychiatric conditions (cerebral palsy, spina bifida, mental retardation, anorexia nervosa) ,metabolic conditions (diabetes mellitus/insipidus) endocrine disorders (hypothyroidism), previous thoracic or abdominal surgery (control patients: normal defecation patterns, treated for various symptoms like chronic abdominal pain, food allergies)			-Patients without faecal impaction on US: 8 N.S 2. Left colon -Patients with faecal impaction on US: 18 -Patients without faecal impaction on US: 9 p=0.0104 3. Rectosigmoid: -Patients with faecal impaction on US: 32 -Patients without faecal impaction on US: 16 p=0.0015	the patient) <u>Reviewer's comments:</u> No data on diet or use of laxatives previous to the measurement of CTT The same individual performed all the US scans, but not other data on this were reported (as blinding, individual's experience in radiology, etc) It is not clear what number of children underwent each of the tests It is not clear whether "enlarged" and "overfilled" colon mean the same for the authors, as no measurements of "enlarged" colon are reported. Data on number of children diagnosed with "overfilled colon" are not reported. It is not clear how many children were diagnosed with faecal impaction by US Children apparently underwent DRE but no results are reported Control group did not differ from patients regarding gender, the comparison regarding age is not clearly reported <u>Source of funding:</u> Not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		Setting: gastroenterology outpatient clinic				

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Benninga et al. Colonic transit time in constipated children: does pediatric slow-transit constipation exist? 1996. Journal of Pediatric Gastroenterology and Nutrition 23[3], 241-251	Study type: Diagnostic case control Evidence level: III Study aim: To investigate the presence of slow colonic transit in children with constipation using radiopaque markers	148 children Inclusion criteria: -Patients: otherwise healthy children with complaints of constipation with/without encopresis, encopresis alone or recurrent abdominal pain. They fulfilled at least 2 of the following criteria for paediatric constipation: a) 2/fewer bowel movements/week b)2/more soiling or encopresis episodes/week c) passage of very large amounts of stool once every 7-30 days d) a palpable abdominal mass or rectal mass -Controls: healthy children.	148 children -Patients (n=94): a. PSTC (paediatric slow transit constipation): 24 children 17 boys Mean age 8 years (range 5-14) b. NDTC (normal delayed transit constipation) 70 children 46 boys Mean age 8 years (range 5-14) -Controls (n=54): 15 children (for rectal manometry) 10 boys Mean age 11 years (range 7-15) Country: the Netherlands	Test: Colonic transit time (CTT) with radiopaque markers Reference -Clinical variables	Total transit time (hours, median, range) -PSTC (n=24) 189 (104.4 to 380.4) -NDTC (n=70) 46.8 (3.6 to 99.6) Segmental transit time (hours, median, range) Right colon: -PSTC (n=24) 27.0 (3.6 to 60) -NDTC (n=70) 8.4 (0 to 32.4) Left colon: -PSTC (n=24) 37.2 (0 to 110.4) -NDTC (n=70) 7.2 (0 to 36.0) Rectosigmoid: -PSTC (n=24) 116.4 (49.2 to 226.8) -NDTC (n=70) 27.0 (0 to 90.0) Clinical variables: -Daytime soiling (yes/no) (no. , %) -PSTC (n=24) 22 (92) -NDTC (n=70)	Additional information from study: Total and segmental CTT done as described by Metcalf Based on upper limit (mean + 2SD) of previous study in 63 constipated children (Corazziari, 1985), children in current study arbitrarily separated in 2 groups: 1. CTT>100 h: paediatric slow transit constipation (PSTC) 2. CTT<100 h: normal- or delayed-transit constipation (NDTC) (normal transit ser at < 63h) Further analysis of the NDTC group after separation into a group with total CTT<63h and one with total CTT between 63 and 100h showed same significant differences compared with PSTC children as did the total PSTC group allowing the merge of these children CTT performed on patients taking their normal diet, any treatment with laxatives discontinued at least 4 days prior o test. No enemas given before transit studies. Reviewers' comments: Researchers not blinded Values for both total and segmental transit times expressed as medians in the text and the heading of a table, and as means in the table itself. We have chosen to report them as median values because authors stated in the

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		Siblings and friends of paediatric patients and medical staff Soiling defined as loss of loose stools, encopresis as loss of formed stools A palpable rectal mass defined as the presence of a firm and large faecal lump in the rectal ampulla <u>Exclusion criteria:</u> Hirschsprung's disease, spinal/ anal anomalies, surgery of colon, metabolic diseases, mental retardation, on drugs other than laxatives <u>Setting:</u> outpatient clinic of tertiary academic			48 (69) p=0.05 - Daytime soiling episodes / week (median, range) -PSTC (n=24) 14.0 (0 to 7) -NDTC (n=70) 5.0 (0 to 56) p<0.01 -Nightime soiling (yes/no) (no., %) -PSTC (n=24) 17 (71) -NDTC (n=70) 8 (11) p<0.01 - Nightime soiling episodes / week (median, range) -PSTC (n=24) 7 (0 to 7) -NDTC (n=70) 0 (0 to 7) p<0.01 -Normal stools (no., %) -PSTC (n=24) 18 (75) -NDTC (n=70) 33 (49) p=0.03	statistical analysis section that results were expressed as median and range for continuous variables <u>Source of funding:</u> major grant from the Stitching Kinderpostzegels Nederland and from an endowment from Zyma Nederland (Imporal)

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		teaching hospital			-Pain during defecation (no., %) -PSTC (n=24) 8 (33) -NDTC (n=70) 28 (60) p=0.01 -No rectal sensation (no., %) -PSTC (n=24) 8 (33) -NDTC (n=70) 10 (14) p=0.03 -Palpable abdominal mass (no., %) -PSTC (n=24) 17 (71) -NDTC (n=70) 27 (39) p=0.02 -Palpable rectal mass (no., %) -PSTC (n=24) 17 (71) -NDTC (n=70) 9 (13) p<0.01 No significant differences regarding: sex, age, toilet training statue, age at which toilet training started, bowel movements/week, large amounts of stools very 7-30	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					days, encopresis episodes/week, abdominal pain, poor appetite, daytime or nightime urinary incontinence Proportion of children with PSTC and rectal palpable mass, night time soiling or both: 0.34, 0.39 and 0.82 respectively. (multivariate analysis) only 7% of children without any of these characteristics had PSTC	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Benninga et al. Defaecation disorders in children, colonic transit time versus the Barr-score. 1995. European Journal of Pediatrics 154[4], 277-284	Study type: diagnostic case control Evidence level: III Study aim: to objectivate the presence or absence of faecal retention in each child using CTT and compare these findings to the Barr score	211 children Inclusion criteria: complains of infrequent defection, soling, encopresis or recurrent abdominal pain (RAP) -Group 1: patients who met at least 2 of the 4 criteria for paediatric constipation (PC): 1) stool frequency less than 3 times/week 2) 2 or more soling/encopresis episodes/week 3) periodic passage of very large amounts of stools once every 7-30 days 4) a palpable abdominal or rectal mass -Group 2: only encopresis and/or soiling (ES), without	211 children Group 1 (PC) N=129 64% boys Median age: 8 years (5-14) Group 2 (isolated ES) N=54 81% boys Median age: 9 years (5-17) Group 3 (RAP) N=23 39% boys Median age: 9 years (5-16) Country: the Netherlands	Test: Colonic transit time (CTT) with radiopaque markers Reference test: Plain abdominal radiography (read using the Barr score) Barr scoring system: Quantifies the amount of faeces in four different bowel segments: ascending colon (0,1, or 2 points);, transverse colon (0,3, 4 or 5 points) descending colon (0,3, 4 or 5 points) and rectum (0,2 or 5 points) and also the consistency of the faces i.e. scybala (0,1,2 or 3 points); granular (0,2, 4 or 5 points)	Total CTT (hours, mean and range): -Group 1 (PC, n=129): 79.3 (2.4 to 384) -Group 2 (isolated ES, n=54): 41.4 (16.6 to 104.4) -Group 3 (RAP, n=23): 32.5 (4.8 to 69.6) -Healthy controls (n=23, mean + 2SD) (Arhan *et al.)* 29.0 (62) p=0.03 group 2 vs. group 3 Segmental CTT (hours, mean and range): -Right colon: Group 1 (PC, n=129): 13.2 (<1.2 to 60) Group 2 (isolated ES, n=54): 7.9 (<1.2 to 26.4) Group 3 (RAP, n=23): 7.7 (1.2 to 21.6) -Healthy controls (n=23, mean + 2SD) (Arhan *et al.)* 7.7 (18) p<0.01 group 1 vs. group 2 and group 1 vs. group 3 -Left colon:	Additional information from study: Significant differences in the study population regarding clinical variables: more PC children reported large amount of stools, a palpable abdominal mass and rectal mass as compared to RAP children (p<0.001). More PC children reported abdominal pain and no rectal sensation as compared to ES children (p<0.05) Two experienced paediatric radiologists familiar with the Barr criteria and without any knowledge of the clinical condition of the patient, independently analysed in random order the first (day 4) and second (day 7) plain abdominal radiographs of the markers studies of the initial 101 consecutive patients. Barr scores were assessed in the different segments and total scores calculated. A radiograph was considered positive if Barr score>10 Normal range for segmental and total CTT taken from upper limits obtained in healthy controls (mean ± 2SD), as described by Arhan et al. Total CTT > 62h: delayed Total CTT > 100h: slow transit constipation (based on study by Corazziari et al.) Normal limits for segmental transit times (h): right colon (18), left colon (20), rectosigmoid (34) Colonic transit time assessment method: Metcalf

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		any of the other criteria for PC. Soiling defined as the loss of loose stools. Encopresis defined as (in)voluntary passage of a normal bowel movement in the underpants or another unorthodox location with a frequency of 2 or more times/week after the age of 4 in the absence of any organic cause -Group 3: RAP defined as at least 3 episodes/week of non specified RAP, severe enough to interfere with day-to day activities over at least a 3-month period, without any of the other symptom of PC <u>Exclusion</u>			Group 1 (PC, n=129): 16.1 (<1.2 to 110.4) Group 2 (isolated ES, n=54): 6.8 (<1.2 to 25.2) Group 3 (RAP, n=23): 7.0 (1.2 to 25.2) -Healthy controls (n=23, mean + 2SD) (Arhan *et al.)* 8.7 (20) p<0.01 group 1 vs. group 2 and group 1 vs. group 3 -Rectosigmoid Group 1 (PC, n=129): 49.7 (<1.2 to 226.8) Group 2 (isolated ES, n=54): 26.7 (4.8 to 93.6) Group 3 (RAP, n=23): 18.9 (1.2 to 49.2) -Healthy controls (n=23, mean + 2SD) (Arhan *et al.)* 12.4 (34) p<0.01 group 1 vs. group 2 and group 1 vs. group 3 p=0.05 group 2 vs. group 3 <u>CCT</u> -Interobserver agreement:	Measurements of CTT performed with patients on their habitual diet. Treatment with laxatives ([ills or enemas) discontinued for at least 4 days before the CTT study 5 patients excluded from study: 4 not able to swallow capsule, 1 had “uninterpretable” abdominal X-ray Comparison of the Barr-score with the marker method performed using the mean Barr-score of the two observers obtained on radiograph I. Similar analysis using radiograph II revealed no differences compared to radiograph I, therefore only results with radiograph I are presented in detail According to authors the radiopaque markers were no hindrance for the 2 observers in assessing the Barr-scores <u>Reviewers’ comments:</u> There are missing data not accounted for: only 101 abdominal radiographs were available for analysis, but there is no clear explanation for this <u>Source of funding</u>: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		criteria: Hirschsprung's disease, spinal/ anal anomalies, prior surgery of colon, metabolic diseases, mental retardation, use of drugs other than laxatives Setting: gastroenterology outpatients clinic			Radiograph 1 (n=101): Perfect agreement: 62% Difference of one marker: 25% Radiograph 2 (n=101): Perfect agreement: 92% Difference of one marker: 6% Barr scores (n=101) (mean of two observers) -Group 1 (PC, n=57) Radiograph 1: ≥10 : 60% Radiograph 2: ≥10 : 63% -Group 2 (isolated ES, n=30) Radiograph 1: ≥10 : 47% Radiograph 2: ≥10 : 60% -Group 3 (RAP, n=14) Radiograph 1: ≥10 : 47% Radiograph 2: ≥10 : 63% -Interobserver agreement (agreement between the 2 observers for the different segments on the same radiograph): k from 0.28 (fair) to 0.60 (moderate) -Intraobserver agreement (difference in quantity and quality of stool between radiograph I and II as scored	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					by same radiologist): k from 0.05 (poor) to 0.47 (moderate) for both observers -Intraobserver agreement (agreement on the existence of constipation as measured by a Barr-score of 10 or more points between radiographs I and II): fair for both observers, k= 0.22 and 0.25 respectively <u>Correlation of the Barr-score with Metcalf's makers method:</u> Correlation between positive Barr score (≥10) and delayed total CTT (>62h): k=0.22 (fair) for all children. K values by group: -PC group: 0.20 -ES group: 0.02 -RAP group: 0.46 Abnormal Barr scores found in at least 46% of patients with normal transit times. Positive Barr scores correlated only with total CTT exceeding 100 h	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Papadopoulou et al. The clinical value of solid marker transit studies in childhood constipation and soiling. 1994. European Journal of Pediatrics 153[8], 560-564	Study type: Diagnostic prospective case series Evidence level: III Study aim: to assess the acceptability, the reliability of interpretation and the clinical value of solid marker transit studies in children with soiling and spurious diarrhoea (otherwise known as overflow incontinence)*	52 children Inclusion criteria: Constipation and/or soiling. One patient had neurological problems due to ganglioneuromatosis. Constipation defined as less 3 bowel movements/week. Soling defined as involuntary passage of fluid or semi-solid stools into clothing 2/more times/week Exclusion criteria: Hirschsprung's disease Setting: hospital	52 children Median age: 8 years (range 2-13.5 years) Sex distribution not reported Country: UK	Test: Colonic transit time (CTT) with radiopaque markers Reference: Frequency of bowel movements and soiling	Patterns of transit time (n=52): -normal transit: 21 (40%) -mild delay: 4 (8%) -moderate delay: 9 (17%) -severe delay: 18 (35%) Patterns of marker distribution: -pancolonic transit delay: 15 (29%) -segmental transit delay: 5 (10%) -outlet obstruction: 11 (21%) Correlation between transit delay and clinical symptoms: a) Fewer than 2 bowel movements/week (%): -Children with severe delay (n=18): 87 -Children with normal transit (n=21): 27 p<0.001 b) More than 3 soiling episodes/week (%): -Children with severe delay (n=18): 92 -Children with normal transit (n=21): 35 p<0.005	Additional information from study: -To assess reliability of test interobserver error between 2 observers was measured: each independently assessing 30 abdominal X-rays and interobserver error by carrying out duplicate estimations by the same observer on the same 30 days -Assessment criteria of severity of transit delay: a. normal transit: < 12 markers in colon (<40% of given markers) b. mild delay: 12-18 markers in colon (41-60% of given markers) c. moderate delay: 19-24 markers in colon (61-80% of given markers) d. severe delay: >24 markers in colon (>80% of given markers) -Assessment criteria of different patterns of marker distribution: a. pancolonic transit delay: no single segment contains >75% of markers remaining in colon b. segmental transit delay: >75% of markers remaining in colon clustered in one segment c. outlet obstruction: >60% of given markers clustered in rectosigmoid -In 6 patients the transit studies were repeated after colonic washout. Significant improvements in transit found after colonic emptying (p<0.05) (exact number not reported in text, just a bar graph)

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
	* reviewer's note				No correlation found between duration of symptoms and severity of delay <u>Correlation between marker distribution and transit</u> -Children with severe delay (n=18): Outlet obstruction: 39% Pancolonic transit delay: 56% Segmental transit delay (in descending colon): 5% -Children with mild delay (n=4): Pancolonic transit delay: 25% Segmental transit delay (in rectosigmoid): 75% P<0.005 <u>Correlation between marker distribution and symptoms:</u> -Fewer than 2 bowel movements/week (%) : a. Outlet obstruction: 100% b. Pancolonic transit delay: 83% c. Segmental transit delay : 33% a vs. c and b vs. c: p<0.05 -More than 3 soiling episodes/week (%): a. Outlet obstruction: 100% b. Pancolonic transit delay:	Laxative treatment not interrupted previous to measurements (97% were on laxatives) <u>Reviewers' comments:</u> Researchers not blinded No data on the type of diet children were on when measurements were made No data reported on the correlation between transit delay and clinical symptoms for children with mild/moderate delay <u>Source of funding:</u> not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					57% c. Segmental transit delay: 0% a vs. c and b vs. c: p<0.05 <u>Observer errors:</u> <u>(coefficient of variation):</u> -interobserver: 2.1 % -intraobserver: 3.1 %	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Staiano et al. Colonic transit and anorectal manometry in children with severe brain damage. 1994. Pediatrics 94[2 Pt 1], 169-173	Study type: diagnostic case control study Evidence level: III Study aim: to study colonic transit and anorectal motility in children with severe brain damage, looking for differences from asymptomatic children and from patients with functional faecal retention and normal neurologic development.	42 children Inclusion criteria: -patients: children with brain damage referred for gastroenterologic evaluation of constipation -Controls: 1. functional faecal retention: 2. asymptomatic: normal frequency of defecation and no history of current/previous gastrointestinal disease Exclusion criteria: secondary constipation excluded by clinical interview, physical examination, barium enema, and anorectal manometry studies and/or multiple suction	42 children Group1: children with brain damage N=16 10 boys Mean age 5.1 ± 3.5 years (range 1.5 to 12 years) Group 2: children with functional faecal retention (FFR) N=15 9 boys Mean age 6.0 ± 2.9 years (range 2 to 11 years) Group 3: children with no gastrointestinal problems N=11 7 boys Mean age 5.6 ± 3.9 years (range 2 to 12 years) Country: Italy	Test: -Total gastrointestinal transit time (TGITT) -Colonic segmental gastrointestinal transit time (SGTT) Reference standard: None	Total gastrointestinal transit time (TGTT) (hours, mean ± SD): -children with brain damage: 106.4 ± 6.1 -children with functional faecal retention (FFR): 98.6 ± 5.1 p value N.S Segmental gastrointestinal transit time (SGTT): (mean, SEM) Left colon: total number of markers at 48 h -brain damaged: 7.3 ± 1.3 -functional faecal retention (FFR): 3.0 ± 1.0 p< 0.05 total number of markers at 72 h: -brain damaged: 3.3 ± 0.8 -functional faecal retention (FFR): 0.5 ± 0.3	Additional information from study: Severe brain damage: spastic tetraparesis/diplegia, generalised hypotonia Children off all laxatives and/or suppositories during the measurement of total and segmental transit times Tracing coded and analysed by one of the authors unaware of the clinical status of the child (not clear whether this is CTT or manometry) Reviewers' comments: 29 of the children originally undergoing evaluation for severe brain damage were found to have constipation, but only 16 were included in the study. It is not clear why the other 13 were excluded Functional faecal retention not defined Exact values for all segmental transit times in the 2 groups not reported Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		rectal biopsies Setting: hospital			p<0.01 Distribution of markers in right colon and rectum not significantly different between the two groups	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Koletzko et al. Is histological diagnosis of neuronal intestinal dysplasia related to clinical and manometric findings in constipated children? Results of a pilot study. 1993. Journal of Pediatric Gastroenterology and Nutrition 17[1], 59-65	Study type: Case series (multicentre) Evidence level: III Study aim: to investigate the relationship of clinical, manometric, and histological findings in a group of children with chronic constipation in order to evaluate the role of anorectal manometry in the diagnosis of neuronal intestinal dysplasia (NID) and the relationship of histological and manometric findings to	48 children Inclusion criteria: Initial symptoms of chronic constipation or soiling, or obstructive symptoms in early life suggestive of Hirschsprung's disease Exclusion criteria: Anorectal malformation or mielomengoncele Setting: hospital	48 children 25 boys Mean age: 6.4 ± 5.2 years Country: Switzerland	Test: Colonic transit time (CTT) with radiopaque markers Reference: none	Total transit time (hours, mean ± SD) -Children with normal histology (n=15): 70.0 ± 42.6	Additional information from study: Hirschsprung's disease diagnosed in 9 children excluded from further analysis Abortive neuronal intestinal dysplasia (NID) and classic NID diagnosed in 17 and 6 patients respectively. Mean colonic transit times measured using the Metcalf method, in only 30 children of the total population Reviewers' comments: CTT results for children diagnosed with abortive and classic NID not reported for the purposes of this review as they are considered organic causes of constipation No data reported on diet, use of laxatives previous to the investigations Segmental transit times results not reported, and not clear whether they were measured Researchers not blinded Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
	clinical severity of constipation and outcome					

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Martelli et al. Can functional constipation begin at birth? 1998. Gastroenterology International 11[1], 1-11Italy.	Study type: Diagnostic retrospective case series Evidence level: III Study aim: to analyse epidemiologic, manometric and radiologic data in a large population of young patients presenting in a paediatric tertiary care hospital in order to classify different types of idiopathic constipation according to age of onset, sex and pelvic floor function	1182 children Inclusion criteria: Constipation with/without encopresis Constipation defined as less than 3 spontaneous stools/week without any laxative or motility-influencing drug. Encopresis defined (in France) as incontinent associated with faecal impaction, at or after the age of 3 years. Faecal impaction considered to be present when consistency of faeces persisting in rectum more solid than that of stools spontaneously emitted	1182 children 63% boys Group 1: constipated children without encopresis (C patients) N=855 59%boys 65% < 4 years old (C-4 patients) 35% > 4 years old (C+4 patients) Median age at first evaluation: C-4: 11 months (range 4 to 15 years) C+4: 7.7 years (range 4 to 15 years) Group 2: constipated children with encopresis (C+E patients) N=327 78% boys Median age at first evaluation: 8.5 years (range 4 to 15 years)	Test: Colonic transit time (CTT) with radiopaque markers Reference: none	Total transit time (hours, median, range) -C+E patients (n=168): 67.2 (2 to 168) -C+4 patients (n=112): 54.6 (9 to 168) -C-4 patients (n=77) 49.6 (8 to 161) -Controls (n=21) *Arhan et al. 1983* 22.8 (9.4 to 56.4) p<0.0001 C+4/C-4/C+E patients vs. controls p<0.05 C+E patients vs. C+4 patients Segmental transit time (hours, median, range) 1-Right colon: -Controls (n=21): *Arhan et al. 1983* 7.2 (0.6 to 19.2) -C-4 patients (n=77): 14.8 (0 to 96) -C+4 patients (n=168): 12 (0 to 48) -C+E patients (n=112): 14 (0 to 144) p<0.0005 C+4/C-4 patients vs. controls p<0.0001 C+E patients vs.	Additional information from study: Patients classified into 4 groups: -"Normal" transit time -"Pancolic" constipation: delay in the 3 sites -"Terminal" constipation: delay in the rectosigmoid with/without delay in right or left colon -"Non terminal" constipation: right and/or left delay but normal rectosigmoid transit time Reviewers' comments: Researchers not blinded Not all children underwent CTT No data on diet or use of laxatives previous to CTT measurement Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		Exclusion criteria: children aged < 48 months. Local/general causes of constipation: anal lesions (anal fissures, anal malposition), neurogenic constipation (Hirschsprung's disease, neurointestinal dysplasia, spinal cord disorders, chronic intestinal pseudobstruction),endocrine (hypothyroidism), metabolic disorders (diabetes mellitus, renal acidosis, hypercalcemia), still breast-fed patients with not symptoms other than fewer than 3 stools/week Setting:	Country: France		controls 2-Left colon: -Controls (n=21): *Arhan et al. 1983* 7.4 (1.2 to 22.8) -C-4 patients (n=77): 12.4 (0 to 72) -C+4 patients (n=168): 12 (0 to 96) -C+E patients (n=112): 13.6 (0 to 96) p<0.0005 C-4 patients vs. controls p<0.005 C+4/C+E patients vs. controls 3-Rectosigmoid: *Arhan et al. 1983* -Controls (n=21): 10.4 (1.21 to 34.2) -C-4 patients (n=77): 18.4 (0 to 106) -C+4 patients (n=168): 26.4 (0 to 108) -C+E patients (n=112): 30.2 (0 to 142) p<0.005 C-4 patients vs. controls p<0.0001 C+4/C+E patients vs. controls Classification of constipation according to segmental colonic transit times (n, %):	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		paediatric tertiary care hospital			1.Normal transit: -C-4 patients (n=77): 33 (43) -C+4 patients (n=168): 34 (30.5) -C+E patients (n=112): 38 (22.5) -Total (n=357): 105 (29) p<0.001 C+E vs. C-4 patients 2.Non terminal constipation: -C-4 patients (n=77): 18 (23) -C+4 patients (n=168): 26 (23) -C+E patients (n=112): 37 (22) -Total (n=357): 81 (23) 3.Terminal constipation: -C-4 patients (n=77): 17 (22) -C+4 patients (n=168): 42 (37.5) -C+E patients (n=112): 70 (41.5) -Total (n=357): 129 (36) p<0.05 C+4 vs. C-4 patients p<0.005 C+E vs. C-4 patients 4..Pancolic constipation: -C-4 patients (n=77): 9 (12) -C+4 patients (n=168): 10 (9) -C+E patients (n=112): 23 (14) -Total (n=357): 42 (12): 42 (12) (p values not reported were not significant)	

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Corazziari et al. Gastrointestinal transit time, frequency of defecation, and anorectal manometry in healthy and constipated children. 1985. Journal of Pediatrics 106[3], 379-382	Study type: Diagnostic case control Evidence level: III Study aim: to quantify bowel function in healthy children in regard to frequency of defecation, gastrointestinal transit time and manometric characteristics of the anorectal tract and to compare variables of bowel function in children with chronic constipation with those in the normal population	141 children Inclusion criteria: -Patients: long-standing constipation, complaints of reduced bowel frequency associated with straining at defecation, or presence of visible fresh blood on faeces or frequent use of mild laxatives -Controls: healthy children free of bowel complaints Exclusion criteria: secondary constipation excluded after clinical interview and examination, barium enema, anorectal motility studies, rectosigmoidosc	141 children Patients: N=63 40 boys Mean age 5.4 ± 4.1 years (2 months to 4 years) Controls: N=78 37 boys Mean age 5.5 ± 3.2 years (2 months to 12 years) Country: Italy	Test: Total gastrointestinal transit time (TGITT) [1] Reference: -Frequency of defecation	Total gastrointestinal transit time (TGITT) (hours, mean ± SD, range) -healthy controls (n=78) 25.0 ± 3.7 (19 to 33) -patients with TGITT>33h (n=53) 81.4% -patients with TGITT<33h (n=10) 18.6% Segmental transit time N=39 (out of 53 children with prolonged transit time) Colon: lowest in 3 patients Rectum: lowest in 24 patients Colon and rectum: lowest in 12 patients Frequency of defecation (times/week): -healthy controls (n=78) 6.3 ± 1.3 (range 4 to 9) -patients with TGITT>33h (n=53) 2.5 ± 0.9 (range not reported) -patients with TGITT<33h	Additional information from study: No patients receiving laxatives during investigation Retention of contents in a given large bowel segment considered abnormally prolonged when transit index ≤60 (i/e when on average, ≥ 30% of markers were retained in that given segment at least 33 h after ingestion of radiopaque pellets). Transit index of 60 chosen because the lower confidence limit (?) of a normal adult population did not exceed this value Reviewers' comments: Not clear what type of diet patients were following during investigation Segmental colonic transit times (right and left colon and rectosigmoid) measured but results not reported Accurate figures for CTT in patients not reported Segmental transit time not measured in controls Results reported for the healthy controls are not clearly stated in the paper that there actually belong to this group, but as results for the patients group are explicitly related to them, it was assumed the others belonged to the

[1] Italian papers included in this review (Corazziari, Cucchiara, Staiano) measured "total gastrointestinal transit time (TGITT)". Because of the similarity in the figures with the other studies' CTTs we assumed that TGITT is the name by which CTT known in Italy.

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		opy, rectal biopsy. Metabolic and endocrinologic abnormalities. Setting: unclear			(n=10) 5.1 ± 0.73 (range not reported) Stool frequency and TGITT significantly correlated in patients with prolonged transit time (r=0.75; p<0.001) and in healthy controls (r=0.78; p<0.001) In 7 of 53 patients with TGITT>33 h, the bowel frequency overlapped the range observed in the controls	controls Researchers not blinded Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Cucchiara et al. Gastrointestinal transit time and anorectal manometry in children with fecal soiling. 1984. Journal of Pediatric Gastroenterology and Nutrition 3[4], 545-550	Study type: Diagnostic case-control Evidence level: III Study aim: to determine motility characteristics of the anorectum and to measure total gastrointestinal transit time (TGITT) in children with chronic constipation, with/without faecal overflow	99 children Inclusion criteria: -patients: constipation of several months of duration with/without soiling -controls: healthy children without gastrointestinal complaints referred to outpatients paediatric clinic for routine examination Exclusion criteria: history of anorectal surgery, spinal abnormalities, psychiatric/neurological disorders Setting: outpatients paediatric clinic	99 children -Patients (n=53) 40 boys mean age 8.3 years (range 4.8 to 12.9) -Controls (n=46) 24 boys mean age 8.1 years (range 4.2 to 12) Country: Italy	Test: -Total gastrointestinal transit time (TGITT) Reference: none reported	Total transit time (hours, mean ± SD, range) a) Patients with soiling (n=32) 58 ± 14.3 (36 to 86) b) Patients without soiling (n=21) 61.1 ± 15 (36 to 96) c) Controls (n=46) 25.6 ± 3.7 (19 to 33) a) vs. c) $p < 0.001$ b) vs. c) $p < 0.001$	Additional information from study: Controls matched for age and weight but not sex with the constipated children TGITT measurements performed with children taking their usual diet Reviewers' comments: No definitions of constipation/soiling given Researchers not blinded No data on use of laxatives previous to the CTT but a barium enema, without previous cleansing of the colon and limited to the rectosigmoid was performed to demonstrate the presence of stenosis, megarectum or Hirschsprung's disease Segmental transit times not measured Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Arhan et al. Idiopathic disorders of fecal continence in children. 1983. Pediatrics 71[5], 774-779	Study type: Diagnostic case control Evidence level: III Study aim: to describe the clinical presentation of children with idiopathic disorders of faecal continence and to demonstrate that they have functional abnormalities of large-bowel motility	176 patients Inclusion criteria: -Patients: one of the following: 1) history of less than 3 spontaneous stools/week 2) evidence of faecaloma (stools of harder consistency than those passed spontaneously) at rectal examination 3) presence of faecal material in the entire descending colon or faecaloma in the rectosigmoid area diagnosed radiologically -Controls: children with no intestinal abnormalities who had to undergo a radiography of the abdomen for medical	176 patients aged 2 to 15 years 64% boys Controls: 23 children (no further data reported) Country: France	Test: Colonic transit time (CTT) with radiopaque markers -Reference: none	Segmental transit time of one radiopaque marker (hours, min; mean ± SD) 1. Ascending colon: -normal children (n= 23): 7:10 ± 1:4 -constipated children (with/without spina bifida occulta) (n=176): 13:24 ± 1:5 p<0.05 2. Descending colon -normal children (n= 23): 7:37 ± 1:3 -constipated children (with/without spina bifida occulta) (n=176): 13:49 ± 1:37 p<0.05 3. Rectum -normal children (n= 23): 11:4 ± 1:5 -constipated children (with/without spina bifida occulta) (n=176): 30:22 ± 2:42 p<0.05 No significant differences between children with and without spina bifida occulta	Additional information from study: Markers ingested 24h after beginning a diet containing 0.5g/kg of crude fibres Functional studies performed when rectum free of stool either spontaneously or as a result of cleansing enemas Reviewers' comments: No clear definition of constipation given Researchers not blinded Not clear how many children underwent CTT Total transit time not measured As no data are reported on the characteristics of the control group it is not possible to tell whether they could be significantly different from the patients Source of funding: partially by the Institut national de la Sante et de la Recherche Medicale (INSERM), CRL No.80-7002, grant MT-3511 from the CRM, and by the French Canadian sub commission for health matters

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		reasons Exclusion criteria: none stated Setting: hospital				

Radioisotopes Markers

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Cook et al. Radionuclear transit to assess sites of delay in large bowel transit in children with chronic idiopathic constipation. 2005. Journal of Pediatric Surgery 40[3], 478-483	Study type: Diagnostic retrospective case series Evidence level: III Study aim: To review the authors' results of scintigraphic studies on children with severe chronic constipation and to assess the use of the geometric centre (GC) and visual interpretation of images in categorising these children	101 consecutive nuclear transit time performed on children with severe constipation over a 2-year period Inclusion criteria: All patients seen by the senior author or a gastroenterologist paediatrician. All had symptoms of severe chronic constipation and/or encopresis that had not responded to at least six months of medical therapy with laxatives, dietary alterations and behaviour modification Exclusion criteria: Obviously palpable	101 children 62 boys Mean age 7.3 ± 3.7 years Country: Australia	Test: Colonic transit time (CTT) with radioisotopes Reference Standard : None stated Three categories of colonic transit according to visual assessment -Normal transit time: tracer reached the caecum by 6 hours, passed through the colon and was largely excreted by 6 hours -Slow colonic transit time (SCT): when the tracer reached the caecum at 6 hours but most radioactivity was retained in the proximal colon at 24, 30 and 48 h -Functional faecal retention/outlet obstruction	Mean sum of GC for the 4 imaging periods (mean ± SD, range) 1-Normal transit time (n=24): 15.7±3.3 (7.3-19.1) 2-SCT (n=50): 11.2±1.9 (7.5-16.3) p<0.001 as compared to normal transit time and FFR groups 3-FFR (n=22): 15.1±1.5 (12.7-18.2) 4-Borderline (n=5) not reported GC at each of the 4 imaging periods (mean ± SD, range) 1-Normal transit time (n=24): 6h: 2.0±0.5 (1-3.5) 24h: 3.9±1.1 (1-5.9) 30h: 4.6±1.2 (2-5.9) 48h: 5.2±0.9 (2.3-6) 2-SCT (n=50): 6h: 1.8±0.3 (1-2.5) 24h: 2.6±0.5 (1.9-4.4) 30h: 3.1±0.6 (1.8-4.5) 48h: 3.7±0.9 (1.9-5.7)	Additional information from study: Four imaging periods: 6, 24, 30 and 48h Intake of laxatives stopped 5 days before the transit time and patients fasted for 4 h before start of test. Rectal disimpaction not carried out before study in any patient. Radiopharmaceutical technetium 99m-calcium phytate colloid, suspended in 20mL of milk was administered by mouth. A nuclear medicine radiologist from the hospital performed qualitative visual assessment of the images acquired at each time interval. Colonic transit times was estimated by analysis of the images acquired between 6 and 48 hours Geometric centre (GC): six regions of interest were defined: 1-precolonic region 2-caecum and ascending colon as far as the hepatic flexure 3-transverse colon from hepatic to splenic flexure 4- descending colon from splenic flexure to start of sigmoid 5-sigmoid colon 6-faeces GC refers to the median point of the distribution of activity within the colon. It was calculated by multiplying the fraction of the administered activity in a region, by a region number and the 6 numbers for each image episode were

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
		faecaloma in rectum or sigmoid colon. Anorectal malformation, spinal deformity, Hirschsprung's disease, bowel washout or enema in the week before study to remove faecaloma <u>Setting:</u> continence clinic		(FFR): the tracer reached the rectosigmoid by 24 to 30 h but was not passed at 48 h -Borderline: according to authors "more like functional retention than slow transit trough the colon"	p<0.05 at 6h and p<0.001 at 24, 30 and 48 h, as compared to normal transit and FFR groups 3-FFR (n=22): 6h: 2.0±0.4 (1.2-3) 24h: 3.6±0.7 (2.5-5) 30h: 4.4±0.5 (3.5-5.4) 48h: 5.1±0.3 (4.4-5.7) 4-Borderline (n=5) not reported No significant difference in the GC at any imaging time when comparing patients with normal transit with those with FFR. Two of the 101 children (not clear in which group) had a GC of 1.0 at 6 h indicating that 100% of the tracer was located in the small bowel, suggesting impairment.	added <u>Reviewers' comments:</u> No control group, or comparison with a reference test Not clear definition of constipation reported No diagnosis prior to the application of the test was made Researchers not reported blinded <u>Source of funding:</u> Not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Chitkara et al. The role of pelvic floor dysfunction and slow colonic transit in adolescents with refractory constipation. 2004. American Journal of Gastroenterology 99[8], 1579-1584	Study type: Diagnostic retrospective case series Evidence level: III Study aim: to examine the symptoms and pelvic floor function by anorectal manometry (ARM) and balloon expulsion test (BET) in adolescents ≤ 18 years of age referred to a tertiary care centre for symptoms of refractory constipation, and to describe the results of scintigraphic colonic transit measurements in the patients who	67 adolescents Inclusion criteria: -constipation unresponsive to first line, symptomatic treatments - completion of clinically indicated ARM and BET for the evaluation of constipation -age ≤ 18 yr -able and willing to follow instructions in the balloon expulsion study as judged by experienced test operator -presence of gastrointestinal complaints in the absence of: Exclusion criteria: colonic resection or systemic organic disease (diabetes mellitus, hypothyroidism,	67 adolescents Mean age: 14.7± 3.3 yr 67% female Group 1: (n=16) Functional constipation (FC) Group 2: (n=18) Functional faecal retention (FFR) Groups 3: (n=33) Constipation-predominant irritable bowel syndrome IBS(C-IBS) Country: USA	Test: Colonic transit time (CTT) with radioisotopes Reference tests: -Clinical variables (nausea, vomiting, bloating, weight loss and incomplete rectal evacuation)	Colonic transit time (n=41) (FC=12; FFR=8; C-IBS=21) -Geometric centre at 24 h Total: 2.03 ± 0.99 FC: 1.73 ± 0.29 FFR: 2.04 ± 0.38 -Slow colonic transit (%) Total: 30 FC: 42 FFR: 14 -Fast colonic transit (%) Total: 7.5 FC: 0 FFR: 0 No significant association of abnormal GC at 24h (fast or slow) and individual gastrointestinal symptoms (no further details reported)	Additional information from study: Patients were classified in three groups according to paediatric Rome II criteria based on the symptoms and diagnoses provided by the clinician who evaluated the patient prior to the ARM and BET Patients instructed to discontinue all medications known to affect intestinal motility 48 h prior to study. Patients given the radioisotope after overnight fast A geometric centre at 24h of ≤ 1.6 was classified as slow colonic transit and > 3.8 considered fast colonic transit. Reviewers' comments: Methodology poorly described. Researchers not reported blinded. Intrarater/interrater reliability measurements not reported Only 61% of total sample underwent colonic transit time, but not clear explanation for this Not clear on what basis the cut off points for the geometric centre were determined Insufficient data to allow calculation of other parameters of diagnostic value of CTT (Sensitivity, Specificity, PPV and NPV) Results for C-IBS patients not reported, as population outside the remit of this

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
	also underwent this test	mielomeningocele, mental retardation/developmental delay, Hirschsprung's disease) <u>Setting:</u> tertiary care centre				guideline <u>Source of funding:</u> In part by the GlaxoSmithKline Institute of Digestive General Research Award to D. Chiktara ad NIH grants to M. Camilleri

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Shin et al. Signs and symptoms of slow-transit constipation versus functional retention. 2002. Journal of Pediatric Surgery 37[12], 1762-1765	Study type: Retrospective case series Evidence level: III Study aim: to correlate symptoms, signs, transit times and immunohistochemistry to determine the diagnostic differences between slow transit constipation (STC) and functional faecal retention (FFR)	180 children Inclusion criteria: Severe, intractable constipation which did not respond to at least 6 months of medical therapy instituted by a general practitioner or paediatrician Exclusion criteria: None reported Setting: unclear	180 children 92 boys Mean ages: 10.5 years (STC); 6 years (FFR) Country: Korea & Australia	Test: Colonic transit time (CTT) with radioisotopes Reference: -Clinical variables -Stool characteristics	FFR (n=19) STC (n=161) FFR vs. SCT (Clinical variables (%)) -Constipation: 89 vs.91 -Soling: 42 vs.64 -Bloating: 26 vs. 46 -Abdominal pain: 42 v. 51 -Anal pain: 16 vs. 19 -Vomiting: 7 vs. 16 -Failed toilet training: -Poor appetite: 42 vs. 22 -Behavioural problems: 21 vs. 22 -Prematurity: 6 vs. 5 -Meconium passage > 24 after birth: 41 vs. 33 (35% unknown) -Family history of constipation: 61 vs. 52 -Constipation present at birth: 11 vs. 26 (p=0.17) (p values not reported are not significant) FFR vs. SCT (Stool characteristics (%)) -Volume: Small moderate: 68 vs. 47 Large: 26 vs. 52 Not known: 5 vs. 2 -Consistency: Hard/firm: 78 vs. 58 Soft/variably soft: 16 vs. 39	Additional information from study: Clinical stories reviewed retrospectively and augmented by interview or questionnaire No gender differences between both groups Normal CCT defined as the presence of tracer in the caecum by 6 h, in the rectosigmoid by 30 h and passed in the faces by 48h. Slow CCT defined as global colonic delay with hold-up of tracer proximal to the rectosigmoid at 30 and 48 h (with no rectal faecaloma). FFR identified by hold-up of tracer proximal to the rectosigmoid at 48 h preceded by normal transit Visual inspection of collected radiographic images augmented by use of a “colonic transit index” (sum of the geometric centres of radioactivity at 6, 24, 30 and 48 h) Normal values for CTT derived from several studies of transit time in healthy children Slow-transit constipation, STC: slow transit through the colon FFR: chronic constipation caused by delay of anorectal release Reviewers’ comments: Exclusion criteria not reported Questionnaires not piloted. No data on

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					(p<0.001) Not known: 5 vs. 3 -Frequency: >1 week: 56 vs. 40 1/week: 26 vs. 22 <1 week: 11 vs. 28 Not known: 5 vs. 10	intrarater/interrater reliability No data on diet or use of laxatives previous to CTT No data of individual(s) performing readings: blinding, etc. Actual figures for CTT not reported Source of funding: Not reported

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Vattimo et al. Total and segmental colon transit time in constipated children assessed by scintigraphy with 111In-DTPA given orally. 1993. Journal of Nuclear Biology and Medicine 37[4], 218-222	Study type: Diagnostic. Prospective case series Evidence level: III Study aim: Not clearly stated, it might read like: to present the results of children referred for constipation who underwent total and segmental transit time by scintigraphy with 111In-DTPA	39 children Inclusion criteria: Constipation defined as 2 or fewer bowels motions/week or straining for more than 25% of the defecating time Exclusion criteria: Normal children (no other details given) Setting: unclear, but children were outpatients	39 children 23 females Age range: 2-13 years Country: Italy	Test: Colonic transit time (CTT) with radioisotopes Reference test: none reported	Total transit time (hours, mean ± SD) -Normal transit time (n=13) 27.79 ± 4.10 -Mainly rectosigmoid retention (n=5) 53.36 ± 29.66 -Prolonged transit time in all segments (n=14) 62.09 ± 7.23 -More prolonged transit time in rectosigmoid tract (n=7) 92.36 ± 24.16 Segmental transit time (hours, mean ± SD) -Normal transit time (n=13) Right colon: 9.11 ± 2.53 Left colon: 9.80 ± 3.50 Rectosigmoid: 8.88 ± 4.09 -Mainly rectosigmoid retention (n=5) Right colon: 10.38 ± 2.34 Left colon: 10.40 ± 4.00 Rectosigmoid: 32.58 ± 29.64 -Prolonged transit time in all segments (n=14)	Additional information from study: -RC: right colon from caecum to mid-transverse -LF: left colon from mid-transverse to descending colon-sigmoid junction -RS: rectosigmoid from the sigmoid junction to rectum From the point of view of radiation dosimetry the most heavily irradiated organs were the lower large intestine and the ovaries and the level of radiation burden depended on the colon transit time Reviewers' comments: No data reported on diet or use of laxatives previous to the measurement of CTT It is unclear whether the children suffered from severe/intractable constipation. Otherwise if might be difficult to justify this study No data on the researchers or their performance was reported Results for children with dolichocolon (n=7) not reported as this would be secondary constipation Source of funding: not stated

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
					Right colon: 21.81 ± 5.29 Left colon: 23.32 ± 6.14 Rectosigmoid: 16.95 ± 4.52 -More prolonged transit time in rectosigmoid tract (n=7) Right colon: 19.78 ± 9.03 Left colon: 21.05 ± 5.70 Rectosigmoid: 51.53 ± 17.82 <u>Interval between defecations: (hours, mean ± SD)</u> -Normal transit time (n=13) 23.38 ± 5.42 -Mainly rectosigmoid retention (n=5) 35.60 ± 14.54 -Prolonged transit time in all segments (n=14) 53.00 ± 15.97 -More prolonged transit time in rectosigmoid tract (n=7) 85.71 ± 32.25	

Pharmacological and Surgical Interventions for Disimpaction in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Youssef et al. Dose response of PEG 3350 for the treatment of childhood fecal impaction. 2002. Journal of Pediatrics 141[3], 410-414	Study Type: RCT Evidence level: 1- Study aim: to investigate the efficacy and safety of 4 different doses of polyethylene glycol (PEG) 3350 in the treatment of childhood faecal disimpaction	41 children Inclusion criteria: children with functional faecal retention as defined by Rome criteria, aged 3 to 18, male or female, with evidence of faecal impaction at physical examination Exclusion criteria: previous gastrointestinal surgery, no allergy /sensitivity to PEG solution or phosphates, signs and symptoms suggestive of obstruction (vomiting, abdominal distension	41 children 27 male median age 7.5 years (3.,3 to 13.1) Country: USA	Intervention: Polyethylene glycol PEG 3350 Comparisons (4 arms): 1) 0.25 g/kg per day 2) 0.5 g/kg per day 3) 1.0 g/kg per day 4) 1.5 g/kg per day Each of them to be taken for 3 consecutive days, premixed with a solution flavoured in orange Crystal Light (Kraft Food, Inc) in the morning with breakfast at a dose of 10mL/kg/day. If volume exceeded 240 ml, the remaining daily dose was equally divided throughout the remaining meals. Maximum dose	Follow-up period: 5 days after starting treatment (48 hour after their last drug use) Outcome Measures: a. Primary outcome: -clearance of faecal impaction b. Secondary outcomes: -number of bowel movements -characteristics of stools -safety	Clearance of faecal impaction (number of patients, %) -Achieved total: 30 (75) (Values for each group are estimates taken from a Bar chart.): a) 0.25 g/kg per day (n=10): 5 b) 0.5 g/kg per day (n=10): 4 c) 1.0 g/kg per day (n=10): 9 d) 1.5 g/kg per day (n=9): 10 p<0.05 c and d (95%) vs. a and b (55%) Number of bowel movements in 5 days: >3 bowel movements during the 5-day study: 33 (83%) of total sample (Values for each	Additional information from study: Functional faecal retention: difficulty passing stools >3 months (straining, grunting, stool “getting stick”) and passage of stools <3 times/week Planned to enrol 10 children in each group All medications for constipation discontinued 7 days before baseline examination and also during the duration of study Faecal impaction: a palpable mass in the left abdomen and/or a dilated rectum filled with a large amount of hard stool on rectal examination Presence or absence of faecal impaction assessed by abdominal and rectal examination. Physical examinations performed by 2 examiners to confirm presence of faecal impaction Investigators blinded to randomisation allocation sequence and concealment maintained until patients enrolled completed All medications dispensed to families in a clear container labelled with only a random sequence number generated by manufacturer. All containers initially contained PEG 3350: 50g, 100g, 200g or 300g. Each container was then

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		and abdominal mass that extended beyond the level of the umbilicus)		100 g daily		group are estimates taken from a Bar chart. Baseline value is less than 2 for all groups): a) 0.25 g/kg per day (n=10): 6 b) 0.5 g/kg per day (n=10): 8 c) 1.0 g/kg per day (n=10): 11 d) 1.5 g/kg per day (n=9): 12 p<0.005 for each group compared to the others -time of first bowel movement after initiation of treatment (mean ± SD) 1.89 ± 0.46 days (total sample) <u>Characteristics of stools and symptoms during treatment</u> No significant differences in any of the following parameters among the 4 groups:	constituted to a 2000 ml solution for respective four doses Characteristics of stools measured by diaries provided to parents. Diaries had visual analog scales marked from 0 to 10, each mark evenly spaced 1 cm apart, 0 minimum and 10 maximum. Children and parents asked to report each defecation and its associated straining (0, very easy and no pushing; 1 to 10, very difficult and much effort), consistency of stool (0, too loose and watery; 1 to 10 very hard), amount of stools per defecation (0, very little; 1 to 10, a lot) associated gas (0, none; 1 to 10 too much) and cramping (0, none; 1 to 10 very painful) 5th day after initiation of treatment chosen for follow-up visit because of author's previous clinical experience with PEG 3350 showed initial effect between 1 and 2 days after beginning use of medication Clearance of faecal impaction defined as rectal vault that was either empty or had a small amount of soft stools. In those with abdominal examination findings, resolution of the left lower quadrant mass in addition to an empty rectal vault was defined as successful disimpaction. Clearance of faecal impaction confirmed by 2 examiners Success of disimpaction not significantly related to the independent factors of

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						straining, consistency, stool amount, gas and cramping (copy actual results) <u>Adverse effects:</u> -Nausea (5%) -Vomiting (5%) -Bloating/flatulence: 18% -Pain/cramping: 5% -Loose stools (13%) -Diarrhoea: higher doses groups (5/20) vs. lower doses group (2/20); p<0.02 <u>Acceptability of study medication by children:</u> 95% of children took PEG 3350 on the first attempt <u>Mean daily volumes required to take the appropriate study dose:</u> no significant differences between groups All children said they would repeat a 3-day regimen of PEG3350 to help treat future faecal impaction Duration of	age, duration of constipation, current use of medication for constipation and baseline constipation score One child receiving 1.5 g/kg/day did not show up at follow-up visit <u>Reviewer comments:</u> Small sample, no sample size calculation Methods of randomisation and allocation concealment not described Examiners performing physical examination not clearly reported blinded. Unclear whether the two examiners who confirmed clearance of faecal impaction were the same who assessed children at baseline Unclear who prepared the 2000 ml solution for respective four doses <u>Source of funding:</u> supported by Braintree Laboratories Incorporated, General Clinical Research Centre, Children's Hospital of Pittsburgh, Pennsylvania

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						constipation at baseline significantly longer for the group receiving 1.5 g/kg per day as compared to the group receiving 0.5 g/kg per day ($p<0.03$)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Tolia et al. A prospective randomized study with mineral oil and oral lavage solution for treatment of faecal impaction in children. 1993. Alimentary Pharmacology and Therapeutics 7[5], 523-529	Study Type: RCT Evidence level: 1- Study aim: to compare the efficacy and acceptability of the treatment of faecal impaction using either mineral oil or pineapple isotonic intestinal lavage solution containing polyethylene glycol-3350 (Colyte)	48 children Inclusion criteria: children aged > 2 years with constipation, normal growth and development, absence of Hirschsprung's disease excluded on the basis of history and physical examination by the presence of firm to hard faecal impaction in the anal canal and rectal ampulla on an otherwise normal; complete physical examination Exclusion criteria: medical history of recurrent vomiting	48 children Data available for 36 patients who completed study: -Group I (mineral oil): 11 males Mean age: 6.88 ± 3.26 years -Group II (flavoured lavage solution): 6.44 ± 2.36 years Country: USA	Intervention: 2-8 tablespoons of mineral oil in 2 divided doses for 2 days. Dose empirically determined (30 ml/10 kg of body weight) If parents had difficulty in administering the oil they were asked to disguise it by blending it with 120-180 ml of orange juice Comparison: pineapple flavoured balanced oral lavage solution containing polyethylene glycol-3350 (Colyte) (sweetened with Nutra-Sweet) to drink in the dose of 20 ml/kg/h for 4 h once daily on 2 consecutive days. Maximum amount/hour: 1 litre	Follow-up period: 2 days Outcome Measures: 1.History: -number of bowel movements after treatment -vomiting -compliance -cramps/bloating -first bowel movement after treatment consider same treatment 2.Physical examination: -palpable abdominal masses -abdominal distension) -consistency of stool -anal fissure -anal sphincter tone -perineal soiling	Frequencies (%) (total sample for all outcomes, n=36) 1.History: a. number of bowel movements after treatment (>5 / 1 to 5/ none): -Group I (mineral oil, n=17): 2/10/5 -Group II (lavage solution, n=19): 9/8/2 p<0.005 b. vomiting (none/occasional/a lot): -Group I (mineral oil, n=17):17/0/0 -Group II (lavage solution, n=19): 12/6/1 p<0.005 c. compliance (good/fair/poor): -Group I (mineral oil, n=17): 14/3/0 -Group II (lavage solution, n=19): 6/7/6 p<0.01 d. cramps/bloating (none/ a few/a lot):	Additional information from study: Constipation defined as the passage of infrequent, large sized, firm to hard stools with or without associated rectal pain or bleeding Randomisation performed by a computer-generated table Significantly more patients in the lavage group gave a history of previous treatment with mineral oil (p<0.05). No significant differences at baseline between 2 groups regarding: duration of constipation, frequency of stooling, associated encopresis, rectal bleeding, previous treatments with enemas/fibre diet, palpable abdominal masses, abdominal distension, anal fissure, perineal soiling, sphincter tone and consistency of stool. Parents kept diaries assessing: compliance of child with medication, time of first bowel movement after treatment, number of bowel movements on each day, consistency of bowel movements, abdominal distension, cramps, nausea and vomiting, and willingness to repeat the same treatment in the future if impaction recurred After treatment patients re-evaluated by the same physician who repeated the abdominal and rectal examination in the same way as before 12 patients failed to return for

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		and/or aspiration, central nervous system problems or known history of liver, kidney and heart disease		In addition patients received a single oral dose of metoclopramide (0.1 mg/kg) before dinking the lavage solution on both days to prevent nausea and vomiting		-Group I (mineral oil, n=17): 13/4/0 -Group II (lavage solution, n=19): 10/8/1 N.S e. first bowel movement after treatment (< 1 day/>1 day/none): -Group I (mineral oil, n=17): 6/6/5 -Group II (lavage solution, n=19): 14/3/2 p<0.01 f. consider same treatment (yes/maybe/no): -Group I (mineral oil, n=17): 12/3/2 -Group II (lavage solution, n=19): 11/6/2 N.S 2.Physical examination: -palpable abdominal masses (none/a few/many): -Group I (mineral oil, n=17): 10/4/3	reassessment in two days Post-treatment history and physical examination further analysed after stratifying for previous use of mineral oils and stratified results did not differ significantly from unstratified analysis. Results presented are unstratified <u>Reviewer comments:</u> Small sample size. No sample calculation made Method of allocation concealment not described Physician-researchers not reported blinded Intention to treat analysis not performed Unclear how descriptive outcomes converted to numerical before analysis <u>Source of funding:</u> Block Drug Company, Inc. (Jersey City, NJ, USA) provided the supplies for the study

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						-Group II (lavage solution, n=19): 17/1/1 p<0.005 -abdominal distension (none/some): -Group I (mineral oil, n=17): 11/6 -Group II (lavage solution, n=19): 11/8 N.S -consistency of stool (soft/firm/hard): -Group I (mineral oil, n=17): 12/3/2 -Group II (lavage solution, n=19): 14/3/2 N.S -anal fissure (none/healing): -Group I (mineral oil, n=17): 15/2 -Group II (lavage solution, n=19): 15/4 N.S -anal sphincter tone (normal/decreased): -Group I (mineral oil, n=17): 14/3	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						-Group II (lavage solution, n=19): 15/4 N.S -perineal soiling (absent/present): -Group I (mineral oil, n=17): 10/7 -Group II (lavage solution, n=19): 13/6 N.S	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Guest et al. Clinical and economic impact of using macrogol 3350 plus electrolytes in an outpatient setting compared to enemas and suppositories and manual evacuation to treat paediatric faecal impaction based on actual clinical practice in England and Wales. 2007. Current Medical Research and Opinion 23[9], 2213-2225	Study Type: Multicentre retrospective cohort Evidence level: 2- Study aim: to estimate the clinical and economic impact of using macrogol 3350 plus electrolytes (macrogol 3350; Movicol, Movicol Paediatric Plain) in an outpatient setting compared to enemas and suppositories and manual evacuation to treat paediatric faecal impaction	224 children Inclusion criteria: aged between 2 and 11 years, suffering from intractable constipation and initially disimpacted between 01/01/01 and 31/01/06 Exclusion criteria: not initially disimpacted between previous dates or had any condition contraindicating the use of macrogol 3350	224 children aged 2 to 11 years 5 centres in England and Wales -macrogol 3350 plus electrolytes n=112 children n=5 centres -enemas and suppositories n=101 children n=5 centres -manual evacuation of the bowel under anaesthesia n=11 children n= 2 centres Country: UK	Intervention: macrogol 3350 plus electrolytes Comparison 1: enemas and suppositories Comparison 2: manual evacuation of the bowel under anaesthesia	Follow-up period: 12 weeks (including maintance treatment)[2] Outcome Measures: -Percentage of patients disimpacted within 5 days -Time to initial disimpaction -time for disimpaction for those who did not disimpact within 5 days -reported adverse effects	Percentage of patients disimpacted within 5 days (%, Confidence limit) -macrogol 3350 plus electrolytes (n=5 centres): 97% (94%, 100%) -enemas and suppositories (n=5 centres): 73% (58%, 89%) -manual evacuation of the bowel under anaesthesia (n=2 centres): 89% (67%, 100%) p<0.001 Time to initial disimpaction and time for disimpaction for those who did not disimpact within 5 days: No significant differences amongst the 3 groups Doses required for successful	Additional information from study: Clinical data contained in patients' case notes transcribed onto case report forms designed specifically for this study by one independent nurse, who examined the case notes of all patients at all centres Patients stratified according to centre and initial treatment for disimpaction. Individual clinical outcomes quantified for each treatment at each centre. Clinical centre was the unit of analysis Reviewer comments: No clear definition of "intractable constipation" given Very small sample size for the manual evacuation of the bowel Not reported which enemas and suppositories children were treated with for disimpaction Having another nurse (or other professional) independently examining the case notes or reviewing the transcriptions might have decreased the risk of potential bias According to the reported results it is unclear that clinical centre was the unit of analysis Source of funding: sponsored financially

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						<u>disimpaction within 5 days (mean, 95% CI):</u> -macrogol 3350 plus electrolytes (sachets): 29 (13 to 44) -enemas (units): 2 (1 to 3) -suppositories (units): 1 (1 to 2) <u>Percentage of patients on different treatments during the week before initial treatment:</u> Significantly more children disimpacted with manual evacuation were taking lactulose and senna compared with other 2 groups ($p<0.001$) Significantly more children disimpacted with Macrogol were taking picosulphate compared with other 2 groups ($p<0.01$) Significantly more children disimpacted with enemas and suppositories were	by Norgine Pharmaceuticals Ltd, Harefiled, UK, manufactures of Movicol (macrogol 3350 plus electrolytes)

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						taking lactulose and other combinations (p<0.01), other laxatives (p<0.001) or were not treated ((p<0.001) when compared with other 2 groups No significant differences between the 3 groups for patients taking lactulose only or those taking Senna <u>Adverse effects:</u> a. Vomiting (%): -macrogol 3350 plus electrolytes (n=112 patients): 2 -enemas and suppositories (n=101 patients): 2 -manual evacuation of the bowel under anaesthesia (n=11 patients): 18 p<0.01 No significant differences among 3 groups for: urinary tract infection, dermatitis around anus, thrush and gastric illness	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Candy et al. Treatment of faecal impaction with polyethelene glycol plus electrolytes (PGE + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy. 2006. Journal of Pediatric Gastroenterology and Nutrition 43[1], 65-70	Study Type: Prospective case series (phase 1 of the study)* Evidence level: 3 Study aim: to assess the efficacy of polyethylene glycol 3350 plus electrolytes (PEG + E; Movicol ®) as oral monotherapy in the treatment of faecal impaction in children and to compare PEG + E with lactulose as maintenance therapy in a randomised trial	65 children Inclusion criteria: children aged 2 to 11 years with intractable constipation that had failed to respond to conventional treatment and would require hospital admission for disimpaction (otherwise been admitted for enemas, manual removal or intestinal lavage with PEG + E solutions) Exclusion criteria: any condition contraindicating the use of PEG+E or lactulose,	65 children Mean age: 5.7 years(56% children 5 to 11 years) 68% boys Country: UK	Intervention: Polyethylene glycol 3350 (13.8 g powder dissolved in at least 125 ml water per sachet) plus electrolytes (PEG + E; Movicol ®) administered orally in hospital according to an escalating dosing regime until disimpaction was achieved (up to 7 days) -PEG + E dosing regime No. PEG + E sachets : a. 2 to 4 years Day 1: 1 Day 2: 2 Day 3: 2 Day 4: 3 Day 5: 3 Day 6: 4 Day 7: 4 b. 5 to 11 years	Follow-up period: 9 days Outcome Measures: 1. Successful disimpaction without any additional intervention 2. Time to disimpaction (primary efficacy endpoint) 3. Maximum dose required to achieve disimpaction 4. Safety	1. Successful disimpaction (No, %): -total (n=63) yes: 58 (92) no: 5 (8) -age 2 to 4 (n=28) yes: 25 (89) no: 3 (11) -age 5 to 11 (n=35) yes: 33 (94) no: 2 (6) 2. Time to disimpaction (days) (mean, SD; median, range): -total (n=63) 5.7 ± 1.2 6.0 (3 to 7) -age 2 to 4 (n=28) 5.8 ± 1.2 6.0 (3 to 7) -age 5 to 11 (n=35) 5.6 ± 1.1 6.0 (3 to 7) 3. Maximum dose required (sachets/day): -total (n=63): 6	Additional information from study: Definition of impaction was functional or procedural: Children were eligible if they would, in the normal course of events, have been admitted and treated for faecal impaction Phase 1 of the study planned as noncomparative because of good success rate obtained at initial experience in treating impacted children with PEG + E in the authors' unit: it was considered unethical to randomise the children to an alternative treatment Sample size: intended to recruit 60 children to obtain approximately 45 children continuing to end of phase 2 Successful disimpaction indicated by the passage of watery stools. Dose regime chosen because it had shown to be effective in a previous study from the same unit After disimpaction children continued to received PEG + E at the dose that achieved disimpaction for 2 more days to ensure that complete disimpaction of the bowel had occurred Use of additional interventions necessary to achieve disimpaction

* Study comprised two phases. Outcomes for the second phase (RCT) regarding maintenance therapy will be presented at the next review

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		including intestinal perforation or obstruction, allergy to any of the ingredients of the trial products, paralytic ileus, toxic megacolon, Hirschsprung's disease , severe inflammatory bowel disease, uncontrolled renal/hepatic/ cardiac disease, uncontrolled endocrine disorder or any neuromuscular condition affecting the bowel <u>Setting:</u> hospital		Day 1: 2 Day 2: 3 Day 3: 4 Day 4: 5 Day 5: 6 Day 6: 6 Day 7: 6 <u>Comparison</u>: none		-age 2 to 4 (n=28): 4 -age 5 to 11 (n=35): 6 4. Mean number (SD) of sachets required to achieve disimpaction: -total (n=63): 19.6 (7.5) -age 2 to 4 (n=28): 14.3 (4.5) -age 5 to 11 (n=35): 23.6 (6.8) No significant differences between the two age groups for any of the outcomes measured The 2 children who failed to disimpact in the 7 days specified in the study protocol were continued on PEG+E administration and eventually disimpacted <u>4. Safety:</u> -Number of children experiencing adverse effects: 39 (62%). (non of these judged by investigator to be serious)	(laxatives, suppositories, enemas, washouts or manual removal) necessary to achieve disimpaction was also recorded 3 children withdrew before receiving any study medication and 2 children failed to disimpact within the time allowed, but they were included in results <u>Reviewer comments:</u> No explicit definition of "watery stools" given It is not clear who assessed the outcome "passage of watery stools", although it looks like it was probably the researchers Individual assessing outcomes not reported blinded to study objectives Not reported whether there were any differences between the children who withdrew before receiving any medication, those who failed to disimpact and the ones who completed the study and disimpacted during the time allowed Not clear whether vomiting affected the dose required to achieve disimpaction or whether children receive any medication to prevent / stop vomiting <u>Source of funding:</u> supported by Norgine Pharmaceuticals Ltd.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						Most commonly reported events: gastrointestinal (51% children) (abdominal pain, nausea, pruritus, ani / proctalgia and vomiting) No differences in the overall incidence of adverse effects or of gastrointestinal effects for the two age groups, except for vomiting (32% of age 2 to 4 children vs. 9% of aged 5 to 11 children)) results showed a direct correlation between incidence of vomiting and day of dosing	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Pashankar et al. Efficacy and optimal dose of daily polyethylene glycol 3350 for treatment of constipation and encopresis in children. 2001. Journal of Pediatrics 139[3], 428-432	Study Type: Prospective case series Evidence level: 3 Study aim: to examine the efficacy and dosing of PEG in children with constipation	24 children Inclusion criteria: constipated children between ages of 18 months and 12 years Exclusion criteria: history of Hirschsprung's disease, anorectal malformations, abdominal surgery or any systemic illness that could lead to constipation	(data available for only 20 children who completed study) 9 boys aged 18 months to 11 years Mean age 6.09 ± 4.2 years 11 children: constipation alone 9 children: constipation + soiling Country: USA	Intervention: PEG solution, initial dose ~1g/kg body weight per day (14 ml/kg/d solution) given in 2 divided doses for 8 weeks Parents instructed to dissolve 17 g of PEG powder in each 240 ml (8 ounces) of water, juice or other clear-liquid beverage, families allowed free choice of clear liquid beverage. For determination of best dose for each child, parents asked to increase or decrease volume of PEG solution by 20% every 3 days as required to yield 2 soft-to-loose stools (consistency score of 3 to 4) per day Comparison: none	Follow-up period: 8 weeks Outcome Measures: -soiling frequency -presence of abdominal faecal mass -presence of faecal rectal impaction -dilated rectal vault -painful defecation -fear of defecation /stool withholding	Soiling frequency (n=9) (mean ± SEM) : before treatment: 10.0 ± 2.4 during treatment: 1.3 ± 0.7 p= 0.003 Total resolution of soiling: 4 patients (44.4%) Presence of abdominal faecal mass (n=18) before treatment: 44% during treatment: 0% p<0.0029 Presence of faecal rectal impaction (n=18) before treatment: 83% during treatment: 22% p<0.0006 Dilated rectal vault (n=18) before treatment: 78% during treatment:	Additional information from study: Diagnosis of constipation based on symptoms of at least 3 months' duration including at least 2 of: hard stools, painful defection, withholding of stools, faecal soiling, palpable faecal mass and fewer than 3 bowel movements/week Administration of all other medications for constipation stopped on enrolment. No enemas or cathartics given either. Initial doses of PEG prescribed based on authors' previous experience with this agent Stool consistency assessed by history on a scale of 1 to 5 as follows: 1, hard; 2, firm; 3, soft; 4, loose and 5, watery Patients examined on enrolment and at the end of 8 weeks of therapy for the presence or absence of a palpable faecal mass, faecal impaction and rectal dilatation Children of appropriate developmental status advised to sit on toilet for 5 minutes after each meal Patients bowel habits before PEG treatment compared with those recorded on diary forms during the last 2 weeks (weeks 7 and 8) of treatment 4 subjects dropped from study because of failure to return required symptoms diaries: 2 of these had an excellent response to therapy by parent report

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						11% p<0.0001 <u>Painful defecation (n=20)</u> before treatment: 75% during treatment: 0% p<0.0001 <u>Fear of defecation /stool withholding (N=20)</u> before treatment: 70% during treatment: 5% p<0.0001 <u>Final effective dose during last 2 weeks of treatment (mean ± SEM) (g/kg/day):</u> 0.84 ± 0.27 (range 0.27 to 1.42) <u>Palatability:</u> all children reported willingness to take PEG and found it highly palatable (to prepare PEG patients used sweeteners, fruit juices, water and cow's milk) <u>Adverse effects:</u> no significant except for	and two were lost to follow up <u>Reviewer comments:</u> Small sample size, no sample size calculation No data reported on who performed physical examination on enrolment and at the end of 8 weeks of therapy Not clear why data on physical examination available for only 18 children <u>Source of funding</u>: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						diarrhoea during adjustment of dose. Flatulence (n=2) Abdominal pain (n=10)	

Pharmacological Interventions for Ongoing Treatment/ Maintenance in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Candy et al. Treatment of faecal impaction with polyethelene glycol plus electrolytes (PGE + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy. 2006. Journal of Pediatric Gastroenterology and Nutrition 43[1], 65-70	Study Type: Double-blind RCT** Evidence level: 1+ Study aim: to assess the efficacy of polyethylene glycol 3350 plus electrolytes (PEG + E; Movicol ®) as oral monotherapy in the treatment of faecal impaction in children and to compare PEG + E with lactulose as maintenance therapy in a randomised trial	65 children Inclusion criteria: children aged 2 to 11 years with intractable constipation that had failed to respond to conventional treatment and would require hospital admission for disimpaction (otherwise been admitted for enemas, manual removal or intestinal lavage with PEG + E solutions) Exclusion criteria: any condition contraindicating the use of PEG+E or	-Phase 1: 65 children -Phase 2: 58 children 67% boys Mean age: 5.7 ± 2.6 years (range 2 to 11 years) Country: UK	Intervention: Polyethylene glycol 3350 (13.8 g powder dissolved in at least 125 ml water per sachet) plus electrolytes (PEG + E; Movicol ®) Comparison: Lactulose (10 g powder dissolved in at least 125 mL water) For both medications children received oral maintenance doses commencing with ½ of the numbers of sachets required for disimpaction/day Disimpaction regime (n sachets): a. 2 to 4 years Day 1: 1 Day 2: 2	Duration of treatment 12 weeks Assessment point (s): Immediately after treatment finished Follow-up period: No follow-up made after treatment finished Outcome Measures: 1. Primary efficacy endpoint: -number of successful defecations/week 2.Secondary efficacy endpoints: -reimpaction	Number of successful defecations/week (last on-treatment value) Mean, SD, range -PEG+E (n=27): 9.4 (4.56; 2 to 24) -Lactulose (n=26): 5.9 (4.29; 2 to 23) Difference in means: 3.5 95% CI: 1.0 to 6.0 p=0.007 Reimpaction rate (n, % children): -PEG+E (n=27): 0 -Lactulose (n=26): 7 (23%) p=0.011 Number of sachets used each day: -PEG+E (n=27): 0.91 (0.41) -Lactulose (n=26):	Additional information from study: Sample size: intended to recruit 60 children to obtain approximately 45 children continuing to end of phase 2 Children and investigators blinded to medication which was dispensed according to randomisation list generated by the study sponsor Blindness reasonably maintained as appearance of 2 products very similar and both packed in sachets of an identical size 5 children did not complete phase 1: 3 children withdrew before receiving any study medication and 2 children failed to disimpact within the time allowed 58 children entered phase 2. 5 were excluded from the ITT population as they did not provide any on-treatment efficacy data. 10 children (17%) did not complete phase 2: 7 on lactulose reimpacted, 2 on lactulose did not want to continue, 1 on PEG+E did not complete the diary card No significant differences at baseline between 2 groups regarding: age, sex, height and weight No children withdrew form the study for

** This is phase 2 of the study. Phase 1 was a prospective case series already discussed in the review for disimpaction

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		lactulose, including intestinal perforation or obstruction, allergy to any of the ingredients of the trial products, paralytic ileus, toxic megacolon, Hirschsprung's disease , severe inflammatory bowel disease, uncontrolled renal/hepatic/ cardiac disease, uncontrolled endocrine disorder or any neuromuscular condition affecting the bowel		Day 3: 2 Day 4: 3 Day 5: 3 Day 6: 4 Day 7: 4 b. 5 to 11 years Day 1: 2 Day 2: 3 Day 3: 4 Day 4: 5 Day 5: 6 Day 6: 6 Day 7: 6 Additional laxative treatment with senna allowed as rescue medication if the response to a single agent alone was judged inadequate by investigator	rate -number of sachets used each day -use of senna as rescue medication -amount of stool -predominant bowel movement form -pain -straining -rectal bleeding -abdominal pain -soiling -overall assessment of treatment 3. Safety	2.41 (0.91) <u>Use of senna as rescue medication</u> -PEG+E (n=27): 0 -Lactulose (n=26): 8 (31%) p=0.002 No significant differences in mean values per patient between 2 groups with respect to: amount of stool, predominant bowel movement form, pain, straining, rectal bleeding, abdominal pain, soiling and overall assessment of treatment <u>Safety (% children) (n=58):</u> -PEG+E: 64 -Lactulose: 83 Similar incidence in each age group. Most commonly reported events gastrointestinal and resolved during the study. No clinically significant abnormal values observed in	safety reasons <u>Reviewer comments:</u> No clear definition of constipation given Method of allocation concealment not described Results not controlled for confounders Missing data on 2 children who did not enter phase 2 of the study <u>Source of funding:</u> supported by Norgine Pharmaceuticals Ltd.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						urine and plasma electrolytes after 12 weeks of maintenance therapy	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Dupont et al. Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. 2005. Journal of Pediatric Gastroenterology and Nutrition 41[5], 625-633	Study Type: RCT Evidence level: 1+ Study aim: to assess the safety of a polyethylene glycol (PEG) 4000 laxative without additional salts in paediatric patients	96 children Inclusion criteria: children with constipation despite their usual dietary treatment for at least 1 month, aged 6 months to 3 years, ambulatory Exclusion criteria: history of intractable faecaloma, Hirschsprung's disease, neurologic, endocrine or metabolic disorders, allergic disease or allergies	96 children 51 male -Age (months) median (25^{th} to 75th percentiles) PEG 4000: 28 (19.5–33.7) Lactulose: 25.8 (12.3–33) Country: France	Intervention: PEG 4000 -Starting dose: 1 sachet (4g) and 1 placebo to be taken at breakfast Comparison: Lactulose -Starting dose: 1 sachet (3.33g) and 1 placebo to be taken at breakfast For both drugs, dose could be doubled if ineffective in children aged 13 months to 3 years If maximum authorised dose unsuccessful, one micro-enema of glycerol per day could be prescribed for a maximum of 3 consecutive days. If child not produced stools after treatment 2 enemas could be administered at a	Duration of treatment: 3 months Assessment point (s): Day 42 (D42) and day 84 (D84) after starting treatment Follow-up period: No follow-up performed after treatment finished Outcome Measures: -Efficacy: stool frequency frequency of hard stools enema use faecal impaction abdominal pain appetite -Biological tolerance: ion electrolytes	Stool frequency (number of stools/wk, median (interquartile range) -D42 NS in babies Toddlers: PEG 4000 (n=51): 8 (6–10) Lactulose (45): 6 (5–7) (P=0.013). -D84 NS in babies or toddlers Frequency of hard stools -D42 PEG 4000: 9% (4 of 46) Lactulose (45): 34% (14 of 41) P = 0.003 -D84 PEG 4000 (n=51): 6% (3 of 47) Lactulose (45): 28% (11 of 40) P = 0.008 Enema use -D42:	Additional information from study: Constipation defined as less than 1 stool/day for > 1 month in children 6 to 12 months old and less than 3 stools/week for > 3 months in children aged 13 months to 3 years PEG 4000 and lactulose packaged in a double-blind and double-dummy design, by means of coupled sachets, according to a randomisation list. Double dummy design required because of the difference of taste between the drugs. Numbered boxes provided to investigators at each site in equal numbers. Investigators randomly allocated either PEG 4000 or lactulose to the children for a 3-month period, with the same strategy for dose adaptation 3 children not included because of a baseline laboratory value ONR (out of normal range) before amendment applied. 2 children in PEG 4000 group dropped out before any study drug intake, so the intention to treat population included 51 children (10 babies and 41 toddlers) in the PEG 4000 group and 45 (12 babies and 33 toddlers) in the lactulose group. 76 of these children included in the *per protocol* analysis and 20 excluded by the independent scientific committee for at least one major deviation, 11 in the PEG 4000 group and 9 in the lactulose group. Reasons for exclusion were no laboratory test at D84, one or more one missing laboratory results at D84,

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				48-h interval. This procedure only allowed twice during the study, If child produced liquid stools for >1 day or > 2 or 3 stools/day depending on age, dose could be decreased by 1 pair of sachets/day to a minimum of 1 pair of sachets every other day and possibly to transitory interruption	total protein albumin vitamin A vitamin D folates -Clinical tolerance: body height body weight adverse effects	PEG 4000: 30% (14 of 48) Lactulose: 43% (19 of 44) -D84: PEG 4000: 17% (8 of 48) Lactulose: 41% (17 of 42) P = 0.012 <u>Faecal impaction</u> PEG 4000 (n=51): 1 (2%) Lactulose (45): 6 (13%) P=0.049 <u>Abdominal pain disappearance:</u> -D42 PEG 4000: 82% (9 out 11 at baseline) Lactulose: 38% (3 out of 8 at baseline) P<0.08 -D84 PEG 4000: 55% (6 out 11 at baseline) Lactulose: 63% (5 out of 8 at baseline) P<1.00	delayed laboratory test at D84 (n = 12), inadequately long exposure to the study drug (n = 2), personal reasons (n = 5) and unauthorized concomitant treatment (n = 1) No clinically relevant differences between 2 treatment groups at baseline for clinical or biologic parameters Stool frequency, abdominal pain, vomiting, and nausea recorded on Self-Diary Evaluation Booklet <u>Reviewer comments:</u> Methods of randomisation and allocation concealment not clearly described No sample calculation performed Results not controlled for potential confounders <u>Source of funding:</u> not stated

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						<u>Appetite score improvement</u> PEG 4000 (n=51): +19% Lactulose (45): -4% p<0.003 <u>Clinical tolerance (ITT population)</u> -6 adverse effects (all non serious): 5 diarrhoea (5 episodes in 2 children in both treatment groups) 1 anorexia (on lactulose) -median (interquartile range) duration of either new onset or worsened flatulence (days): PEG 4000: 3 (1 to 4.5) Lactulose: 5 (3 to 19.5) P=0.005 -median (interquartile range) duration of either new onset or	

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						worsened vomiting episodes (days): PEG 4000: 1 (1 to 2) Lactulose: 2 (1 to 6) P<0.05 -anal irritation: 5% (2 out of 40 children, both on lactulose) -no difference between PEG 4000 and lactulose groups with regards to other digestive tolerance outcomes -Body height and body weight unaffected during the 3-monht treatment for both boys and girls <u>Biological tolerance (ITT population):</u> No significant difference between treatment groups for the % of children with ONR values on D84 compared to baseline status. No treatment-related changes found in serum iron, electrolytes, total protein, albumin and vitamins A, D and folates	

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						Dose used (sachets/day) (median (interquartile range)) -Babies: 1 (0.9 to 1) PEG 1 (1 to 1.3) lactulose P = 0.67 -Toddlers 1 (1 to 1.3) PEG 1.1 (0.9 to 1.5) lactulose P = 0.58 Treatment stopped in 1 child because of lack of efficacy (lactulose group).	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Voskuijl et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. 2004. Gut 53[11], 1590-1594	Study Type: RCT Evidence level: 1+ Study aim: to compare the clinical efficacy and safety of PEG 3350 (Transipeg; polyethylene glycol with electrolytes) and lactulose in paediatric constipation	100 children Inclusion criteria: children aged 6 months to 15 years with constipation Exclusion criteria: organic causes for defecation disorders, including Hirschsprung's disease, spina bifida occulta or hypothyroidism	91 children 49 male age range: 6 months to 15 years Age (y) (mean (SD)) PEG 3350 6.5 (3.2) Lactulose 6.5 (3.4) Country: the Netherlands	Run-in phase (1 week before treatment): No laxatives allowed. At the end all patients received 1 enema daily for 3 days: -Children ≤ 6 years: 60 ml Klyx (sodium dioctylsulfosuccinate and sorbitol) -Children > 6 years: 120 ml Klyx 1. Initial phase: Intervention: PEG 3350 -children aged 6 months to 6 years (inclusive): one sachet (2.95g) per day -children older than 6 years: 2 sachets (5.9g) per day Comparison: Lactulose -children aged 6 months to 6 years	Duration: 8 weeks (RCT) 18 weeks (case series) Assessment point (s): 1, 2, 4 and 8 weeks after starting treatment Follow-up period: 26 weeks after entering case series phase Outcome Measures: 1. Efficacy: -frequency of stools -frequency of encopresis -overall treatment success 2. Safety -Incidence and severity of gastrointestinal	Defecation frequency/week -PEG 3350: 7.12 (5.14) -Lactulose: 6.43 (5.18) N.S Encopresis frequency/week: -PEG 3350: 3.11 (5.41) -Lactulose: 2.84 (3.59) N.S Success percentages (95% CI) PEG 3350: 56 (39 to 70) Lactulose: 29 (16 to 44) P=0.02 Overall treatment success independent of age (< 6 years and ≥ 6 years) and use of laxatives for more than 1 year prior to the start of the study. In children treated for less than 1 year a	Additional information from study: Childhood constipation defined as having at least 2 to 4 of the following symptoms for the last 3 months: less than 3 bowel movements/week, encopresis more than once/week, large amounts of stool every 7 to 30 days (large enough to clog the toilet) and palpable abdominal or rectal mass on physical examination Estimated that a total sample of 90 patients would be adequate to show a difference of at least 30% more success at 8 weeks using PEG 3350 compared to lactulose, with a 2 tailed alpha level of 0.05 with a power of 80% Unlabelled number boxes with unlabelled sachets prepared by the AMC pharmacy and handed out to patients after randomisation. The box contained 180 sachets containing either lactulose 6g/sachet or PEG 3350 2.95g per sachet. Toilet training advised after each meal (5 minutes) and small gifts and praise used to enhance compliance No significant differences at baseline between the 2 groups with respect to: age, sex, defecation frequency, encopresis, large amounts of stool and faecal impaction 9 dropouts: 4 on PEG 3350, 5 on lactulose. 2/each group lost to follow-up,

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				(inclusive): one sachet (6g) per day -children older than 6 years: 2 sachets (12g) per day 2. Follow-up phase Intervention: PEG 3350 -children aged 6 months to 6 years (inclusive): one sachet (2.95g) per day -children older than 6 years: 2 sachets (5.9g) per day Comparison: none	adverse effects	significant difference in success found between those treated with PEG 3350 (63%) or lactulose (31%), p=0.02 Medication (sachet/day): -PEG 3350: 1.99 (0.3) -Lactulose: 2.4 (0.4) p=0.03 no significant differences between 2 groups at 1, 2, 4 and 8 weeks for defecation and encopresis frequency Side effects: No serious or significant side effects recorded Significantly more adverse effects (abdominal pain, pain at defecation and straining at defecation) in patients taking lactulose as compared to PEG ($p<0.05$). No	1/each group reason unknown. 2 on lactulose were helicobacter positive, 1 on PEG due to bad palatability of study medication Overall treatment success defined 3 or more bowel movement/week and 1 encopresis episode or less every 2 weeks Reviewer comments: Method of randomisation and allocation concealment not described Case series phase outcomes not reported for the purpose of this review ITT analysis not performed Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						significant differences between 2 groups regarding: bloating, diarrhoea, flatulence, nausea, hard stool consistency and vomiting. Significantly more children complained of bad palatability of PEG compared to lactulose and this caused the premature withdrawal of 1 patient.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Gremse et al. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. 2002. Clinical Pediatrics 41[4], 225-229	Study Type: RCT (crossover) Evidence level: 1- Study aim: to compare the efficacy of PEG 3350 and lactulose in the treatment of chronic constipation in children	44 children Inclusion criteria: patients aged 2 to 16 years, referred for subspecialty evaluation of constipation Exclusion criteria: organic disease of the large or small intestine, known allergy to PEG or lactulose, previous gastrointestinal surgery, renal; or heart failure, bowel obstruction, ileus, pregnancy, lactation, galactosemia, diabetes mellitus	44 children Age range: 2 to 16 years (mean 7.8 ± 3.7) Country: USA	Intervention: PEG 3350 without electrolytes (MiraLax) 10g/m2/d orally for 2 weeks Mean weight adjusted dose: 0.3 g/kg/d (range 0.2 to 0.5) Comparison: Lactulose 1.3 g/kg/d orally for 2 weeks (no washout period)	Duration of treatment: 2 weeks each period Assessment point (s): Immediately after each treatment period Follow-up period: No follow-up made after treatment completed Outcome Measures: -Stool frequency -Stool form -Easy of passage -Effectiveness (global assessment, as reported by parent or guardian) -Laxative	Mean number of bowel movements -PEG 3350 (n=37): 14.8 ± 1.4 -Lactulose (n=37): 13.5 ± 1.5 Stool form (mean sum of scores) -PEG 3350 (n=37): 25.9 ± 3.0 -Lactulose (n=37): 27.9 ± 1.5 Stools passage (mean sum of scores) -PEG 3350 (n=37): 28.5 ± 4.2 -Lactulose (n=37): 26.2 ± 5.1 Effectiveness (% effective) -PEG 3350 (n=37): 84 -Lactulose (n=37): 46 p=0.002 Laxative preference (% preferred) : -PEG 3350 (n=37): 73	Additional information from study: 7 patients withdrew during the first 2-week treatment period due to lack of efficacy of the assigned intervention: 6 patients taking lactulose at time of withdrawal Stool form scoring: 0 hard, 1 firm, 2 soft, 3 loose, 4 watery Stool passage scoring: 0 hard, 1 difficult, 2 easy, 3 urgency, 4, no control Stool frequency, form and easy of passage recorded by parent or guardian in symptom diary Reviewer comments: No definition of constipation given Baseline characteristics between groups not compared Method of randomisation and allocation concealment not described Non blinded study Small sample size, no sample size calculation No follow-up period Intention to treat analysis not performed 15.9 % dropout rate Results not controlled for potential confounders Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
					preference (based on efficacy, ease of administration and side effects)	-Lactulose (n=37): 27	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Loening-Baucke. Polyethylene glycol without electrolytes for children with constipation and encopresis. 2002. Journal of Pediatric Gastroenterology and Nutrition 34[4], 372-377United States.	Study Type: Prospective cohort Evidence level: 2+ Study aim: to determine the efficiency, acceptability, and treatment dosage of MiraLax (polyethylene glycol 3350 without electrolytes) during a 12-month treatment period in children with functional constipation and encopresis	49 children Inclusion criteria: children ≥4 years of age referred for functional constipation and encopresis Functional constipation defined as delay/difficulty in defecation and encopresis (≥1/week) for more than 1 year Exclusion criteria: Children <4 years of age; children who refused the toilet for stooling but who had no constipation, Hirschsprung's disease, chronic intestinal pseudo-obstruction,	-Miralax group: 28 children 20 boys Mean age ± SD: 8.7 ± 3.6 years Range 4.1 to 17.5 years -MOM group: 21 children 17 boys Mean ± SD: 7.3 ± 3.0 years Range: 4.0 to 13.9 years Country: USA	Intervention: MiraLax 17 dissolved in 240 mL of a beverage such as juice or Kool-Aid initial dose: 0.5 to 1 g/kg/daily Comparison: MOM Initial dose: 1 to 2.5 mL/kg Large laxative dosages divided into 2 daily doses. Parents told to adjust the dose of medication by 30 mL for MiraLax and by 7.5 mL (one-half tablespoon) for MOM every 3 days to a dosage that resulted in 1 to 2 soft bowel movements/day and prevented soiling and abdominal pain. If child retained	Duration of treatment: 12 months Assessment point (s): 1, 3, 6, and 12 months after initiating treatment Follow-up period: No follow-up made after treatment finished Outcome Measures: -bowel movement frequency -consistency of stools -soiling frequency -abdominal pain frequency -medication dosage -clinically	Bowel movement frequency (mean, results are estimates taken form bar chart as not reported in text) -baseline: PEG: 3.2 MOM: 2.5 -1 month PEG: 9.0 MOM: 6.5 -3 months PEG: 9.5 MOM: 7.0 -6 months PEG: 8.8 MOM: 6.3 -12 months PEG: 6.8 MOM: 7.2 P<0.01 when comparing values at every assessment point to baseline for both treatments Soiling frequency (mean, results are estimates taken form bar chart as not reported in text)	Additional information from study: Initial dose of Miralax 0.5 g/kg daily suggested for children whose rectums were loaded with stool but who had no fecal abdominal masses at the initial physical examination and no history of long intervals between huge bowel movements. Those with palpable abdominal fecal masses or history of infrequent huge bowel movements started on 1 g/kg daily Milk of Magnesia given if family could afford only the use of a cheaper laxative or if child had previously received MOM without refusal. For these children, MOM reintroduced or adjusted to adequate dosage. Parents told how to improve the taste by mixing the child's preferred flavoring with plain MOM. Initial daily dosage of 1 mL/kg body weight suggested for children with rectal fecal masses only at initial evaluation and if no history of infrequent large bowel movements. Dosage of 2.5 mL/kg prescribed for those with fecal abdominal masses at the initial evaluation or history of huge, infrequent bowel movements. Regular stool sittings for 5 minutes after each meal required for initial months Patients and parents provided with diary sheets to record each outcome measured Doing well defined as 3 or more bowel

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		or previous surgery of the colon or anus		stools despite compliance with assigned laxative, daily senna added to treatment.	significant side effects -compliance with medication	-baseline: PEG: 12.0 MOM: 8.5 -1 month PEG: 3.0 MOM: 0.5 -3 months PEG: 1.8 MOM: 0.2 -6 months PEG: 1.0 MOM: 0.8 -12 months PEG: 0.9 MOM: 0.1 P<0.01 when comparing values at every assessment point to baseline for both treatments P<0.01 when comparing values between 2 groups at 1 and 12 months <u>Children with abdominal pain (%):</u> -baseline: PEG: 61 MOM: 81 -1 month	movements/week and 2 or fewer soiling episodes / month. Improved defined as 3 or more bowel movements / week and more than 75% decrease in soiling but not more than 1 soiling / week. Not doing well defined as fewer than 3 bowel movements / week, less than 75% decrease in soiling frequency, use of senna, or refusal to take the assigned laxative. Recovered defined as 3 or more bowel movements / week and 2 or fewer soiling episodes / month while not taking laxatives. No significant baseline differences between 2 groups <u>Reviewer comments:</u> No sample size calculation performed Outcomes for consistency of stools not reported Not reporting on the clinically significant side effects (or lack of them) for MOM <u>Source of funding:</u> Dr. Loening-Baucke recipient of grant support from Braintree Pharmaceuticals, Braintree, MA, U.S.A., for continuing studies on childhood constipation

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						PEG: 14 MOM: 14 -3 months PEG: 13 MOM: 5 -6 months PEG: 8 MOM: 11 -12 months PEG: 4 MOM: 0 P<0.01 when comparing values at every assessment point to baseline for both treatments <u>Medication dosage</u> (Mean doses and range for children who were doing well or improved) (PEG, g/kg; MOM, mL/kg) 1 month PEG: 0.6 ± 0.2 (0.3 to 1.1) MOM: 1.4 ± 0.6 (0.6 to 2.6) 3 months PEG: 0.6 ± 0.3 (0.3 to 1.4) MOM:	

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						1.2 ± 0.5 (0.6 to 2.4) 12 months PEG: 0.4 ± 0.1(0.1 to 0.7) MOM: only 2 children still required MOM. Their dosages were 0.4 and 1.6 mL/kg, both less than the initial treatment dosage. mean doses for both treatments at 12 months did not differ significantly between children with or without initial palpable abdominal faecal masses. None of the patients required an increased dosage of either medication over time 5 children received a stimulant laxative in addition to PEG and 1 child received a stimulant laxative in addition to MOM (*P* > 0.2) <u>Clinically significant side effects</u>	

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						PEG: no significant clinical side effects. Some children had diarrhea. None of the children in the PEG group became dehydrated. Children receiving PEG and their parents did not report increased flatus, abdominal distention, or new onset of abdominal pain <u>Compliance with medication:</u> -PEG: No children reported disliking the taste, no parents reported that child refused to take it in juice or Kool-Aid Parental noncompliance with administering the laxative and supervising toilet use: 14% children -MOM: 33% children refused to take it Parental noncompliance with	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						administering the laxative and supervising toilet use: 4% children	

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Loening-Baucke et al. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. 2006. Pediatrics 118[2], 528-535	Study Type: RCT Evidence level: 1- Study aim: to compare the efficacy, safety and patient acceptance of polyethylene glycol (PEG) 3350 without added electrolytes vs. milk of magnesia (MOM) over 12 months	79 children Inclusion criteria: age ≥ 4 years and presence of functional constipation with faecal incontinence Exclusion criteria: stool toileting refusal, faecal incontinence but no constipation, previous refusal of one of study medications, children who came from far away for a second opinion, Hirschsprung's disease, chronic intestinal pseudobstruction, previous surgery involving colon or anus	79 children 65 boys age range: 4 to 16.2 years (median 7.4; mean 8.1 ± 3.0) Country: USA	General: disimpacted with 1 or 2 phosphate enemas in the clinic on the day of the visit , if necessary and started laxative therapy that evening Intervention: polyethylene glycol (PEG) 3350 without added electrolytes 0.7 g/kg body weight daily for 12 months capful of PEG (17 g) mixed in 8 oz of beverage (juice, Kool-Aid, Crystal Light or water) making a solution of ~2g/30 mL Comparison: milk of magnesia (MOM) 2mL/kg body weight daily for 12 months plain MOM could be mixed into apple sauce or milkshakes, or	Duration of treatment: 12 months Assessment point (s): 1, 3, 6 and 12 months after initiating treatment Follow-up period: No follow-up made after treatment finished Outcome Measures: 1. Primary outcomes: -improvement -recovery 2. Secondary outcomes: -improvement in stool frequency per week -improvement in episodes of faecal	Improvement rate (%) -at 12 months: PEG (n=34): 62 MOM (n=21): 43 NS Recovery rate (%) -at 12 months: PEG (n=34): 33 MOM (n=21): 23 NS Bowel movement frequency (mean ± SD, episodes/week) -Baseline: PEG (n=39): 3.5 ± 3.7 MOM (n=40): 3.5 ± 6 -at 12 months: PEG (n=34): 6.8 ± 3.1 MOM (n=21): 8.2 ± 3.9 P<0.005 for both groups compared to baseline Faecal Incontinence frequency (mean ± SD, episodes/week) -Baseline: PEG (n=39): 12.2 ± 13	Additional information from study: Functional constipation defined by duration of ≥ 8 weeks and ≥ 2 of the following: frequency of bowel movements <3 stools/week, >1 episode of faecal incontinence/week, large stools noted in rectum or felt during abdominal examination, passing of stools so large that they obstructed the toilet Randomisation performed by children drawing a sealed envelope with and enclosed assignment Investigators, children and their parents aware of the study group assignment Estimated that 38 subjects required in each group to be able to detect a difference in failure rates between the 2 groups of 30% in 12 months (40% vs. 10%), at the .05 significance level with .80 power. Authors hypothesized that PEG would be as successful as MOM in treating chronic constipation and faecal incontinence. Authors' previous study showed that 33% of children refused to take MOM during the first 12 months of treatment. Children treated with minimal effective dosage of PEG or MOM, allowing for a daily stool and preventing abdominal pain and faecal incontinence. Parents instructed to aim for 1 or 2 stools of milkshake consistency each day. Parents asked to increase dosage if stools too hard or not frequent enough

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				chocolate and other flavouring could be added Large doses of both medications could be divided into 2 doses	incontinence per week -resolution of abdominal pain -safety profile -patient's acceptance and compliance	MOM (n=40): 13.5 ± 15.5 -at 12 months: PEG (n=34): 1.4 ± 3.5 MOM (n=21): 0.5 ± 1.6 P<0.005 for both groups compared to baseline <u>Abdominal pain (%)</u> -Baseline: PEG (n=39): 71.8 MOM (n=40): 52.5 -at 12 months: PEG (n=34): 3 MOM (n=21): 0 P<0.005 for both groups compared to baseline At 12-month frequency of bowel movements, frequency of episodes of faecal incontinence, and percentage of children with abdominal pain not significantly different between PEG and MOM group	and to decrease the dosage if stools watery or too numerous. Small changes, such as 2 oz of PEG or 0.5 tbsp of MOM every 3 days, were recommended. Regular stool sittings for 5 minutes after each meal required initially. Toilet sitting frequency reduced after children recognized urge to defecate and initiated toilet use themselves. No significant differences at baseline between the 2 groups regarding: age, sex, primary faecal incontinence, previous treatment with laxatives, history of retentive posturing, frequency of bowel movements, bowel movements obstructing the toilet, frequency of faecal incontinence, presence of abdominal pain, presence of abdominal faecal mass and presence of rectal faecal mass By 12 months a total of 27 dropouts/lost to follow-up. PEG: 2 children lost to follow-up monitoring, 2 (5%) had refused PEG, 1 child allergic to PEG, 2 children were receiving senna. These 7 children counted as not improved and not recovered. MOM: 2 Children lost to follow-up monitoring, 3 children had discontinued study participation, 14 children (35%) had refused to take MOM, and 1 child was receiving senna Efficacy analyses performed with intention to treat population, other outcomes calculated from available

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						<u>Patient Acceptance</u> Several children complained about taste of PEG and MOM. 2 children (5%) continued to refuse PEG vs. 14 children (35%) continued to refuse MOM during the 12 months of the study (P < .001 <u>Treatment doses (mean ± SD):</u> -PEG (g/kg body weight) 1 month: 0.7 ± 0.2 3 months: 0.6 ± 0.3 additional senna at some point: 3 children -MOM (mL/kg body weight) 1 month: 1.2 ± 0.7 3 months: 1.2 ± 0.8 additional senna at some point: 1 child mean doses similar in children who improved and who did not improve for both treatments	follow-up data <u>Reviewer comments:</u> Results not controlled for potential confounders High drop-out / lost to follow-up rate: 30.4% <u>Source of funding:</u> Braintree Laboratories (Braintree, MA) supported study with an unrestricted research grant. According to authors, the funding source had no involvement in the study design, collection, analysis, interpretation of data, writing of the report or decision to submit the article for publication

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						<u>safety profiles</u> PEG: 1 child allergic No other significant clinical effects for either medication, apart from transient diarrhoea disappearing with dose reduction -Laboratory tests: PEG: 1 child with elevated platelets before and after treatment, 1 child with decreased sodium levels at 6 months, but normal at 12 months MOM: 1 child high platelet count, 1 low serum sodium level, elevated AST, 1 elevated ALT	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments

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Perkin. Constipation in childhood: a controlled comparison between lactulose and standardized senna. 1977. Current Medical Research and Opinion 4[8], 540-543	Study Type: RCT (crossover) Evidence level: 1- Study aim: to compare effectiveness and side effects between a standardised senna syrup and lactulose in the treatment of childhood constipation	21 children Inclusion criteria: children aged <15 years with a history of constipation treated at home for 3 months or more Exclusion criteria: any cause of constipation requiring surgical or medical correction in addition to laxation	21 children Country: UK	Intervention: Senna syrup 10 to 20 ml daily for 1 week Comparison: Lactulose 10 to 15 ml daily for 1 weeks Each preparation given throughout the appropriate treatment week in a daily dose varied according to the age of the patient 1 intermediate week with not treatment	Duration: 1 week each period with 1 week no treatment in between Assessment point (s): immediately after treatment completed Follow-up period: No follow up made after treatment finished Outcome Measures: -stool consistency -number of stools passed each day -adverse effects	Number of patients passing stools of any kind each day: Lactulose vs. Senna N.S Number of patients passing normal stools each day (mean) -Lactulose: 13.4 -Senna: 8.43 p <0.01 Adverse effects (n patients): a- senna week: 12 (8 colic, 1 diarrhoea, 2 colic+ diarrhoea, 1 colic + distension) b- no treatment week: 4 (3 colic, 1 colic + distension) c- lactulose week 1 (colic) p<0.001 (a vs. c) NS (b vs. c)	Additional information from study: Patients given either treatment according to a code-list of random numbers, placed in a series of sealed envelopes, one of which was opened each time a child entered the trial 1 dropout: 1 patient on senna at the beginning of study failed to attend at the end of 1st week No written or oral indication of any medical preference for other preparation given and patients presented with single bottle of one or other of the preparations according to the coded instruction at start of trial. On 3rd week a bottle of alternative preparation was given Outcomes recorded by parents in written diaries 4-point scale of stool consistency: loose, normal, hard, none Reviewer comments: No clear definition of constipation given Very small sample size, no sample size calculation Inadequate method of allocation concealment Patients' baseline characteristics not reported Study not reported as blinded Results not controlled for confounders Very short treatment period According to authors the number of stools passed each day was recorded,

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							but is not reported <u>Source of funding:</u> not stated

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Farahmand. A randomised trial of liquid paraffin versus lactulose in the treatment of chronic functional constipation in children. 2007. Acta Medica Iranica 45[3], 183-188Iran, Islamic Republic of.	Study Type: RCT Evidence level: 1- Study aim: to compare the clinical, efficacy and safety of liquid paraffin and lactulose in the treatment of functional childhood constipation	247 children Inclusion criteria: chronic functional constipation Exclusion criteria: organic causes for defecation disorders including Hirschsprung' s' disease, spina bifida occulta, hypothyroidism, cystic fibrosis, neurological abnormalities, intestinal pseudo obstruction	247 children 127 male aged 2 to 12 years old (mean 4.1± 2.1 years) Country: Iran	General: 1 or 2 enemas daily for 2 days to clear any rectal impaction (30 cc/10 kg of paraffin oil) Intervention: Liquid paraffin orally, 1 to 2 ml/kg, twice daily for 8 weeks Comparison: Lactulose orally, 1 to 2 ml/kg, twice daily for 8 weeks For determination of best dose for child, parents asked to increase the volume of each drug by 25% every 3 days as required to yield 1 or 2, firm-loose stools	Duration of treatment: 8 weeks Assessment point (s): 4 and 8 weeks after treatment started Follow-up period: 12 weeks after treatment finished Outcome Measures: -stool frequency -encopresis frequency -success rate -optimal dose of drug -side effects	Stool frequency (mean ± SD) -before treatment (per week): Liquid paraffin (n=127) 1.6 ± 1 Lactulose (n=120) 1.8 ± 1.2 p=0.155 -during first 4 weeks (per week): Liquid paraffin (n=127) 12.1 ± 3.2 Lactulose (n=120) 9.2 ± 2.1 p<0.001 -during last 4 weeks (per week): Liquid paraffin (n=127) 13.1 ± 2.3 Lactulose (n=120) 8.1 ± 3.1 p<0.001 Encopresis frequency (mean ± SD) -Before treatment (per week): Liquid paraffin (n=127) 10 ± 4.7 Lactulose (n=120) 9 ± 4.85	Additional information from study: Diagnosis of chronic functional constipation based on having at least 2 of the following symptoms for the last 3 months: less than 3 bowel movements/week, faecal soiling more than once/week, large amounts of stool every 7 to 30 days and palpable abdominal or faecal mass on physical examination Apart form laxative treatment, parents given instructions to increase their daily fibre intake to an amount of grams equal to their age plus 10. Toilet training after each meal advised to enhance compliance Treatment success defined as 3 or more bowel movements/week and encopresis episodes less than 2/week No significant baseline differences between the 2 treatment groups regarding: age, sex, duration of constipation, defection frequency, number of patients with history of encopresis, large amount of stool, faecal impaction in rectum, rectal bleeding, lost to follow-up after 8 weeks, bad palatability of study medication Reviewer comments: Method of randomisation and allocation concealment not described Non blinded study No sample calculation performed No withdrawals/dropouts reported

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						p=0.1 -during first 4 weeks (per week): Liquid paraffin (n=127) 1 ± 4.3 Lactulose (n=120) 2 ± 4.6 p=0.07 -during last 4 weeks (per week): Liquid paraffin (n=127) 0 ± 0 Lactulose (n=120) 3 ± 4.1 p<0.001 <u>Success rate (%, CI 95%)</u> -during first 4 weeks: Liquid paraffin (n=127) 90 Lactulose (n=120) 52 p<0.001 -at end of 8 weeks: Liquid paraffin (n=127) 85 Lactulose (n=120) 29 p<0.001	Results not controlled for potential confounders <u>Source of funding:</u> not stated, but authors reported “no conflicts of interests”

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						Optimal dose of drug -Final effective dose (mean, ml/kg/day): Liquid paraffin (n=127) 1.72 ± 0.13 Lactulose (n=120) 2.08 ± 0.21 p<0.001 Side effects (during 4 to 12 week) (not clear whether, n or %, but probably %) (estimates taken from bar chart, outcomes not reported in text): Lactulose (n=120) Abdominal pain: 10 Bad palatability: 15 Pain at defecation: 10 Bloating: 10 Diarrhoea: 10 Anal oil leakage: 20 Flatulence: 10 Nausea: 10 Hard stool: 20 Vomiting: 0 Liquid paraffin (n=127) Abdominal pain: 50 Bad palatability: 40 Pain at defecation: 50 Bloating: 20 Diarrhoea: 30	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						Anal oil leakage: 40 Flatulence: 20 Nausea: 5 Hard stool: 6 Vomiting: 0	

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Urganci et al. A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation. 2005. Pediatrics International 47[1], 15-19	Study Type: RCT Evidence level: 1- Study aim: to determine and compare efficacy, safety and optimal dose of liquid paraffin and lactulose in children with chronic functional constipation	40 patients Inclusion criteria: children 2 to 12 years old referred for evaluation of constipation with evidence of faecal impaction Exclusion criteria: Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating diseases, neurological abnormalities, previous surgery of colon	40 patients 22 male mean age 3.7 ± 2.7 years Country: Turkey	Intervention: Liquid paraffin Comparison: Lactulose Medication administered orally as a suspension at 1 mL/kg, twice daily for each drug For determination of best dose for each child, parents asked to increase or decrease the volume of each drug by 25% every 3 days as required, to yield 2 firm-loose stools per day. Maximum dose used throughout the study: 3 mL/kg per day for each drug	Duration of treatment: 8 weeks Assessment point (s): 4 and 8 weeks after initiation of treatment Follow-up period: No follow-up made after treatment finished Outcome Measures: -stool consistency -stool frequency -optimal dose of drugs -compliance rate	Stool consistency (mean ± SD) -first 4 weeks: Liquid paraffin (n=20): 2.17 ± 0.5 Lactulose (n=20): 1.71 ± 0.5 p<0.01 -last 4 weeks: Liquid paraffin (n=20): 2.29 ± 0.2 Lactulose (n=20): 2.21 ± 0.4 N.S Stool frequency (mean ± SD) (per week) -first 4 weeks: Liquid paraffin (n=20): 13.3 ± 4.2 Lactulose (n=20): 10.2 ± 4.4 p<0.05 -last 4 weeks: Liquid paraffin (n=20): 16.1 ± 2.2 Lactulose (n=20): 12.3 ± 6.6 p<0.05 Optimal dose of drugs (mean ± SD) (mL/kg/day)	Additional information from study: Diagnosis of constipation based on symptoms of ay least 3 months duration including at least 2 of the following: hard stool, painful defecation, rectal bleeding, encopresis and < 3 bowel movements/week Open-label randomised study Children also met with a nutritionist, were given instructions to increase daily fibre intake to amount of gram equal to their age plus 10, parent asked to have children sit on the toilet 4 times daily after meals Stool frequency and stool consistency recorded by parents in daily diary forms. Stool consistency scoring: 1, hard; 2, firm; 3, loose No significant baseline differences between 2 groups Effective treatment defined as clearance of impaction: more than 3 bowel movements/week and improvement in stool consistency Patients considered compliant if ≥ 80% of prescribed dose taken correctly. Patients instructed to take both empty and full containers to calculate amount of medication taken Reviewer comments: Randomisation method not described

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						-data reported in table, assumed that for the whole study period: Liquid paraffin (n=20): 1.88 ± 0.27 Lactulose (n=20): 2.08 ± 0.27 N.S -data reported in text for the last 4 weeks of treatment: Liquid paraffin (n=20): 1.72 ± 0.18 Lactulose (n=20): 1.82 ± 0.57 <u>Compliance rate (%)</u> -first 4 weeks: Liquid paraffin (n=20): 95 Lactulose (n=20): 90 N.S -end of 8 weeks: Liquid paraffin (n=20): 90 Lactulose (n=20): 60 p=0.02 <u>Adverse effects:</u>	No sample size calculation performed No clear definition of “evidence of faecal impaction” given Apparently no children dropped out the study/were lost to follow-up Study not controlled for potential confounders <u>Source of funding:</u> not stated

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						No patient stopped treatment because of adverse effects (adverse effects not reported). During first 4 weeks, taste aversion in 1 child on liquid paraffin and abdominal distension in 2 patients on lactulose influenced compliance. During last 4 weeks, poor symptom control in 5 patients, side-effects (abdominal distension and cramping) in 3 on lactulose, and watery stools in 2 on liquid paraffin influenced compliance	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Sondheimer et al. Lubricant versus laxative in the treatment of chronic functional constipation of children: a comparative study. 1982. Journal of Pediatric Gastroenterology and Nutrition 1[2], 223-226	Study Type: RCT Evidence level: 1- Study aim: to compare the efficacy of mineral oil and standardised senna concentrate in the treatment of functional constipation in children	37 children Inclusion criteria: patients treated for chronic functional constipation in specialist clinic Exclusion criteria: neurological impairment, faecal soiling in the absence of retained stool	37 children 26 male age range: 3 to 12 years Country: USA	General: 5-day course of oral bisacodyl (most patients) and daily enema for 3-5 days in addition (a minority) Intervention: Mineral oil orally twice daily in doses sufficient to induce loose stools and leakage of oil per rectum. After 1rst week of treatment, dose reduced until leakage ceased. This dose (range 1.5 to 5.0 cc/kg/day) maintained for minimum 3 months. Comparison: Senokot (tablet or syrup), doses sufficient to induce at least 1 bowel movement daily during first 2 weeks of treatment. This dose maintained	Duration: Unclear, probably 6 months Assessment point (s): 1, 3 and 6 months after initiating treatment Follow-up period: -Mineral oil group, mean 10.1 months -Senokot group, mean 10.5 months Outcome Measures: -daily bowel movements -daily soiling -compliance with medication	Daily bowel movement (% patients) *at 1 month:* N.S *at 3 months:* -Mineral oil (n=18): 100 -Senokot (n=18): 72 p<0.05 *latest follow-up*: -Mineral oil (n=18): 89 -Senokot (n=18): 50 p<0.05 Daily soiling (% patients) *at 1 month:* -Mineral oil (n=18): 11 -Senokot (n=18): 39 p<0.05 *at 3months:* -Mineral oil (n=18): 11 -Senokot (n=18): 50 p<0.05 *latest follow-up*: -Mineral oil (n=18): 6 -Senokot (n=18): 44	Additional information from study: Diagnosis of chronic functional constipation made on basis of historical features and physical exam demonstrating dilated rectum, excessive retained stool directly within anal verge and in most cases, evidence of perianal soiling Children assigned to 1 of 2 treatment groups according to the last digit of their hospital number. All patients seen by same physician. Parents informed that 1 of 2 acceptable medications would be used to accomplish the discussed objectives No significant baseline differences between 2 groups regarding mean age, median age at onset of symptoms and percent of patients who had received prior treatment with constipation, sex ratio, faecal soiling, overt retentive behaviour, enuresis, “difficult” toilet training and primary failure of toilet training. Patients allowed to discontinue medications after 3 months if symptom control unsatisfactory ` 1 patient on mineral oil lost o follow-up after 3-month visit and not considered in results. No dropouts/lost to follow-up in other group During 1rst month patients/parents kept records of medication, stool frequency

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				for 3 months. Tapering accomplished by changing from daily to every other day and then every 3rd day medication		p<0.05 <u>Compliance with medication (% reliably compliant)</u> -Mineral oil (n=19): 68 -Senokot (n=18): 78 <u>% successfully discontinued regular medication at latest follow-up:</u> -Mineral oil (n=18): 55 -Senokot (n=18): 22 an additional 33% discontinued Senokot because of unacceptable symptom control 45% in each group remained on regular medication <u>Episodes of symptoms recurrence /treatment/ month (Mean ± SD):</u> -Mineral oil (n=18): 0.09 ± 0.08 -Senokot (n=18): 0.34 ± 0.36 p<0.01	and faecal soiling. From then on outcomes measured by telephone interviews and during consultations <u>Reviewer comments:</u> Study inadequately randomised. Allocation concealment not described Clinicians/researchers not blinded. Blinding procedures for parents/patients not clearly described No sample size calculation performed Results not controlled for potential confounders Definition of “reliably compliant” not given <u>Source of funding:</u> not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Thomson et al. Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study.[erratum appears in Arch Dis Child. 2008 Jan;93(1):93]. 2007. Archives of Disease in Childhood 92[11], 996-1000	Study Type: RCT (cross over, multicentre) Evidence level: 1+ Study aim: to assess the efficacy and safety of polyethylene glycol 3350 plus electrolytes (PEG + E) for the treatment of chronic constipation in children	51 children Inclusion criteria: chronic constipation for at least 3 months Exclusion criteria: current or previous faecal impaction decided by either physical examination or abdominal X-ray, previous intestinal perforation/obstruction, paralytic ileus, Hirschsprung's disease, severe inflammatory conditions of the intestinal tract, severe gastroesophageal reflux, diabetes, receiving	51 children 29 girls mean age 5.4 years (range: 24 months to 11 years) Country: UK	Intervention: PEG + E (6.9 g powder/sachet) Comparison: Placebo (6.9 g powder/sachet) Washout period in between: 2 weeks Dosing regime for both PEG + E and placebo (number sachets/day): -children aged 2 to 6 years days 1-2: 1 days 3-4: 2 (taken together) days 5-6: 3 (2 morning, 1 evening) days 7-8: 4 (2 morning, 2 evening) -children aged 7 to 11 years days 1-2: 2 (taken together) days 3-4: 2 (taken together) days 5-6: 5 (2 morning, 3 evening)	Duration of treatment: 2 weeks each treatment period separated by a 2-week placebo washout Assessment point (s): immediately after each treatment period, including washout Follow-up period: No follow-up made after treatment completed Outcome Measures: 1. Primary efficacy endpoint: -number of complete defecations per week 2. Secondary	Number of complete defecations per week (Mean (SD), range) (data do not include washout period) a. ITT population -PEG+E (n = 47): 3.12 (2.050) 0.00–8.87 -Placebo (n = 48) 1.45 (1.202) 0.00–3.73 Treatment difference: 1.64 p Value (95% CI) <0.001 (0.99 to 2.28) b. PP population -PEG+E (n = 36): 3.63 (1.980) 0.00–8.87 -Placebo (n = 36): 1.63 (1.229) 0.00–3.73 Treatment difference: 1.96 <0.001 (1.19 to 2.72) (95% CI, 95%	Additional information from study: Chronic constipation defined according to Rome criteria as fewer than 3 complete bowel movements/week, and at least 1 of the following: pain on defecation on at least 25% of days; at least 25% of bowel movements with straining, and at least 25% of bowel movements with hard or lumpy stools Random sequence group computer generated before start of recruitment using block size of 4 patients and study medication labelled accordingly. Random blocks (with numbers stored in sealed code-break envelopes) sent to investigator sites as required. As children enrolled, sites allocated treatment supplies sequentially, started with lowest possible number. Both the children (and their parents/guardians) and those administering treatment were blinded to allocation schedule A sample size of 50 children was planned to achieve 40 evaluable children, giving 90% power to detect a true treatment difference of 0.3 bowel movements/week using a two-tailed significance test at the 5% level. As dropout rate was higher than originally estimated, recruitment target was increased to 60 children At baseline, clinically significant abnormalities on physical examination (mainly associated with faecal loading but not

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		doses of stimulant laxatives considered by local observers to be at higher end of their own doses spectrum		days 7-8: 6 (3 morning, 3 evening) For both groups if diarrhoea, doses was decreased by 2 sachets or miss a day. If loose stools doses decreased by 1 sachet	efficacy outcomes: -total number of defecations -pain on defecation -straining on defection -stool consistency -percentage of hard stools -abdominal pain on defecation -faecal incontinence 3. Adverse events	confidence interval; ITT, intention to treat; PP per protocol) <u>Secondary efficacy outcomes, ITT population (mean, SD)</u> a. Total number of defaecations PEG+E (n = 47): 5.68 (2.771) Placebo* (n = 47): 4.10 (2.503) Treatment difference: 1.58 p Value (95% CI)= 0.003 (0.55 to 2.60) b. Pain on defaecation PEG+E (n = 47): 0.49 (0.727) Placebo (n = 47): 0.77 (0.863) Treatment difference: -0.28 p Value (95% CI): 0.041 (–0.52 to –0.01) c. Straining on defaecation PEG+E (n = 47): 0.72 (0.789) Placebo (n = 47):	impaction) recorded for 8 children (5/27 in the PEG+E/placebo group, 3/24 in the placebo/PEG+E group). Before randomisation, 47 children taking other laxatives (most frequently lactulose) 13/51 children (7/27 in the PEG+E/placebo group, 6/24 in the placebo/PEG+E group) recorded at least one deviation from the study protocol (1 child recorded 2 protocol deviations). Main reason for deviation was non-compliance with study medication (7/51 children), followed by failure to supply sufficient bowel movement data (4/51 children), and taking concomitant non-study laxative medication after randomisation (3/51 children). <u>Reviewer comments:</u> Blinding procedures not clearly described Unclear whether outcomes assessors were also blinded to treatment allocation Study not controlled for potential confounders <u>Source of funding:</u> Norgine Ltd. One of the authors was an employee of Norgine Ltd at the time the study was written. The others declared that they had nothing to declare

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						1.37 (1.041) Treatment difference: -0.65 p Value (95% CI): 0.001 (–0.97 to –0.33) d. Stool consistency PEG+E (n = 47): 1.73 (0.497) Placebo (n = 47): 2.21 (0.556) Treatment difference: –0.48 p Value (95% CI): 0.001 (–0.68 to –0.27) e. Percentage hard stools PEG+E (n = 47): 14.64 (26.041) Placebo (n = 47): 38.19 (39.508) Treatment difference: -23.55 p Value (95% CI): <0.001 f. Abdominal pain on defaecation PEG+E (n = 47): 0.67 (0.789) Placebo (n = 47): 0.79 (0.903) Treatment difference: 20.12 p Value (95% CI)	

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						NS g. Faecal incontinence PEG+E (n = 47): 4.70 (6.344) Placebo (n = 47): 4.85 (7.863) Treatment difference: 20.15 p Value (95% CI) NS <u>Mean effective dose of PEG 3350 (g/kg/day):</u> 0.6 (2 to 6-year-old) 0.7 (7 to 11-year-old) <u>Adverse events:</u> PEG+E (31/49, 63%) Placebo (28/49, 57%) during periods I and III. None serious, most judged by investigator to be moderate or mild in severity 20 children (41%) on PEG+E: 41 events 22 children (45%) on placebo: 45 events, judged by investigator to be at least possibly related to the study treatment. Most	

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						gastro-intestinal disorders (particularly abdominal pain), PEG+E (39%, 39 events); placebo (45%, 41 events). 1 child in placebo/PEG+E group withdrawn at week 3 because of abdominal pain, assessed by investigator as being related to treatment, this child was taking placebo at the time of withdrawal. New clinically significant abnormalities on physical examination (mainly associated with faecal loading): 13 children (8/27 in the PEG+E/placebo group, 5/24 in the placebo/ PEG+E group). When analysed for what these children were taking for the 2 weeks before the physical examination, 23 out of the 24 reports (95.8%) occurred when child taking placebo. Only 1 report of an abnormal abdominal	

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						examination while patient on PEG+E Mean weight similar before and after treatment, no significant difference found between the 2 groups for change in weight while on treatment (p=0.357)	

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Nurko et al. PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial. 2008. Journal of Pediatrics 153[2], 254-261 Nurko et al., 2008	Study Type: RCT (multicentre) Evidence level: 1+ Study aim: To establish the efficacy and best starting dose of polyethylene glycol (PEG) 3350 in the short-term treatment of children with functional constipation	103 children Inclusion criteria: Children aged 4 to 16 years with chronic constipation. Patients taking other laxatives only included if they had <3 bowel movements/week while taking the laxative Exclusion criteria: Taking a stable dose of PEG3350, evidence of faecal impaction, guiac-positive stool, anorectal malformations, Hirschsprung's disease, myelomeningocele, hypothyroidism or other	103 children 69 boys mean age: 8.5 ± 3 years Country: USA	General: Behavioural treatment: instructions to sit on toilet for 10 minutes twice after meals, positive reinforcement using age-appropriate printed calendars and special stickers for days without episodes of faecal incontinence and others with bowel movements Intervention (Group 1): Polyethylene glycol (PEG) 3350 Miralax): 0.2g/kg per day-single dose Maximum: 8.5 g per day Comparison 1 (Group 2): Polyethylene glycol (PEG) 3350 Miralax): 0.4g/kg per day-single dose Maximum: 17 g	Duration of treatment: 3 weeks Assessment point (s): 7 and 14 days after medication started Follow-up period: N.A Outcome Measures: **Efficacy:** -primary outcome: proportion of children who responded to treatment -secondary outcomes: weekly number of bowel movements weekly number of faecal incontinence episodes	Proportion of children who responded to treatment (% children) Group 1 (n=26): 77 Group 2 (n=27): 74 Group 3 (n=26): 73 Placebo (n=24): 42 P<0.04 each group vs. placebo P=0.026 all treatments groups vs. placebo NS between treatment groups Weekly number of bowel movements (BM) Group 1 (n=26): Before 1.7±0.9 Group 2 (n=27): Before 1.5±1.0 Group 3 (n=26): Before 1.5±0.5 Placebo (n=24): Before 1.6±0.7 Overall difference between treatment groups and placebo	Additional information from study: Chronic constipation diagnosed when for at least 3 months there was a history of <3 spontaneous bowel movements/week and ≥ 1 associated symptoms including: straining, hard stools sensation of incomplete evacuation, production of large bowel movements that may obstruct the toilet or painful defecation Faecal impaction defined as presence of faecal hypogastric mass palpable on abdominal examination and presence of hard stool on rectal examination. diagnosis of faecal impaction made by 2 independent observers, no disagreement found in the assessment of any patient Sample size calculation performed Patient randomly assigned in blinded fashion in a 1:1:1:1 ratio within each participant site. Randomisation schedule at each site constructed by using random blocks of 20 patients, which provided balanced treatment assignments in order to ensure the specified treatment ratio Miralax and placebo provided as a powder containing flavouring in identically labelled bottles reconstituted with water to 4000 mL by study personnel in the pharmacy. Dosing calculated by pharmacy staff and water added. All dose calculated to be given

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		organic causes of constipation		per day <u>Comparison 2 (Group 3):</u> Polyethylene glycol (PEG) 3350 Miralax): 0.8g/kg per day-single dose Maximum: 34 g per day <u>Comparison 3:</u> Placebo	changes in stool consistency straining proportion of children who responded to treatment in the second week **Safety:** -incidence and severity of adverse effects	p=0.017 P=0.015 dose-response trend <u>Weekly number of faecal incontinence episodes mean ± SD)</u> Group 1 (n=26): Before 3.8±4.8 After 3.0±4.6 Group 2 (n=27): Before 3.5±4.9 After 1.8±2.6 Group 3 (n=26): Before 7.2±18.7 After 3.5±7.8 Placebo (n=24): Before 2.4±3.8 After 1.4±3.7 NS amongst different groups <u>Changes in stool consistency (mean ± SD)</u> Group 1 (n=26): Before 2.8±0.8 After 2.1±0.7 Group 2 (n=27): Before 2.6±0.9 After 1.7±0.6	on a 10-mL/kg basis by pharmacy staff. The blinded research team received the reconstituted identical jugs, which were distributed to patient's parents/caregivers. No difference in colour, appearance r taste amongst different doses. Patients took single dose per day. No adjustment of study medication allowed during study. No other laxatives allowed during study Families completed daily diary that included number and characteristics of bowel movements an documentation of episodes of faecal incontinence Response to treatment defined as ≥3 bowel movements during the second week of treatment. Patients considered failures and withdrawn from study if they had no bowel movements (BM) for 7 days or developed faecal impaction at any point. No significant differences in baseline characteristics between the 4 groups 14 patients did not complete the 2-week treatment: -8 because of treatment failure (5 with impaction (2 Group 1, 3 Group 2), and 3 with > 7 days without a BM) (2 Group 1, 1 Group 3)] - 3 because of adverse events (1 increased abdominal pain (placebo), 1 fever, malaise, headache (placebo), 1 exacerbation bipolar (placebo)) - 1 withdrawal (lack of response

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						Group 3 (n=26): Before 2.9±0.7 After 1.5±0.7 Placebo (n=24): Before 3.0±0.8 After 2.4±0.9 P<0.003 each group vs. placebo P<0.003 test for trend P<0.003 overall difference between treatment groups <u>Straining scores (mean ± SD)</u> Group 1 (n=26): Before 2.3±1.1 After 1.4±0.9 Group 2 (n=27): Before 1.9±1.2 After 1.0±1.0 Group 3 (n=26): Before 2.0±1.0 After 0.9±0.6 Placebo (n=24): Before 2.7±1.2 After 1.5±1.2 P<0.003 each group vs. placebo P<0.003 test for trend P<0.003 overall	(placebo)) - 2 non compliance (1 Group 2, 1 Group 3) - 3 serious adverse events occurred requiring hospitalisation (2 cases impaction, 1 case of exacerbation of bipolar/depression) IIT analysis performed There were no significant predictors of success by controlling for age, duration of constipation, prior laxative use, presence of stool in rectum, sex and presence of faecal incontinence at baseline <u>Source of funding:</u> Supported in part by Braintree Laboratories Inc.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						difference between treatment groups <u>Proportion of children who responded to treatment in the second week</u> Group 1 (n=26): 58% (with no faecal incontinence 31%) Group 2 (n=27): 48% (with no faecal incontinence 26%) Group 3 (n=26): 62% (with no faecal incontinence 31%) Placebo (n=24): 29% (with no faecal incontinence 8%) P<0.27 group 3 vs. placebo <u>Incidence and severity of adverse effects</u> Group 1 (n=26): 9 (34.6%) Group 2 (n=27): 16 (59.3%) Group 3 (n=26): 17 (65.4%)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						Placebo (n=24): 14 (58.3%) NS difference amongst groups No differences in the type of non-gastrointestinal related events, most common was headache. Higher incidence of GI-related events in patients receiving PEG vs. placebo. As dose of PEG increased, it also increased incidence of flatulence, abdominal pain, nausea and diarrhoea. No electrolyte abnormalities or differences in laboratory values amongst groups <u>Treatment Failures</u> Group 1 (n=26): 6 (4 BM frequency criteria, 2 with stool impaction) Group 2 (n=27): 7(3 BM frequency criteria, 4 with stool	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						impaction) Group 3 (n=26): 7 (6 BM frequency criteria, 1 with stool impaction) Placebo (n=24): 14 (all related to BM frequency criteria)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Wald et al. Evaluation of biofeedback in childhood encopresis. 1987. Journal of Pediatric Gastroenterology and Nutrition 6[4], 554-558	Study Type: RCT Evidence level: 1- Study aim: to evaluate the efficacy of biofeedback for childhood encopresis	50 children Inclusion criteria: encopresis of at least 6 months of duration Exclusion criteria: not stated	50 children 40 boys Age range 6 to 15 years (mean 8.4) Country: USA	Intervention: Biofeedback , one 25 to 30-minute session Children with abnormal expulsion pattern taught a technique to normalise their patterns and they and children with normal expulsion pattern told to use the technique whenever they attempted to defecate Reinforcement sessions at 2, 4 and 8 weeks Comparison: Mineral oil orally in graded amounts (range 1 to 4 tablespoons/day), designed to induce a soft bowel movement daily	Duration of treatment: 12 weeks Assessment point (s): Immediately after treatment completed Follow-up period: 6 and 12 months after treatment finished Outcome Measures: -frequency of defecation -frequency of gross incontinence -frequency of staining or minor soiling -parental perception of clinical status and overall satisfaction	Children in remission or markedly improved (%) (results are estimates taken from a bar chart as exact figures not reported in text) -3 months: biofeedback (n=24): 54 mineral oil (n=26): 54 -6 months: biofeedback (n=24): 50 mineral oil (n=26): 62 -12 months: biofeedback (n=24): 50 mineral oil (n=26): 59 NS for any treatment period No significant differences in outcomes for children with abnormal expulsion pattern vs. children with normal expulsion patterns	Additional information from study: At baseline 2 groups comparable respect to age, sex, duration and severity of soiling, anorectal motility parameters and expulsion patterns Single blinded design Initial and follow-up office visits at 2, 4 and 8 weeks similar in duration for both groups. All outcomes recorded by parents in written calendar. Follow-up interviews by telephone performed at 3, 6 and 12 months by investigator unaware of treatment or results of anorectal studies Based on outcomes, children placed in groups at each assessment: 1-some improvement, 2-some improvement, but major soiling (<1/week), 3-marked improvement (rare major soiling <1/week or minor soiling) 4-complete remission 2 dropouts at 3 months (1 from each group), 3 additional dropouts at 6 months (2 biofeedback) and 5 lost to follow-up at 12 months (3 biofeedback). All dropouts designated as treatment failures for each subsequent assessment point Reviewer comments: No clear definition of encopresis given Method of randomisation and allocation concealment not described No sample size calculation. ITT analysis

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							apparently performed Unclear how the 4 outcomes groups were defined from the clinical variables <u>Source of funding:</u> not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Berg et al. A controlled trial of 'Senokot' in faecal soiling treated by behavioural methods. 1983. Journal of Child Psychology and Psychiatry and Allied Disciplines 24[4], 543-549	Study Type: Quasi RCT Evidence level: 1- Study aim: to see whether behaviour therapy would suffice on its own in the treatment of severe and persistent faecal soiling or would be improved by employing a laxative as well	44 children Inclusion criteria: children who had soiling as a main complaint and uncomplicated functional faecal incontinence after an initial assessment and physical examination Exclusion criteria: not clearly stated	40 children mean age: 7.9 years (S.D. = 2.3) gender not reported Country: UK	General: Behavioural treatment, focusing on use of the toilet and freedom from soiling Intervention: Senokot Comparison 1: placebo tablets in similar dosage to Senokot Comparison 2: No medication Children started on 1 tablet at night. On the next visit to the clinic, if no improvement in 'use of the toilet' and 'being clean' on the charts dosage increased to 2 tablets. Number of tablets increased to 3 on following visit if improvement had still not occurred. When soiling getting better and child using toilet	Duration of treatment: 3 months Assessment point (s): 3 months after starting treatment Follow-up period: 6 months to 1 year after first entering trial (but after 3 months the study was a case series for Senokot only, therefore not reported here) Outcome Measures: -severity of soiling -number of soiling-free children	Severity of soiling: -At 3 months: Senokot (n=14) Placebo (n=11) No tablets (n=15) NS between the 3 groups (outcomes not reported by group) Number of soiling-free children -Relieved (less than once/week or not at all) Senokot (n=14): 5 (35%) Placebo (n=11): 2 (18%) No treatment (n=15): 9 (60%) -Not relieved Senokot (n=14): 9 Placebo (n=11): 9 No treatment (n=15): 6 NS between the 3 groups	Additional information from study: Children randomly allocated to 1 of 3 treatment groups, A, B and virtually in a random fashion No significant baseline differences between the 3 groups Psychiatrist and psychologists did not know which tablets actually contained the laxative. Tablets made up in packs labelled A and B. Methods used in behavioural treatment: identifying targets, discussing use of rewards, star charting, reinforcement of using the toilet appropriately and staying clean, mainly by Mothers advised to avoid castigating children. Initially, children taken to toilet 3 times a day, then prompted to go unaccompanied, then expected to go on own initiative 4 children dropped out after only 1 or 2 visits Severity of soiling rating: 0 = none, 1 = less than once a week, 2 = at least once a week but less than daily, 3 = daily Reviewer comments: No definitions of soiling/functional faecal incontinence given Inadequate randomisation Allocation concealment not described Soiling frequently apparently assessed by interviewing parent at time of consultation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				dosage kept the same. Once child going regularly to toilet and not soiling tablets stopped altogether			No sample size calculation performed Not clear whether the 4 children who dropped out had already received any study medication There is a mistake in the paper regarding outcomes for the “no tablets” groups, therefore not reported here Results not controlled for potential confounders <u>Source of funding:</u> Messrs Reckitt and Coleman provided the medication and gave their support in carrying out this trial

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Bu et al. Lactobacillus casei rhamnosus Lcr35 in children with chronic constipation. 2007. Pediatrics International 49[4], 485-490	Study Type: RCT Evidence level: 1+ Study aim: to investigate the effect of Probiotics (Lactobacillus case rhamnosus, Lcr35) alone in the treatment of chronic constipation in children and to compare the effect with magnesium oxide (MgO) and placebo, respectively	45 children Inclusion criteria: children under 10 years old with chronic constipation Exclusion criteria: organic causes of constipation like Hirschsprung's disease, spina bifida (occulta), hypothyroidism, or other metabolic/renal abnormalities, drugs influencing gastrointestinal function other than laxatives (calcium channel blockers, antidysrythmic agents, anticonvulsivants,	45 children 23 male Age (months, mean, SD) MgO group Probiotic group Placebo group Country: Taiwan	Intervention: MgO 50 mg/kg per day, twice a day Comparison 1: Lcr35 8 X 10^8 c.f.u/day (Antiobiophilus 250 mg, 2 capsules, twice a day) Comparison 2: Placebo (starch in content) Lactulose use (1mL/kg/day) allowed when no stool passage noted for 3 days. Glycerin enema used only when no defecation for >5days or abdominal pain suffered due to stool impaction	Duration of treatment: 4 weeks Assessment point (s): Immediately after treatment completed Follow-up period: No follow up made after treatment finished Outcome Measures: -frequency of defecation -consistency of stools -episodes of soiling -episodes of abdominal pain -use of lactulose or enema	Defecation frequency (times/day) -MgO (n=18) 0.55 ± 0.13 -probiotic (n=18) 0.57 ± 0.17 -placebo (n=9) 0.37 ± 0.10 MgO vs. probiotic NS Placebo vs. probiotic P=0.006 MgO vs. placebo p=0.01 Hard stool (%) -MgO (n=18) 23.5 ± 7.9 -probiotic (n=18) 22.4 ± 14.7 -placebo (n=9) 75.5 ± 6.1 MgO vs. probiotic NS Placebo vs. probiotic p=0.02 MgO vs. placebo p=0.03 Abdominal pain (times) -MgO (n=18) 4.8 ± 3.7	Additional information from study: Chronic constipation defined as a stool frequency of <3 times/week for >2 months and at least 1 of the following minor criteria: anal fissures with bleeding due to constipation, faecal soiling or passage of large and hard stool Children randomly assigned into the 3 groups according to a computer - generated randomisation list Blinding achieved by the use of 3 interventions with similar appearances and placed into identical capsules, which were either swallowed o as a whole or opened and the contents of the capsule administered in milk or fluid Throughout the duration of study all investigators, participants and data analysts were blinded to the assigned treatment Sample size determined by doing primary trial with 9 patients using non-inferiority to test. Equivalent margin chosen with reference to effect of active control in the data of preliminary trial. Unbalance design of allocation number used for more interest in the new drug (Lcr35): allocation rate set at 2:2:1. One sided significance level set at 0.05 and power was 80%. Under these assumptions the smallest sample size was 45 and the sample size of MgO, Lcr35 and placebo was 18, 18 and 9

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		antidepressants, anticholinergic agents)				-probiotic (n=18) 1.9 ± 1.6 -placebo (n=9) 6.7 ± 3.3 MgO vs. probiotic p=0.04 Placebo vs. probiotic p=0.01 MgO vs. placebo NS <u>Use of glycerine enema (times)</u> -MgO (n=18) 1.3 ± 1.9 -probiotic (n=18) 1.6 ± 1.9 -placebo (n=9) 4.0 ± 2.1 MgO vs. probiotic NS Placebo vs. probiotic p=0.04 MgO vs. placebo p=0.03 No significant differences regarding use of lactulose, faecal soiling and change of appetite amongst 3 groups <u>Patients with treatment success (%)</u>	respectively No significant differences at baseline amongst the 3 group regarding: sex, age of enrolment, age of onset of constipation, duration of constipation, previous treatment, defecation period, stool consistency, abdominal pain, faecal soiling, bleeding during defecation, use of enema, taking fruit or vegetable daily Patients asked to discontinue any laxatives previously prescribed 3 days before entering protocol, and also asked to avoid any other probiotics, yogurt or beverage containing probiotics for at least 2 weeks before treatment and during therapy All outcomes measures recorded by parents in a stool diary 4 patients discontinued medication during study period: 2 in MgO, 1 in probiotic, 1 in placebo group (2 patients suffered from acute gastroenteritis and 2 patients lost to follow-up) <u>Reviewer comments:</u> Allocation concealment not described Not clear whether the 2 patients who suffered from acute gastroenteritis had it as consequence of the study medication Study not controlled for potential confounders <u>Source of funding:</u> not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						-MgO (n=18): 72.2 -probiotic (n=18): 77.8 -placebo (n=9): 11.1 MgO vs. probiotic NS Placebo vs. probiotic p=0.01 MgO vs. placebo p=0.01 no adverse effects noted in probiotic and placebo groups, only 1 patient in the MgO group suffered from mild diarrhoea	

Adverse Effects of medium- to long-term use of Laxatives in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Thomson et al. Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study.[erratum appears in Arch Dis Child. 2008 Jan;93(1):93]. 2007. Archives of Disease in Childhood 92[11], 996-1000	Study Type: RCT (cross over, multicentre) Evidence level: 1+ Study aim: to assess the efficacy and safety of polyethylene glycol 3350 plus electrolytes (PEG + E) for the treatment of chronic constipation in children	51 children Inclusion criteria: chronic constipation for at least 3 months Exclusion criteria: current or previous faecal impaction decided by either physical examination or abdominal X-ray, previous intestinal perforation/obstruction, paralytic ileus, Hirschsprung's disease, severe inflammatory conditions of the intestinal tract, severe gastroesophageal reflux, diabetes,	51 children 29 girls mean age 5.4 years (range: 24 months to 11 years) Country: UK	Intervention: PEG + E (6.9 g powder/sachet) Comparison: Placebo (6.9 g powder/sachet) Washout period in between: 2 weeks Dosing regime for both PEG + E and placebo (number sachets/day): -children aged 2 to 6 years days 1-2: 1 days 3-4: 2 (taken together) days 5-6: 3 (2 morning, 1 evening) days 7-8: 4 (2 morning, 2 evening) -children aged 7 to 11 years days 1-2: 2 (taken together) days 3-4: 2 (taken together) days 5-6: 5 (2	Duration of treatment: 2 weeks each treatment period separated by a 2-week placebo washout Assessment point (s): immediately after each treatment period, including washout Outcome Measures: Adverse events	Mean effective dose of PEG 3350 (g/kg/day): 0.6 (2 to 6-year-old) 0.7 (7 to 11-year-old) Adverse events: PEG+E (31/49, 63%) Placebo (28/49, 57%) during periods I and III. None serious, most judged by investigator to be moderate or mild in severity 20 children (41%) on PEG+E: 41 events 22 children (45%) on placebo: 45 events, judged by investigator to be at least possibly related to the study treatment. Most gastro-intestinal disorders (particularly abdominal pain), PEG+E (39%, 39 events); placebo (45%, 41 events). 1 child in placebo/PEG+E group withdrawn at week 3 because of abdominal pain,	Additional information from study: Chronic constipation defined according to Rome criteria as < 3 complete bowel movements/week, and at least 1 of the following: pain on defecation on at least 25% of days; at least 25% of bowel movements with straining, and at least 25% of bowel movements with hard or lumpy stools Random sequence group computer generated before start of recruitment using block size of 4 patients and study medication labelled accordingly. Random blocks (with numbers stored in sealed code-break envelopes) sent to investigator sites as required. As children enrolled, sites allocated treatment supplies sequentially, started with lowest possible number. Both the children (and their parents/guardians) and those administering treatment were blinded to allocation schedule A sample size of 50 children was planned to achieve 40 evaluable children, giving 90% power to detect a true treatment difference of 0.3 bowel movements/week using a two-tailed significance test at the 5% level. As dropout rate was higher than originally estimated, recruitment target was increased to 60 children At baseline, clinically significant abnormalities

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		receiving doses of stimulant laxatives considered by local observers to be at higher end of their own doses spectrum		morning, 3 evening) days 7-8: 6 (3 morning, 3 evening) For both groups if diarrhoea, dose was decreased by 2 sachets or miss a day. If loose stools dose decreased by 1 sachet		assessed by investigator as being related to treatment, this child was taking placebo at the time of withdrawal. New clinically significant abnormalities on physical examination (mainly associated with faecal loading): 13 children (8/27 in the PEG+E/placebo group, 5/24 in the placebo/ PEG+E group). When analysed for what these children were taking for the 2 weeks before the physical examination, 23 out of the 24 reports (95.8%) occurred when child taking placebo. Only 1 report of an abnormal abdominal examination while patient on PEG+E Mean weight similar before and after treatment, no significant difference found between the 2 groups for change in weight while on treatment (p=0.357)	on physical examination (mainly associated with faecal loading but not impaction) recorded for 8 children (5/27 in the PEG+E/placebo group, 3/24 in the placebo/PEG+E group). Before randomisation, 47 children taking other laxatives (most frequently lactulose) 13/51 children (7/27 in the PEG+E/placebo group, 6/24 in the placebo/PEG+E group) recorded at least 1 deviation from the study protocol (1 child recorded 2 protocol deviations). Main reason for deviation was non-compliance with study medication (7/51 children), followed by failure to supply sufficient bowel movement data (4/51 children), and taking concomitant non-study laxative medication after randomisation (3/51 children) Safety monitored by adverse events recording, physical examination findings, and weight changes <u>Reviewer comments:</u> Blinding procedures not clearly described Unclear whether outcomes assessors were also blinded to treatment allocation Study not controlled for potential confounders <u>Source of funding:</u> Norgine Ltd. One of the authors was an employee of Norgine Ltd. At the time the study was written. The others declared that they had nothing to declare

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Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Dupont et al. Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. 2005. Journal of Pediatric Gastroenterology and Nutrition 41[5], 625-633	Study Type: RCT Evidence level: 1+ Study aim: to assess the safety of a polyethylene glycol (PEG) 4000 laxative without additional salts in paediatric patients	96 children Inclusion criteria: ambulatory children with constipation despite their usual dietary treatment for at least 1 month, aged 6 months to 3 years Exclusion criteria: history of intractable faecaloma, Hirschsprung's disease, neurologic, endocrine or metabolic disorders, allergic disease or allergies	96 children 51 male Age (months) (median, (25th–75th percentiles) -PEG 4000: 28 (19.5–33.7) -Lactulose: 25.8 (12.3–33) Country: France	Intervention: PEG 4000 -Starting dose: 1 sachet (4g) and 1 placebo to be taken at breakfast Comparison: Lactulose -Starting dose: 1 sachet (3.33g) and 1 placebo to be taken at breakfast For both drugs, dose could be doubled if ineffective in children aged 13 months to 3 years If maximum authorised dose unsuccessful, one micro-enema of glycerol per day could be prescribed for a maximum of 3 consecutive days. If child not produced stools after treatment 2 enemas could be administered at a	Duration of treatment: 3 months Assessment point (s): Day 42 (D42) and day 84 (D84) after starting treatment Outcome Measures: -Biological tolerance: ion electrolytes total protein albumin vitamin A vitamin D folates -Clinical tolerance: body height body weight adverse effects	Clinical tolerance (ITT population) -6 adverse effects (all non serious): 5 diarrhoea (5 episodes in 2 children in both treatment groups) 1 anorexia (on lactulose) -median (interquartile range) duration of either new onset or worsened flatulence (days): PEG 4000: 3 (1 to 4.5) Lactulose: 5 (3 to 19.5) P=0.005 -median (interquartile range) duration of either new onset or worsened vomiting episodes (days): PEG 4000: 1 (1 to 2) Lactulose: 2 (1 to 6) P<0.05 -anal irritation: 5% (2 out of 40 children, both on lactulose) -no difference	Additional information from study: Constipation defined as <1 stool/day for >1 month in children 6 to 12 months old and <3 stools/week for > 3 months in children aged 13 months to 3 years PEG 4000 and lactulose packaged in a double-blind and double-dummy design, by means of coupled sachets, according to a randomisation list. Double dummy design required because of the difference of taste between the drugs. Numbered boxes provided to investigators at each site in equal numbers. Investigators randomly allocated either PEG 4000 or lactulose to the children for a 3-month period, with the same strategy for dose adaptation 3 children not included because of a baseline laboratory value ONR (out of normal range) before the amendment was applied. 2 children in PEG 4000 group dropped out before any study drug intake, so the intention to treat (ITT) population included 51 children (10 babies and 41 toddlers) in the PEG 4000 group and 45 (12 babies and 33 toddlers) in the lactulose group. 76 of these children included in the *per protocol* analysis and 20 excluded by the independent scientific committee for at least 1 major deviation, 11 in the PEG 4000 group and 9 in the lactulose group. Reasons for exclusion were no laboratory test at D84, 1 or more one missing laboratory results at D84, delayed laboratory test at D84 (n = 12),

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				48-h interval. This procedure was only allowed twice during the study, If child produced liquid stools for more than 1 day or more than 2 or 3 stools/day depending on age, dose could be decreased by 1 pair of sachets/day to a minimum of 1 pair of sachets every other day and possibly to transitory interruption		between PEG 4000 and lactulose groups with regards to other digestive tolerance outcomes -Body height and body weight unaffected during the 3-month treatment for both boys and girls Biological tolerance (ITT population): No significant difference between treatment groups for the % of children with ONR values on D84 compared to baseline status. No treatment-related changes found in serum iron, electrolytes, total protein, albumin and vitamins A, D and folates Dose used (sachets/day) (median (interquartile range)) -Babies: 1 (0.9 to 1) PEG 1 (1 to 1.3) lactulose P = 0.67 -Toddlers	inadequately long exposure to the study drug (n = 2), personal reasons (n = 5) and unauthorized concomitant treatment (n = 1). There were no clinically relevant differences between the 2 treatment groups at baseline for clinical or biologic parameters. Stool frequency, abdominal pain, vomiting, and nausea recorded by parents on Self-Diary Evaluation Booklet Reviewer comments: Methods of randomisation and allocation concealment not clearly described No sample calculation performed Results not controlled for potential confounders Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						1 (1 to 1.3) PEG 1.1 (0.9 to 1.5) lactulose P = 0.58 Treatment stopped in 1 child because of lack of efficacy (lactulose group)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Loening-Baucke. Polyethylene glycol without electrolytes for children with constipation and encopresis. 2002. Journal of Pediatric Gastroenterology and Nutrition 34[4], 372-377United States.	Study Type: Prospective cohort Evidence level: 2 + Study aim: to determine the efficiency, acceptability, and treatment dosage of MiraLax (polyethylene glycol 3350 without electrolytes) during a 12-month treatment period in children with functional constipation and encopresis	49 children Inclusion criteria: children ≥4 years of age referred for functional constipation and encopresis Functional constipation defined as delay/difficulty in defecation and encopresis (≥1/week) for more than 1 year Exclusion criteria: Children <4 years of age; children who refused the toilet for stooling but who had no constipation, Hirschsprung's disease, chronic intestinal pseudo-obstruction, or	-Miralax group: 28 children 20 boys Mean age ± SD: 8.7 ± 3.6 years Range 4.1 to 17.5 years -MOM group: 21 children 17 boys Mean ± SD: 7.3 ± 3.0 years Range: 4.0 to 13.9 years Country: USA	Intervention: MiraLax 17 dissolved in 240 mL of a beverage such as juice or Kool-Aid initial dose: 0.5 to 1 g/kg/daily Comparison: MOM Initial dose 1 to 2.5 mL/kg Large laxative dosages divided into 2 daily doses. Parents told to adjust the dose of medication by 30 mL for MiraLax and by 7.5 mL (one-half tablespoon) for MOM every 3 days to a dosage that resulted in 1 to 2 soft bowel movements/day and prevented soiling and abdominal pain.	Duration of treatment: 12 months Assessment point (s): 1, 3, 6, and 12 months after initiating treatment Outcome Measures: -medication dosage -clinically significant side effects -compliance with medication	Medication dosage (Mean doses and range for children who were doing well or improved) (PEG, g/kg; MOM, mL/kg) 1 month PEG: 0.6 ± 0.2 (0.3 to 1.1) MOM: 1.4 ± 0.6 (0.6 to 2.6) 3 months PEG: 0.6 ± 0.3 (0.3 to 1.4) MOM: 1.2 ± 0.5 (0.6 to 2.4) 12 months PEG: 0.4 ± 0.1(0.1 to 0.7) MOM: only 2 children still required MOM. Their dosages were 0.4 and 1.6 mL/kg, both less than the initial treatment dosage mean doses for both treatments at 12 months did not differ significantly between children with or without initial palpable abdominal	Additional information from study: Initial dose of Miralax 0.5 g/kg daily suggested for children whose rectums were loaded with stool but who had no fecal abdominal masses at the initial physical examination and no history of long intervals between huge bowel movements. Those with palpable abdominal fecal masses or history of infrequent huge bowel movements started on 1 g/kg daily Milk of Magnesia given if family could afford only the use of a cheaper laxative or if child had previously received MOM without refusal. For these children, MOM reintroduced or adjusted to an adequate dosage. Parents told how to improve the taste by mixing the child's preferred flavoring with plain MOM. Initial daily dosage of 1 mL/kg body weight suggested for children with rectal fecal masses only at initial evaluation and if they had no history of infrequent large bowel movements. Dosage of 2.5 mL/kg prescribed for those with fecal abdominal masses at the initial evaluation or history of huge, infrequent bowel movements Regular stool sittings for 5 minutes after each meal required for initial months. Patients and parents provided with diary sheets to record each outcome measured Global assessment of whether child was

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		previous surgery of the colon/anus		If child retained stools despite compliance with assigned laxative, daily senna added to treatment		faecal masses. None of the patients required an increased dosage of either medication over time 5 children received a stimulant laxative in addition to PEG and 1 child received a stimulant laxative in addition to MOM (*P* > 0.2) <u>Clinically significant side effects</u> PEG: no significant clinical side effects. Some children had diarrhea. None of the children in the PEG group became dehydrated. Children receiving PEG and their parents did not report increased flatus, abdominal distention, or new onset of abdominal pain <u>Compliance with medication:</u> -PEG: No children reported disliking the taste, no parents	"doing well," "improved," or "not doing well" was recorded. Doing well defined as 3 or more bowel movements/week and 2 or fewer soiling episodes / month. Improved defined as 3 or more bowel movements / week and a more than 75% decrease in soiling but not more than 1 soiling / week. Not doing well was defined as fewer than 3 bowel movements / week, a less than 75% decrease in soiling frequency, use of senna, or refusal to take the assigned laxative. Recovered defined as 3 or more bowel movements / week and 2 or fewer soiling episodes / month while not taking laxatives. No significant baseline differences between 2 groups <u>Reviewer comments:</u> No sample size calculation performed Outcomes for consistency of stools not reported Not reporting on the clinically significant side effects (or lack of them) for MOM <u>Source of funding:</u> Dr. Loening-Baucke recipient of grant support from Braintree Pharmaceuticals, Braintree, MA, U.S.A., for continuing studies on childhood constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						reported that child refused to take it in juice or Kool-Aid Parental noncompliance with administering the laxative and supervising toilet use: 14% children -MOM: 33% children refused to take it Parental noncompliance with administering the laxative and supervising toilet use: 4% children	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Erickson et al. Polyethylene glycol 3350 for constipation in children with dysfunctional elimination. 2003. Journal of Urology 170[4 Pt 2], 1518-1520	Study Type: Retrospective case series Evidence level: 3 Study aim: To review the efficacy of PEG as a single agent for the treatment of constipation in children with dysfunctional elimination and asses bladder function following treatment	46 children Inclusion criteria: Children diagnosed with dysfunctional voiding and constipation who received polyethylene glycol 3350 between January 2000 and July 2002 Exclusion criteria: Known neurological impairments	46 children 35 girls mean age: 7.7 years (range 4.5 to 11.2 years) 11 boys mean age: 7.6 years (range 4.4 to 11.1 years) Country: USA	Intervention: Polyethylene glycol 3350 without electrolytes (MiraLax) 17 gm (1 capful) mixed with 8 ounces of fluid of parent's choice Starting dose: 8 ounces of mixture each day with instructions to adjust the amount consumed by 1 to 2 ounces every 3 days to achieve the goal of 1 to 2 soft bowel movements per day Final dose normalised to patient weight Average final dose: 0.63 gm/kg (reported in abstract) 0.59 gm/kg (reported in text) Comparison: None	Duration of treatment Mean: 194.3 days (SD 133.5) Assessment points Not clear Outcome Measures: side effects	Side effects: -Diarrhoea: 9/46 children, all female *age at start of PEG (mean ± SD, years):* patients with diarrhoea (n=9): 6.8 ± 1.1 patients without diarrhoea (n=37): 8.2 ± 1.8 p=0.04 duration of follow-up *(mean ± SD, days):* patients with diarrhoea (n=9): 336 ± 153 patients without diarrhoea (n=37): 108 ± 11 p=0.0028 1 child stopped taking PEG because of side effects	Additional information from study: Diagnosis of constipation based on history of Infrequent bowel movements (less than very other day) and/or hard, large or painful bowel movements. Most children also had confirmatory abdominal x-ray demonstrating accumulation of stool in the rectum and throughout the colon 25 patients also underwent biofeedback, and 8 patients began anticholinergic medication during the course of PEG treatment Reviewer comments: Not clear how side effects measured in the first place Not clear how the reviewing process was conducted Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Loening-Baucke et al. Polyethylene glycol 3350 without electrolytes for the treatment of functional constipation in infants and toddlers. 2004. Journal of Pediatric Gastroenterology and Nutrition 39[5], 536-539	Study Type: Retrospective case series Evidence level: 3 Study aim: to evaluate the safety and efficacy of PEG 3350 without electrolytes for the treatment of constipation in children < 2 years of age	75 children Inclusion criteria: Children with constipation <2 years of age at start of PEG therapy Exclusion criteria: Hirschsprung's disease, chronic intestinal pseudo-obstruction, previous surgery of colon/anus, disease states that place limitations on the act of defecation such as hypotonia, cerebral palsy and severe mental retardation	75 children 36 boys mean age 17 months (range 1 to 21 months) Country: USA	Intervention: PEG 3350 without electrolytes (MiraLax) Starting average dose 1g/kg body weight/day Parents asked to adjust dose to yield 1 to 2 soft painless stools/day Comparison: none	Duration of treatment (months, mean ± SD) -short term: 2.3 ± 1.3 (range: 1 to 4) -long term: 10.6 ± 8.1 (range 6 to 37) Assessment points -short term: ≤ 4 months (mean 2 months) -long term: ≥ 6 months (mean 11 months) Outcome Measures: Adverse effects	Adverse effects a. ≤ 4 months (n=71) 5 children (7%): runny stools (Dose of PEG (g/kg body weight/day): Range 0.4 to 2.3 Mean 1.1 ± 1.2 Median (0.82) b. ≥ 6 months (n=47) 1 child (2%): watery stools (he was only brought by his mother for a 6-month follow-up). The diarrhoea disappeared after lowering the dose of PEG. (Dose of PEG (g/kg body weight/day): Range 0.3 to 2.1 Mean 0.8 ± 0.4 Median (0.67) Parents did not report increased flatus, abdominal distension, vomiting or new onset abdominal pain. None stopped PEG because of adverse effects.	Additional information from study: Constipation defined according to NASPGHAN criteria Reviewer comments: Authors reviewed charts from their own clinics. Not clear how the reviewing process was conducted Not completely clear how side effects were measured in the first place, it seems that parents were asked about the at the time of consultation Source of funding: not stated

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						Complete blood counts (in 24 children), electrolytes (in 9 children), renal functions (in 8 children) and liver functions (in 8 children) occasionally done in children on long-term PEG treatment, and all were within normal limits.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Michail et al. Polyethylene glycol for constipation in children younger than eighteen months old. 2004. Journal of Pediatric Gastroenterology and Nutrition 39[2], 197-199	Study Type: Retrospective case series Evidence level: 3 Study aim: to determine safety, efficacy, and optimal dose of polyethylene glycol powder for treatment of constipation in patients younger than 18 months	28 children Inclusion criteria: children younger than 18 months treated for constipation with PEG powder Exclusion criteria: organic aetiology for constipation: Hirschsprung's disease, anorectal malformation, bowel obstruction, or systemic illness (hypothyroidism, cystic fibrosis, or lead poisoning associated with constipation. Taking medication that could potentially	28 children -age at initiation of therapy: 3 children: age 0 to 5 months 9: age 6 to11 months 16: age 12 to 17 months gender not reported Country: USA	Intervention: PEG 3350 administered orally, mixed in a ratio of 17 g to 240 mL of fluid, as recommended by the manufacturer. Caregivers for small infants mixed PEG 3350 in formula if it was the sole diet. After initial dose, families asked to titrate the dose to obtain at least one nonformed bowel movement daily. Change in dose permitted within 24 hours, if necessary Mean initial Dose: 0.88 g/kg/day (range, 0.26–2.14 g/kg/day) Mean effective maintenance dose: 0.78 g/kg/day (range, 0.26–1.26 g/kg/day) Comparison:	Duration of treatment Mean 6.2 ± 5 months (range, 3 weeks to 21 months) Assessment points at initial visit and subsequent visits every 8 to 12 weeks Outcome Measures: Side effects	Side effects: Total: 5 (17.9%) of patients 1 (3.6%) infant experienced increased passage of gas per rectum 4 (14.3%) infants experienced transient diarrhoea that resolved after dose adjustment	Additional information from study: Diagnostic criteria for functional constipation in infants and preschool children adapted from Rasquin-Weber and included: 2 weeks of hard stools (the majority of stools), or firm stools 2 or fewer times a week in the absence of structural, endocrine, or metabolic disease No patient placed on a clean-out protocol using any other drug Duration of therapy and side effects retrieved from the patient's chart. Information not available in the chart was obtained by telephone interview. Only 1 family needed to be contacted by telephone Reviewer comments: Authors reviewed charts from their own clinics. Not clear how the reviewing process was conducted Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		change the frequency or consistency of bowel movements		none			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Pashankar et al. Long-term efficacy of polyethylene glycol 3350 for the treatment of chronic constipation in children with and without encopresis. 2003. Clinical Pediatrics 42[9], 815-819	Study Type: Retrospective cohort Evidence level: 2- Study aim: to report efficacy of PEG therapy, effective dose and patient compliance separately for children with constipation and children with constipation and encopresis over the long term	74 children Inclusion criteria: children > 2 years of age with chronic constipation treated at authors' clinic daily with PEG 3350 without electrolytes (MiraLax) for > 3 months Exclusion criteria: history of Hirschsprung's disease, anorectal malformations, abdominal surgery, or any systemic illness leading to constipation	74 children 40 boys mean age: -constipation only: 6.6 years (range 2 to 16.9) -constipation and encopresis: 8.4 years (4.3 to 12.8) Country: USA	Intervention: PEG 3350 without electrolytes (MiraLax) 0.8 g/kg/day administered orally, as recommended by the manufacturer mixed in a ratio of 17 g of powder to 240 mL of water or other beverage. Families allowed free choice of beverage Parents asked to adjust the dose as required to yield 2 soft painless stools per day Comparison: Behaviour modification programme	Duration of treatment Mean 8.4 months (range 3 to 30) Assessment points Unclear Outcome Measures: Adverse effects	Average dose of PEG at time of evaluation: 0.73 g/kg/day (range 0.3 to 1.8) following adjustment of dose by caretakers Adverse effects: no major clinical adverse effects observed	Additional information from study: Diagnosis of chronic constipation based on symptoms of at least 3 months' duration including at least 2 of the following: hard stools, painful defection, encopresis or fewer than 3 bowel movements/week Encopresis defined as constipation with involuntary loss of stools into the underwear beyond a developmental age of 4 years Reviewer comments: Authors reviewed charts from their own clinics. Not clear how the reviewing process was conducted. Some outcomes variables gathered by interviewing patients/parents and examining patients. Unclear how data on adverse effects were obtained Source of funding: Financial assistance provided in part by Braintree Laboratories, Braintree, MA

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Hardikar et al. Macrogol 3350 plus electrolytes for chronic constipation in children: a single-centre, open-label study. 2007. Journal of Paediatrics and Child Health 43[7-8], 527-531	Study Type: Prospective case series Evidence level: 3 Study aim: To evaluate the safety and efficacy of a macrogol 3350-based electrolyte containing preparation in the treatment of chronic constipation in children	81 children Inclusion criteria: Children aged 24 months to 11 years with chronic constipation for at least 6 months, which was either untreated or inadequately treated by laxatives Exclusion criteria: children treated for faecal impaction with bowel washouts during the previous 2 months, or had a past history of intestinal perforation/obstruction, Hirschsprung's disease, paralytic ileum, toxic	77 children 44% boys mean age: 4.9 ± 2.6 years Country: Australia	Intervention: Macrogol 3350 plus electrolytes (Movicol) Each sachet (6.563 g Macrogol) dissolved 62.5 mL of water *Number of sachets first 5 days* -Children aged 2 to 6 years: Days 1 & 2: 1/day Days 3 & 4: 1 twice a day Day 5: 1 three times/day -Children aged 7 to 11 years Day 1 & 2: 1 twice a day Day 3, 4 & 5: 2 twice a day Thereafter and until end of study dosage titrated according to faecal form. This dose increased by 1 sachet/day in the event of continued hard	Duration of treatment Mean 75.5 days Assessment points Adverse effects monitored throughout the study, venous samples for laboratory taken at baseline, 28 days and 84 days. Vital signs measured at baseline and 84 days Outcome Measures: -Safety : adverse effects laboratory tests changes in vital signs	Mean numbers of sachets/day during treatment period: 1.3 (6.9 g) Adverse effects (n=78) 72 children (92%) reported a total of 318 events 241 (76%) assessed as unrelated to study treatment 262 (82%): mild 302 (95%): resolved by end of study 6 serious adverse events in 4 children: 4 affected gastrointestinal system. All assessed by investigator as unrelated or unlikely to be related to study medication and resolved at end of study. 1 serious adverse event (faecal impaction) led to patient's premature withdrawal from study as child was admitted as impatient for bowel washout	Additional information from study: Chronic constipation defined as fewer than 3 complete bowel movements per week over previous14 days in association with either straining or passage of hard stools in at least a quarter of bowel movements If investigator considered it to be clinically necessary patients could be given another laxative provided they had failed to respond to the maximum dose for 3 days No other therapeutic interventions, including an increase in oral fluids or dietary fibre were instituted Any child who developed faecal impaction (faecal loading) which required treatment was withdrawn from study and classified as treatment failure 78 (96%) patients included in safety analysis. 65 (80%) patients completed study. 16 patients withdrew prematurely: 6 unable or refused to take medication, 4 protocol deviation, 3 poor compliance, 1 failed to return for final visit, 1 parent refused to give medication, 1 serious adverse effect Reviewer comments: 6 serious adverse events in 4 children: 4 affected gastrointestinal system, remaining 2 not reported

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		megacolon, severe inflammation of the intestinal tract, urinary tract infection,, uncontrolled renal, hepatic or cardiac diseases, endocrine disorders, or any other severe unstable coexisting disease during he previous 30 days		stools/no bowel movements, and decreased by 1 to 2 sachets/day in the event of loose stools or diarrhoea Comparison: None		Changes in vital signs: No clinically significant changes as result of study medication	Not clear how clinical adverse effects were asked for Source of funding: Movicol sachets supplied by Norgine Ltd. Uxbridge, UK. Study supported by a research grant from Norgine Ltd. Uxbridge, UK and Norgine PTY, Sydney, Australia

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Adler. Effective Treatment of Constipation and Encopresis with Movicol (Macrogol 3350 with Electrolytes) in Children and Adolescents. 2005. Gut 54[Suppl VII], A217 Adler, 2005	Study Type: Prospective Case series Evidence level: 3 Study aim: to assess the effectiveness of Movicol (macrogol 3350 with electrolytes), over the course of long term treatment in children with constipation	134 patients Inclusion criteria: children referred with constipation and/or encopresis to The Queen Silvia Children's Hospital, Sweden Exclusion criteria: Not stated	134 patients 88 males age not clearly reported Country: Sweden	Intervention: Movicol (macrogol 3350 with electrolytes,13.8g sachets) -Mean starting dose: Age 2 to 6: 0.58 sachets Age 7 to 11: 0.51 sachets Doses adjusted in each patient to achieve symptom relief with the minimally effective dosage Comparison: None	Duration of treatment: Mean: 50 weeks (SD ±50 weeks; range 1 to 211 weeks) Assessment point (s): unclear Outcome Measures: -final treatment dose -side effects	Mean dose at end of observational period Age 2 to 6: 0.42 sachets Age 7 to 11: 0.49 sachets -overall mean change: 0.553 to 0.477 sachets/day Side-effects were reported in 10 (7.5%) patients and these were generally mild and transient	Reviewer's' comments It is difficult to asses the quality criteria and to make comments on this study because we have only been able to review the abstract. This abstract was included because it provides some evidence on long-term treatment with Movicol Source of funding: Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Loening-Baucke et al. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. 2006. Pediatrics 118[2], 528-535	Study Type: RCT Evidence level: 1- Study aim: to compare the efficacy, safety and patient acceptance of polyethylene glycol (PEG) 3350 without added electrolytes vs. milk of magnesia (MOM) over 12 months	79 children Inclusion criteria: age ≥ 4 years and presence of functional constipation with faecal incontinence Exclusion criteria: stool toileting refusal, faecal incontinence but no constipation, previous refusal of one of study medications, children who came from far away for a second opinion, Hirschsprung's disease, chronic intestinal pseudobstruction, previous surgery involving colon or anus	79 children 65 boys age range: 4 to 16.2 years (median 7.4; mean 8.1 ± 3.0) Country: USA	General: disimpacted with 1 or 2 phosphate enemas in the clinic on the day of the visit , if necessary and started laxative therapy that evening Intervention: polyethylene glycol (PEG) 3350 without added electrolytes 0.7 g/kg body weight daily for 12 months capful of PEG (17 g) mixed in 8 oz of beverage (juice, Kool-Aid, Crystal Light or water) making a solution of ~2g/30 mL Comparison: milk of magnesia (MOM) 2mL/kg body weight daily for 12 months plain MOM could be mixed into apple sauce or milkshakes, or	Duration of treatment: 12 months Assessment point (s): 1, 3, 6 and 12 months after initiating treatment Outcome Measures: -safety profile -patient's acceptance and compliance	Patient Acceptance Several children complained about taste of PEG and MOM. 2 children (5%) continued to refuse PEG vs. 14 children (35%) continued to refuse MOM during the 12 months of the study (P < 0.001) Treatment doses (mean ± SD): -PEG (g/kg body weight) 1 month: 0.7 ± 0.2 3 months: 0.6 ± 0.3 additional senna at some point: 3 children -MOM (mL/kg body weight) 1 month: 1.2 ± 0.7 3 months: 1.2 ± 0.8 additional senna at some point: 1 child mean doses similar in children who improved and who did not improve for both treatments	Additional information from study: Functional constipation defined by duration of ≥ 8 weeks and ≥ 2 of the following: frequency of bowel movements <3 stools/week, >1 episode of faecal incontinence/week, large stools noted in rectum or felt during abdominal examination, passing of stools so large that they obstructed the toilet Randomisation performed by children drawing a sealed envelope with and enclosed assignment Investigators, children and their parents aware of the study group assignment It was estimated that 38 subjects were required in each group to be able to detect a difference in failure rates between the 2 groups of 30% in 12 months (40% vs. 10%), at the 0.05 significance level with 0.80 power. Authors hypothesized that PEG would be as successful as MOM in treating chronic constipation and faecal incontinence. Authors' previous study showed that 33% of children refused to take MOM during the first 12 months of treatment. Children treated with minimal effective dosage of PEG or MOM, allowing for a daily stool and preventing abdominal pain and faecal incontinence. Parents instructed to aim for 1 or 2 stools of milkshake consistency each day. Parents asked to increase dosage if

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				chocolate and other flavouring could be added Large doses of both medications could be divided into 2 doses		<u>safety profiles</u> PEG: 1 child allergic No other significant clinical effects for either medication, apart from transient diarrhoea disappearing with dose reduction -Laboratory tests: PEG: 1 child with elevated platelets before and after treatment, 1 child with decreased sodium levels at 6 months, but normal at 12 months MOM: 1 child high platelet count, 1 low serum sodium level, elevated AST, 1 elevated ALT	stools too hard or not frequent enough and to decrease the dosage if stools watery or too numerous. Small changes, such as 2 oz of PEG or 0.5 tbsp of MOM every 3 days, were recommended. Regular stool sittings for 5 minutes after each meal required initially. Toilet sitting frequency reduced after children recognized urge to defecate and initiated toilet use themselves. No significant differences at baseline between the 2 groups regarding: age, sex, primary faecal incontinence, previous treatment with laxatives, history of retentive posturing, frequency of bowel movements, bowel movements obstructing the toilet, frequency of faecal incontinence, presence of abdominal pain, presence of abdominal faecal mass and presence of rectal faecal mass By 12 months a total of 27 dropouts/lost to follow-up. PEG: 2 children lost to follow-up monitoring, 2 (5%) had refused PEG, 1 child allergic to PEG, 2 children were receiving senna. These 7 children counted as not improved and not recovered. MOM: 2 Children lost to follow-up monitoring, 3 children had discontinued study participation, 14 children (35%) had refused to take MOM, and 1 child was receiving senna Efficacy analyses performed with intention to treat population, other

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							outcomes calculated from available follow-up data Patients and parents questioned with respect to side effects during each visit <u>Reviewer comments:</u> Results not controlled for potential confounders High drop-out / lost to follow-up rate: 30.4% <u>Source of funding:</u> Braintree Laboratories (Braintree, MA) supported study with an unrestricted research grant. According to authors, the funding source had no involvement in the study design, collection, analysis, interpretation of data, writing of the report or decision to submit the article for publication

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Pashankar et al. Safety of polyethylene glycol 3350 for the treatment of chronic constipation in children. 2003. Archives of Pediatrics and Adolescent Medicine 157[7], 661-664	Study Type: Prospective case series Evidence level: 3 Study aim: to assess the biochemical and clinical safety profile of long-term PEG 3350 treatment in a large cohort of children and also paediatric patient acceptance of long-term PEG therapy	83 children Inclusion criteria: Children > than 2 years old with chronic constipation who were treated daily with PEG >3 months Exclusion criteria: history of Hirschsprung's disease, anorectal malformations, or any systemic illness potentially leading to constipation	83 children Male/female: 48/35 Mean age 7.4 years (range 2.0 to 16.9 years) Country: USA	Intervention: PEG 3350 without electrolytes (MiraLax) Initial dose: 0.8 g/kg per day According to manufacturer's directions, parents instructed to dissolve 17 g of PEG powder in 240 mL of water or other beverage and to give prepared solution in 2 divided doses. Families allowed choice of beverage to suit child's preference. Parents asked to adjust dose of PEG solution as required to yield 2 soft painless stools per day. Over time, parents instructed to gradually decrease dose of PEG if symptoms of constipation and encopresis showed improvement	Duration of treatment mean 8.7 months (range, 3 to 30 months Assessment points Outcome Measures: Adverse effects: -clinical -laboratory	Clinical adverse effects Minor and acceptable over mean duration of therapy 8 patients (10%): frequent watery stools sometime during therapy. Diarrhoea disappeared with reduction of dose 5 children (6%): bloating or flatulence 2 children (2%): abdominal pain 1 patient each (1%): thirst, fatigue, and nausea after receiving PEG solution on an empty stomach None of the patients stopped treatment due to adverse effects and all were to continue PEG therapy. General physical examination findings revealed no new significant abnormalities	Additional information from study: Diagnosis of chronic constipation based on symptoms of at least 3 months' duration, including at least 2 of the following: hard stools, painful defecation, encopresis, or fewer than 3 bowel movements per week All other laxative treatments stopped before starting PEG Parents interviewed using structured questionnaire and asked about dose of PEG given, medication compliance, any possible adverse effects of PEG, and particularly about excessively loose or frequent stools, abdominal pain, flatulence, bloating, and nausea. Parents asked about overall improvement in bowel movement pattern regarding stool frequency and consistency with PEG therapy. Following interview and physical examination, 4 mL of blood obtained for measurement of different parameters Results of blood tests considered abnormal if outside (even by 1 point) the age- and sex appropriate reference range established in authors' hospital. If results abnormal, blood tests repeated within 8 weeks while patient continued to receive therapy Source of funding: Study financially assisted by Braintree Laboratories

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				Comparison: None		compared with the pre-treatment Laboratory evaluation results: Haemoglobin, haematocrit, serum electrolytes, blood urea nitrogen, serum creatinine, serum albumin, and osmolality, normal in all patients (10 patients did not have serum osmolality measured) 9 patients (11%) had slightly elevated ALT level (<1.5 times the upper limit of normal; range, 31 to 45 U/L). 8 of these patients had ALT levels remeasured within 8 weeks, 7 of whom still receiving PEG therapy. 7 of these 8 patients had values in the reference range, 1 had slightly elevated ALT level (<1.2 times normal; 28 U/L). 3 patients (4%) had an elevated aspartate aminotransferase	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						level (<1.5 times normal; range, 42-52 U/L), and all had normal values when remeasured while still receiving PEG therapy Dose and duration of PEG therapy not significantly different in patients with abnormal values compared with those with laboratory values in the reference range	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Clark et al. Serum beta-carotene, retinol, and alpha-tocopherol levels during mineral oil therapy for constipation. 1987. American Journal of Diseases of Children 141[11], 1210-1212	Study Type: Prospective case series Evidence level: 3 Study aim: to prospectively monitor children receiving large doses of mineral oil throughout the early phase of treatment	25 children Inclusion criteria: Children with encopresis, over 1 year old with no previous treatment with mineral oil Exclusion criteria: not stated	25 children mean age: 7.83 years (range 1.75 to 14.27 years) gender not reported Country: USA	Intervention: Following initial disimpaction (not reported with what) , mineral oil, 45 mL twice daily between meals Dose gradually decreased on monthly basis (usually 30 mL/mo) depending on patient's reported performance and results of serial rectal examinations -Mean ± SEM: Month 1: 4.0 ± 1.4 Month 2: 2.9 ± 1.2 Month 3: 2.1 ± 0.5 Month 4: 1.4 ± 0.4 Comparison: none	Duration of treatment 4 months Assessment points 1, 2, 3 and 4 months Outcome Measures: Serum beta-carotene level Retinol level Alfa tocopherol level	Serum levels (micromols/L (micrograms/dL) (mean ± SEM): -Month 1 (n=25): Serum beta-carotene: Baseline: 1.0 ± 0.5 (55.7 ± 26.0) Treatment: 0.7± 0.4 (35.9 ± 22.1) P<0.01 Retinol: NS as compared to baseline -Month 2 (n=17): Serum beta-carotene: Baseline: 1.1 ± 0.6 (59.5 ± 30.6) Treatment: 0.7 ± 0.5 (38.2 ± 28.4) P<0.05 Retinol: NS as compared to baseline -Month 3 (n=10): Serum beta-carotene: Baseline: 1.1 ± 0.6 (60.4 ± 30.0) Treatment: 0.6 ± 0.2 (34.7 ± 12.3) P<0.05 Retinol: Baseline: 1.48 ± 0.84 (42.3 ± 24.1)	Additional information from study: Vitamin supplementation not prescribed Normal serum values for authors' laboratory: -Serum beta-Carotene: >0.6 micromols/L (>30 micrograms/dL) -Retinol: 0.70 micromols/L (20 micrograms/dL) -Alfa tocopherol: >9 micromols/L (>0.4 micrograms/dL) Since number of patients returning for subsequent visits gradually decreased, basal levels were recalculated for each month of treatment using the remaining patients as their own controls Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						Treatment: 2.22 ± 0.77 (63.5 ± 22.1) P<0.01 -Month 4 (n=5): Serum beta-carotene: NS as compared to baseline Retinol: NS as compared to baseline Serum alfa tocopherol levels remained relatively unchanged throughout study. No statistical significant difference between baseline levels and those obtained throughout the 4 months of therapy	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Perkin. Constipation in childhood: a controlled comparison between lactulose and standardized senna. 1977. Current Medical Research and Opinion 4[8], 540-543	Study Type: RCT (crossover) Evidence level: 1- Study aim: to compare effectiveness and side effects between a standardised senna syrup and lactulose in the treatment of childhood constipation	21 children Inclusion criteria: children aged <15 years with a history of constipation treated at home for 3 months or more Exclusion criteria: any cause of constipation requiring surgical or medical correction in addition to laxation	21 children (age and gender not reported) Country: UK	Intervention: Senna syrup 10 to 20 ml daily for 1 week Comparison: Lactulose 10 to 15 ml daily for 1 weeks Each preparation given throughout the appropriate treatment week in a daily dose varied according to the age of the patient 1 intermediate week with not treatment	Duration: 1 week each period with 1 week no treatment in between Assessment point (s): immediately after treatment completed Outcome Measures: -adverse effects	Adverse effects (n patients): a- senna week: 12 (8 colic, 1 diarrhoea, 2 colic+ diarrhoea, 1 colic + distension) b- no treatment week: 4 (3 colic, 1 colic + distension) c- lactulose week 1 (colic) p<0.001 (a vs. c) NS (b vs. c)	Additional information from study: Patients given either treatment according to a code-list of random numbers, placed in a series of sealed envelopes, one of which was opened each time a child entered the trial 1 dropout: 1 patient on senna at the beginning of study failed to attend at the end of 1st week No written or oral indication of any medical preference for other preparation given and patients presented with single bottle of one or other of the preparations according to the coded instruction at start of trial. On 3rd week a bottle of alternative preparation was given Outcomes recorded by parents in written diaries 4-point scale of stool consistency: loose, normal, hard, none Reviewer comments: Very small sample size, no sample size calculation Inadequate method of allocation concealment Patients' baseline characteristics not reported Study probably non blinded Results not controlled for confounders Very short treatment period According to authors the number of stools passed each day was recorded, but is not reported

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Farahmand. A randomised trial of liquid paraffin versus lactulose in the treatment of chronic functional constipation in children. 2007. Acta Medica Iranica 45[3], 183-188Iran, Islamic Republic of.	Study Type: RCT Evidence level: 1- Study aim: to compare the clinical, efficacy and safety of liquid paraffin and lactulose in the treatment of functional childhood constipation	247 children Inclusion criteria: chronic functional constipation Exclusion criteria: organic causes for defecation disorders including Hirschsprung' s' disease, spina bifida occulta, hypothyroidism, cystic fibrosis, neurological abnormalities, intestinal pseudo obstruction	247 children 127 male aged 2 to 12 years old (mean 4.1± 2.1 years) Country: Iran	General: 1 or 2 enemas daily for 2 days to clear any rectal impaction (30 cc/10 kg of paraffin oil) Intervention: Liquid paraffin orally, 1 to 2 ml/kg, twice daily for 8 weeks Comparison: Lactulose orally, 1 to 2 ml/kg, twice daily for 8 weeks For determination of best dose for child, parents asked to increase the volume of each drug by 25% every 3 days as required to yield 1 or 2, firm-loose stools	Duration of treatment: 8 weeks Assessment point (s): 4 and 8 weeks after treatment started Outcome Measures: -optimal dose of drug -side effects	Optimal dose of drug -Final effective dose (mean, ml/kg/day): Liquid paraffin (n=127) 1.72 ± 0.13 Lactulose (n=120) 2.08 ± 0.21 p<0.001 Side effects (during 4 to 12 week) (not clear whether, n or %, but probably %) (estimates taken from bar chart, outcomes not reported in text): Lactulose (n=120) Abdominal pain: 10 Bad palatability: 15 Pain at defecation: 10 Bloating: 10 Diarrhoea: 10 Anal oil leakage: 20 Flatulence: 10 Nausea: 10 Hard stool: 20 Vomiting: 0 Liquid paraffin (n=127) Abdominal pain: 50 Bad palatability: 40 Pain at defecation: 50 Bloating: 20 Diarrhoea: 30	Additional information from study: Diagnosis of chronic functional constipation based on having at least 2 of the following symptoms for the last 3 months: <3 bowel movements/week, faecal soiling >once/week, large amounts of stool every 7 to 30 days and palpable abdominal or faecal mass on physical examination Apart from laxative treatment, parents given instructions to increase their daily fibre intake to an amount of grams equal to their age plus 10. Toilet training after each meal advised to enhance compliance Treatment success defined as 3 or more bowel movements/week and encopresis episodes < 2/week No significant baseline differences between the 2 treatment groups regarding: age, sex, duration of constipation, defection frequency, number of patients with history of encopresis, large amount of stool, faecal impaction in rectum, rectal bleeding, lost to follow-up after 8 weeks, bad palatability of study medication Parents received chart to record side effects Reviewer comments: Method of randomisation and allocation concealment not described Non blinded study

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						Anal oil leakage: 40 Flatulence: 20 Nausea: 5 Hard stool: 6 Vomiting: 0	No sample calculation performed No withdrawals/dropouts reported Results not controlled for confounders <u>Source of funding:</u> not stated, but authors reported “no conflicts of interests”

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Urganci et al. A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation. 2005. Pediatrics International 47[1], 15-19	Study Type: RCT Evidence level: 1- Study aim: to determine and compare efficacy, safety and optimal dose of liquid paraffin and lactulose in children with chronic functional constipation	40 patients Inclusion criteria: children 2 to 12 years old referred for evaluation of constipation with evidence of faecal impaction Exclusion criteria: Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating diseases, neurological abnormalities, previous surgery of colon	40 patients 22 male mean age 3.7 ± 2.7 years Country: Turkey	Intervention: Liquid paraffin Comparison: Lactulose Medication administered orally as a suspension at 1 mL/kg, twice daily for each drug. For determination of best dose for each child, parents asked to increase or decrease the volume of each drug by 25% every 3 days as required, to yield 2 firm-loose stools per day. Maximum dose used throughout the study: 3 mL/kg per day for each drug	Duration of treatment: 8 weeks Assessment point (s): 4 and 8 weeks after initiation of treatment Outcome Measures: -optimal dose of drugs -compliance rate	Optimal dose of drugs (mean ± SD) (mL/kg/day) -data reported in table, assumed that for the whole study period: Liquid paraffin (n=20): 1.88 ± 0.27 Lactulose (n=20): 2.08 ± 0.27 N.S -data reported in text for the last 4 weeks of treatment: Liquid paraffin (n=20): 1.72 ± 0.18 Lactulose (n=20): 1.82 ± 0.57 Compliance rate (%) -first 4 weeks: Liquid paraffin (n=20): 95 Lactulose (n=20): 90 N.S -end of 8 weeks: Liquid paraffin (n=20): 90 Lactulose (n=20): 60	Additional information from study: Diagnosis of constipation based on symptoms of ay least 3 months duration including at least 2 of the following: hard stool, painful defecation, rectal bleeding, encopresis and fewer Open-label randomised study Children also met with a nutritionist, were given instructions to increase daily fibre intake to amount of grams equal to their age plus 10, parent asked to have children sit on the toilet 4 times daily after meals Stool frequency and stool consistency recorded by parents in daily diary forms. Stool consistency scoring: 1, hard; 2, firm; 3, loose No significant baseline differences between 2 groups Patients considered compliant if ≥ 80% of prescribed dose taken correctly. Patients instructed to take both empty and full containers to calculate amount of medication taken Reviewer comments: Randomisation method not described No sample size calculation performed No clear definition of "evidence of faecal impaction" given Apparently no children dropped out the study/were lost to follow-up Study not controlled for potential

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						p=0.02 No patient stopped treatment because of adverse effects (adverse effects not reported). During first 4 weeks, taste aversion in 1 child on liquid paraffin and abdominal distension in 2 patients on lactulose influenced compliance. During last 4 weeks, poor symptom control in 5 patients, side-effects (abdominal distension and cramping) in 3 on lactulose, and watery stools in 2 on liquid paraffin influenced compliance	confounders Source of funding: not stated

Effectiveness of Diet and Lifestyle modifications in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Bongers et al. The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial. 2007. Nutrition Journal 6, 8	Study Type: Double-blind RCT (cross-over) Evidence level: 1+ Study aim: To test the hypothesis that Nutrilon Omneo (new formula, NF) will have a positive effect on stool characteristics in constipated children	38 children Inclusion criteria: Otherwise healthy, term infants with constipation, between 3 to 20 weeks of age, who received at least 2 bottles of milk-based formula per day Exclusion criteria: Hirschsprung's disease, spinal or anal anomalies, previous colonic surgery, metabolic, cerebral and renal abnormalities, children who were treated with laxatives at enrollment	38 children 19 boys median age: 1.7 months Country: The Netherlands	Intervention: Nutrilon Omneo (new formula, NF) -Nutrients per 100 : ml: Energy (kcal) 70 Protein (g) 1.7 *Casein -* *Intact whey protein -* *Whey protein hydrolysate 1.7* Fat (triglycerides) (g) 3.3 *Palmitic acid 0.6 - at the sn-2 position (%) 41.0* *Linoleic acid 0.4* *α-linolenic acid 0.08* Carbohydrates (g) 8.4 *Lactose 2.9* *Maltodextrin 4.0* *Starch 1.5* Fibre (g) 0.8 *Oligosaccharides (90% GOS, 10% lcFOS) 0.8*	Duration of treatment 2 periods of 3 weeks each Assessment point (s): After period 1 and period 2 Follow-up period: No follow-up conducted after treatment finished Outcome Measures: Primary efficacy outcomes: 1) defecation frequency > 3/week 2) normalization of stool consistency 3) no more painful defecation	**Clinical efficacy after period 1** Defecation frequency (mean ± SD) SF (n = 15): 4.9 ± 2.5 NF (n = 20): 5.6 ± 2.8 Difference of means (95% CI): 0.7 (-0.8 to 2.3) N.S Improvement of hard to soft stools (n) SF (n = 15): 50% (5/10) NF (n = 20): 90% (9/10) RR (95% CI): 1.8 (0.9 to 3.5) N.S No painful defecation (n) SF (n = 15): 33% (5/15) NF (n = 20): 35% (7/20) RR (95% CI): 1.0 (0.4–2.7) N.S	Additional information from study: Constipation defined as the presence of at least 1 of the following symptoms: 1) frequency of defecation < 3/week; 2) painful defecation (crying); 3) abdominal or rectal palpable mass Infants randomised by a computer program to either NF or SF in period 1 and crossed-over after 3 weeks to treatment period 2 In order to mimic the taste of Nutrilon Omneo, the whey-based control formula was partly mixed with a formula based on hydrolyzed whey protein (mixture of 75% Nutrilon 1 and 25% Aptamil HA l). Formula cans were labelled with codes to mask identity of the study feedings. Neither the parents nor the physicians were aware of the composition of the formula until the entire study was completed Prior to start of the study, sample size, based on a cross-over design, was calculated to allow detection of a 30% difference in improvement between NF and SF. Under the assumption of a significance level of 0.05 with a power of 0.80, and 2-sided hypothesis testing, a minimal sample size of 34 with 17 children in each group was determined Only 24 children (63%) completed the

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				Minerals and trace elements (mg) *Calcium 53* *Phosphorus 29* *Sodium 23* *Potassium 82* *Chloride 44* *Iron 0.5* *Zinc 0.5* <u>Comparison</u>: Standard formula (SF, mixture of 75% Nutrilon I and 25% Aptamil HA I) Energy (kcal) 67 Protein (g) 1.5 *Casein 0.5* *Intact whey protein 0.6* *Whey protein hydrolysate 0.4* Fat (triglycerides) (g) 3.5 3.3 *Palmitic acid 0.6* *- at the sn-2 position (%) 11.5* *Linoleic acid 0.4* *α-linolenic acid 0.07* Carbohydrates (g)	Secondary outcome: -safety	**Clinical efficacy after cross-over (period 1 and 2)** <u>Defecation frequency (mean)</u> SF (n =12): 5.9/week NF (n =12): 5.5/week Difference of means (95% CI): - 0.5 (-1.6 to 0.6) N.S <u>Frequency of soft stools:</u> 17% (n = 4) of infants had soft stools when receiving NF but hard stools with SF, compared to no infant with soft stools when receiving SF and no infant with hard stools with NF (p = 0.046) <u>Painful defecation</u> not significantly different between the periods on NF and SF <u>Safety</u> Throughout the study there were no serious adverse effects in either group. Both	cross-over study. In period 1, 3 SF patients dropped out; 2 patients stopped because of severe constipation; 1 patient switched to hypoallergenic feeding, because of suspected cow's milk protein allergy. Parents of 1 patient decided that they did not want to cross-over because she was free of symptoms and they started openly with NF instead. 3 patients dropped out after switching to NF; 2 patients stopped after less than 1 week because of recurrence of constipation symptoms. 1 patient was lost to follow-up. 7 patients dropped out after switching to SF; 6 patients stopped after 1 week because of recurrence of constipation symptoms. 1 patient was lost to follow-up Data analysis based on the group of 35 patients that completed period 1 and a subgroup analysis of 24 patients who completed the cross-over No significant differences in baseline characteristics between 2 groups During both periods parents asked to daily record in a diary details on formula intake, formula tolerance (vomiting, flatulence, colic, rash), passage of stools and stool consistency compared to 4 validated photographs of runny, mushy soft, formed soft and hard stools <u>Reviewer comments:</u> Allocation concealment method not

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				7.3 *Lactose 7.2* *Maltodextrin - Starch –* Fibre (g) - *Oligosaccharides (90% GOS, 10% lcFOS) –* Minerals and trace elements (mg) *Calcium 53* *Phosphorus 29* *Sodium 22* *Potassium 69* *Chloride 42* *Iron 0.5* Zinc 0.5 Feeding patterns not described		formulas were well tolerated	described Study not controlled for potential confounders <u>Source of funding:</u> study supported by a grant of Nutricia Nederland BV, Zoetermeer, The Netherlands

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Savino et al. "Minor" feeding problems during the first months of life: Effect of a partially hydrolysed milk formula containing fructo- and galacto-oligosaccharides. 2003. Acta Paediatrica Supplement 91[441], 86-90Norway.	Study Type: Prospective case series Evidence level: 3 Study aim: To investigate whether a new infant formula commercially available in Italy is useful as a dietary option in infants with minor feeding problems	604 children Inclusion criteria: Formula-fed healthy term infants up to 3 months of age seen by paediatrician because of colic and/or constipation and/or regurgitation. Normal birth weight (>2500 g), normal weight gain (≥ 150g/week) and normal physical examination Exclusion criteria: Neonatal problems, use of any kind of medication the week before the beginning of the study or during the study period	604 children (232 with constipation) age at entry (months, total population): 1.35 ± 0.77 gender not reported Country: Italy	Intervention: New formula (NF) Composition per 100 ml Energy: 70 kcal Protein equivalent (g): 1.7 Casein: whey: 100% whey hydrolysate Carbohydrate (g): 8.4 *Lactose:2.9* *Maltodextrine: 4.0* *Starch: 1.5* Prebiotic oligosaccharides (g): 0.8 Fat (g): 3.3 *Palmitic acid:0.60* Minerals (mg) *Sodium: 23* *Potassium: 66* *Chloride: 50* *Calcium: 53* *Phosphorus: 31* *Iron: 0.5* *Zinc: 0.5* Feeding volume based on a feeding *ad libitum*	Duration of treatment 14 days Assessment point (s): On days 1, 7 and 14 Follow-up period: No follow-up conducted after treatment finished Outcome Measures: -stool frequency -parents' evaluation of formula	Stool frequency 232 infants with constipation -increase in number of stools per day during study period: 147 infants (63.4%) -average increase: 0.42 (CI 95%: 0.55 to 0.27; p<0.005) -average increase between day 1 and day 7: 0.41 (CI 95%: 0.51 to 0.23; p<0.05) -average increase between day 7 and day 14: 0.04 (NS) -no improvement of symptoms: 85 infants (26.6%) Mean parent evaluation of formula 7.9 ± 1.8 550 parents (91%) gave a positive judgement (score 6 to 10)	Additional information from study: Constipation defined as a stool frequency of less than 1 stool a day Parents given a questionnaire in order to monitor frequency of symptoms, feeding volume and side effects. Number of stools were recorded daily A total of 932 infants enrolled: 604 completed the study protocol. A total of 358 infants excluded from study: 154 completed only the first step and did not return for the visit on day 14, 131 infants excluded because of incomplete data. 73 infants required medication during the 1rst week of study and were therefore excluded Reviewer comments: No description of the scoring system used to evaluate parent's satisfaction was provided Source of funding: Not stated

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				procedure. Feeding frequency decided by the parents and not influenced by the study protocol			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Pina et al. Prevalence and dietetic management of mild gastrointestinal disorders in milk-fed infants. 2008. World Journal of Gastroenterology 14[2], 248-254China.	Study Type: Prospective case series Evidence level: 3 Study aim: To assess the prevalence of mild gastrointestinal disorders (MGDs) in milk-fed infants in paediatric practice and to evaluate the effectiveness and satisfaction with dietetic treatment: specifically elaborated formulas belonging to the Novalac line of products	3487 children (total population) Inclusion criteria: Infants up to 4 months of age fed with artificial milk formulas, presence of MGDs, possibility of feeding infants with some product of the Novalac line of formulas, continuation of these formula on an exclusive basis for at least 30days with no incorporation of other foods to the diet Exclusion criteria: Not clearly stated	604 children (with constipation) 52.2% boys (of the total population) age at consultation: 1 week to 17 weeks (total population) Country: Spain	Intervention: Novalac Anti-Constipation: formula with adapted concentration of magnesium and lactose No other details regarding feeding volume/frequency were provided Comparison: N.A	Duration of treatment 30 days Assessment point (s): Immediately after treatment was completed Follow-up period: No follow-up made after treatment finished Outcome Measures: -type of stools -presence of pain or discomfort -external help needed for defecation -satisfaction of parents/tutors -adverse events	91.6% of cases of constipation resolved within 7 days Number of daily stools (mean ± SD) Baseline: 0.6 ± 0.7 At 30 days: 1.7 ± 0.8 Type of stools (% children) -Normal: Baseline: 33.40 At 30 days: 95.60 -Hard Baseline: 66.60 At 30 days: 4.40 Presence of pain or discomfort (% children) -Yes: Baseline: 90.00 At 30 days: 10.40 -No: Baseline: 10.00 At 30 days: 89.60 External help needed for defecation -Yes: Baseline: 76.10 At 30 days: 8.80	Additional information from study: Study on effectiveness included 2069 infants with MGDs. Effectiveness was evaluated among 1441 infants who completed follow-up. Premature study termination due to adverse events in 2.7% cases, parent decision in 6.9%, loss to follow-up in 1.64%, protocol violations in 2.46% and non-specified reasons in 16.62% A questionnaire addressing the different symptoms and their intensity was designed for each disorder Satisfaction of parents/tutors with the formulas assessed on final visit by means of a Likert-type scale with 5 possible answers: from very satisfied to very dissatisfied Reviewer comments: No definition of constipation given Not completely clear how outcomes were measured and who measured them No definition of “resolved case” given Source of funding: Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						-No: Baseline: 23.90 At 30 days: 91.20 -satisfaction of parents/tutors: 90.0% of parents satisfied with treatment <u>Adverse events (for all formulas, no subgroup analysis):</u> Reported in 3.9% infants of total population. Most frequent affected digestive tract (1.4%), including diarrhoea and constipation, and respiratory apparatus (0.7%) (E.g. bronchiolitis and bronchitis). 10 infants (0.5%) required hospital admission for septicaemia (n=1), dehydration (n=2), vomiting (n=1), hernia (n=1) and bronchitis or bronchiolitis (n=2)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Chao et al. Therapeutic effect of Novalac-IT in infants with constipation. 2007. Nutrition 23[6], 469-473	Study Type: Open label RCT Evidence level: 1- Study aim: To evaluate a commercialised formula, Novalac-IT (Intestinal Transit, Paris, France) against a "strengthened regular formula", the traditional approach in infants with digestive problems in Taiwan	93 children Inclusion criteria: Children aged 2 to 6 months referred to paediatric gastroenterology clinic at medical centre with constipation ≥ 2 weeks, fed exclusively with formula. Participation in trial proposed before a more complete diagnostic workup for cow's milk protein allergy, Hirschsprung's disease and others Exclusion criteria: unclear	93 children 47 boys mean age 3.8 ± 1.7 months Country: Taiwan	Intervention: Magnesium-enriched infant formula, Novalac-IT Composition per 100 mL: Energy (cal/100 mL): 70.7 Protein (g): 1.70 *Whey/casein: 60/40* Fat (g): 3.54 Carbohydrates (g): 8.06 *100 % Lactose* Major minerals (mg) *Sodium 17.46* *Potassium 61.58* *Chloride 43.40* *Calcium 60.87* *Phosphate 31.46* *Magnesium 9.12* Osmolality: 300 Comparison: 20% strengthened Novalac regular infant formula	Duration of treatment 2 months Assessment point (s): At 2 weeks, 1 month and 2 months Follow-up period: No follow-up conducted after treatment finished Outcome Measures: Remission / improvement / failure according to severity scoring system based on stool consistency, frequency and volume of stools and difficulties in defecation (1 to 3 mild constipation; 4 to 6 moderate; 7 or 8 severe) -Remission:	Improved (number and % of children) -At 2 weeks: Novalac-IT (n=47): 31 (66) Strengthened formula (n=46): 23 (50) N.S -At 1 month: Novalac-IT (n=47): 39 (83) Strengthened formula (n=46): 23 (50) P=0.002 -At 2 months: Novalac-IT (n=47): 42 (89) Strengthened formula (n=46): 25 (54) P<0.001 Good response (number and % of children) -At 2 weeks: Novalac-IT (n=47): 17 (36) Strengthened formula (n=46): 13 (28) -At 1 month: Novalac-IT (n=47):	Additional information from study: Study non-blinded, according to authors this was not possible because all infants were included in 1 centre Randomisation performed applying an envelope drawing system Assigned nurse educated the family to prepare the 20% strengthened formula (20% extra formula) (regular concentration of the formula is 13%) No significant differences in baseline characteristics (clinical or demographic) between the 2 groups Intake of formula and clinical parameters regarding constipation and weight and all relevant information recorded by family daily in a diary during the entire intervention period Severity scoring system developed and evaluated in pilot study: Hard stool: 0, no hard stool; 1, hard and long form, 2; Difficulties with defecation: 0, no difficulties; 1, irritability; 2, crying Frequency of defecation: 0, >3 times/week; 1, 1 to 3 times/week; 2, <1 time/week Stool weight (g//kg/week): 1, >35; 2, 20 to 35; 3, <20 Reviewer comments: No sample size calculation performed

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				Composition per 100 mL Energy (cal/100 mL): 78 Protein (g): 1.89 *Whey/casein: 50/50* Fat (g): 3.96 Carbohydrates (g): 8.69 *70% Lactose, 30% Maltodextrin* Major minerals (mg) *Sodium 21.24* *Potassium 70.20* *Chloride 46.80* *Calcium 70.20* *Phosphate 42.12* *Magnesium 7.02* Osmolality: 300	asymptomatic -Good response: decrease in severity of ≥ 2 -Fair response: decrease in severity of 1 to 3 -Failure: if score did not change or increased	22 (47) Strengthened formula (n=46): 11 (24) <u>Fair response (number and % of children)</u> -At 2 weeks: Novalac-IT (n=47): 14 (30) Strengthened formula (n=46): 10 (22) -At 1 month: Novalac-IT (n=47): 17 (36) Strengthened formula (n=46): 23 (50) <u>Not improved (number and % of children)</u> -At 2 weeks: Novalac-IT (n=47): 16 (34) Strengthened formula (n=46): 23 (50) -At 1 month: Novalac-IT (n=47): 8 (17) Strengthened formula (n=46): 23 (50)	Irrelevant reason given for non-blinding the study Unclear how both formulas were administered No dropouts/lost to follow-up reported Study not controlled for potential confounders <u>Source of funding:</u> Not stated Intestinal Transit provided free samples of Novalac-IT formula. According to authors there was no other grant from the company, which was neither involved in the design of the study

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						<u>Symptoms free (number and % of children)</u> -At 2 weeks: Novalac-IT (n=47): 18 (38) Strengthened formula (n=46): 12 (26) N.S -At 1 month: Novalac-IT (n=47): 28 (60) Strengthened formula (n=46): 16 (35) P=0.029 -At 2 months: Novalac-IT (n=47): 35 (75) Strengthened formula (n=46): 18 (39) P<0.001	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Savino et al. Advances in the management of digestive problems during the first months of life. 2005. Acta Paediatrica 94[SUPP 449], 120-124Norway.	Study Type: Open label RCT Evidence level: 1- Study aim: To evaluate the efficacy on digestive problems of a formula based on palmitic acid predominantly esterified at the β-position, oligosaccharides (GOS and FOS) with a prebiotic activity, partially hydrolysed protein, low lactose content and higher density	123 children Inclusion criteria: Formula-fed healthy term infants up to 4 months of age with constipation Exclusion criteria: Neonatal problems and/or any assumption of any kind of medication the week before the beginning of the study and during the study period	95 children 50 boys age at study entry (months) -intervention group: 1.55 ± 0.88 -control group: 1.28 ± 0.66 Country: Italy	Intervention: New formula (NF) Composition per 100 ml (Omneo / Conformil): Energy: 70 kcal Protein equivalent (g): 1.7 Casein: whey: 100% whey hydrolysate Carbohydrate (g): 8.4 *Lactose:2.9* *Maltodextrine: 4.0* *Starch: 1.5* Prebiotic oligosaccharides (g): 0.8 Fat (g): 3.3 *Palmitic acid:0.60* Minerals (mg) *Sodium:23* *Potassium: 66* *Chloride: 50* *Calcium: 53* *Phosphorus: 31* *Iron: 0.5* *Zinc: 0.5* Comparison: Standard formula	Duration of treatment 14 days Assessment point (s): On days 1, 7 and 14 Follow-up period: No follow-up conducted after treatment finished Outcome Measures: -stool characteristics : frequency and consistency	Stool frequency (number/day) (mean ± SD) -at study entry NF group (n=55): 0.53 ± 0.5 SF group (40): 0.60 ± 0.5 N.S -on day 7 NF group (n=55): 1.79 ± 0.96 SF group (40): 1.31 ± 0.89 difference: 0.48 (CI 95%: 0.09; 0.87) p=0.02 -on day 14 NF group (n=55): 2.04 ± 1.04 SF group (40): 1.64 ± 0.99 difference: 0.40 (CI 95%: -0.03; 0.83) p=0.07 Mean difference in stool frequency between the 2 groups	Additional information from study: Constipation defined as a stool frequency of less than 1 stool a day Parents given a structured questionnaire in order to monitor frequency of symptoms, feeding volume and side effects No significant differences in baseline characteristics between the 2 groups When an infant eligible to study came to the doctor, child was randomly assigned to the study or the control group, the next infant with the same symptoms was matched to the previous infant and assigned to the other group 28 children excluded after randomisation because at entry they had more than 1 evacuation Reviewer comments: Sample size calculation not performed Inadequate randomisation Allocation concealment not described Study not reported as blinded Stool consistency post- treatment not reported No dropouts/lost to follow-up children reported

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				(SF) (composition not reported in paper) Feeding volume based on a feeding *ad libitum* procedure. Feeding frequency decided by the parents and not influenced by the study protocol		<u>adjusted for gender, age at entry, maternal instruction, parity, birth weight , number of feedings/day and stool frequency at entry</u> -Days 0 to 7: 0.60 (CI 95%: 0.19; 1.01) p=0.004 -Days 0 to 14: 0.53 (CI 95%: 0.11; 0.90) p=0.015	<u>Source of funding:</u> not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Kokke et al. A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial. 2008. Journal of Pediatric Gastroenterology and Nutrition 47[5], 592-597	Study Type: Double-blind RCT Evidence level: 1+ Study aim: To assess the clinical efficacy and safety of a dietary fibre mixture and compare it with lactulose in the treatment of childhood constipation	135 children Inclusion criteria: Constipated children referred to hospital outpatient clinic for constipation who fulfilled at least 2 of 4 criteria for constipation: stool frequency <3 times/week, faecal incontinence ≥ 2 times/week, periodic passage of large amounts of stool at least once very 7 to 30 days, or a palpable abdominal or rectal mass Exclusion criteria: Organic causes of defecation	97 children fibre mix group (n=42): 20 boys median age: 5.5 years (1 to 12 years) lactulose group (n=55): 23 boys median age 5.0 years (1 to 12 years) Country: The Netherlands	Intervention: Yogurt drink with mixed dietary fibre (10g/125mL) -Fibre mixture (per 100mL): 3.0 g transgalacto-oligosacharides 3.0 g inulin 1.6 g soy fibre 0.33g resistant starch 3 Comparison: Yogurt drink containing lactulose(10g/125 mL) (Duphalac Lactulose) Both products taken at breakfast and in case of ≥ 2 bottles also at lunch Amount of fibre/fluid intake daily depended on patient's body weight: *Intervention period:*	Duration of treatment 8-week intervention period 4-week weaning period Assessment point (s): At 3, 8 and 12 weeks Follow-up period: No follow-up conducted after treatment finished Outcome Measures: 1. primary outcome: -defecation frequency/week 2. secondary outcomes: -faecal incontinence each day -stool	Defecation frequency/week(mean) -At 8 weeks: Fibre (n=42): 7 Lactulose (n=55): 6 N.S Number of patients with ≥ 1 faecal incontinence episodes/week -At 8 weeks: Fibre (n=42): 9 Lactulose (n=55): 5 N.S Stool consistency (mean) -At 3 weeks: Fibre (n=42): 3.5 Lactulose (n=55): 4.5 P<0.01 -At 8 weeks: Fibre (n=42): 3.6 Lactulose (n=55): 4.0 P=0.01 Number of patients using step-up medication -At 3 weeks: Fibre (n=42): 13	Additional information from study: Randomisation performed by use of sequential numbers allocated to patients at study entry and coordinated by the logistic manager of Numico Research using a block design Bottles with yogurt prepared and packed by Numico Research and transported to hospital. Treatment products could not be distinguished from each other with respect to colour, taste or consistency Sample size based on primary outcome variable, defecation frequency. It was calculated that a random allocation of 150 children would allow for the detection of a mean difference in defecation of 1.0/week between the 2 groups No significant differences found in baseline characteristics between the 2 groups with a power of 80% and alfa=0.05 Defecation noted on a daily basis during treatment period. Faecal incontinence each day assessed "yes" or "no", stool consistency according to Bristol Stool Form Scale. Data recorded daily in bowel diary by parents or patients. Adverse effects defined as any adverse change from baseline (pre-treatment) condition, which occurred during the course of the study after treatment started, whether it was considered to be

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		disorders including Hirschsprung's disease, spina bifida, hypothyroidism or other metabolic/renal abnormalities, mental retardation, use of drugs influencing gastrointestinal function other than laxatives, use of lactulose, other laxatives, prebiotics, probiotics or antibiotics in the previous 4 weeks before the first visit		<15 kg: 1 bottle (125 mL, 10g fibres) 15 to 20kg: 2 bottles (250 mL, 20g) >20 kg: 3 bottles (375 mL, 30g) *Weaning period:* <15 kg: 0.5 bottle/day (week 9 & 10); 0.5 every other day (week 11 &12) 15 to 20kg: 1 bottle/day (week 9 & 10); 1 every other day (week 11 &12) >20 kg: 2 bottles/day (week 9 & 10); 1 bottle/day (week 11 &12) If persistent diarrhoea reported, original dose reduced by 50% If clinical parameters	consistency -use of step-up medication -adverse effects	Lactulose (n=55): 7 P=0.028 -At 8 weeks: Fibre (n=42): 20 Lactulose (n=55): 21 N.S -At 12 weeks: Fibre (n=42): 21 Lactulose (n=55): 26 N.S <u>Adverse effects</u> No serious or significant side effects recorded Fibre (n=42): 1 dose-related persistent diarrhoea Lactulose (n=55): 2 dose-related persistent diarrhoea	related to treatment 33 patients dropped-out during study period: 22 in fibre group after 1 to 56 days (median 7) and 11 in lactulose group after 1 to 51 days (median 8) (p=0.020). Those patients refused to drink the yogurt. 3 patients lost to follow-up: 1 fibre, 2 lactulose. 2 exclusions after randomisation in lactulose group: 1 coeliac disease, 1 spina bifida occulta <u>Reviewer comments:</u> Method of allocation concealment not described Study not controlled for potential confounders Unclear how adverse effects were recorded. ITT analysis not performed <u>Source of funding:</u> The Scientific Research Foundation project SW) 2001. One author received financial support throught project no.9.001, which is a subproject of Business aimed Technological Cooperation project 00176. 2 authors were researchers and employees of Danone Research BV (formerly Numico Research BV)

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				compared to baseline did not improve 3 weeks after start of intervention period, step-up medication (Macrogol 3350) given per protocol			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Loening-Baucke et al. Fiber (glucomannan) is beneficial in the treatment of childhood constipation. 2004. Pediatrics 113[3 Pt 1], e259-e264	Study Type: Double-blind RCT (cross-over) Evidence level: 1+ Study aim: to evaluate whether fiber supplementation with glucomannan is beneficial in the treatment of children with functional constipation	31 children Inclusion criteria: Otherwise healthy children older than 4 years who had chronic functional constipation for ≥6 months with or without encopresis Exclusion criteria: Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating diseases, neurological abnormalities, previous surgery of the colon or anus	31 children 16 boys age: 4.5 to 11.7 years (mean: 7.1 ± 2.0 years) Countries: USA & Italy	General Disimpaction with 1 or 2 phosphate enemas if rectal impaction felt during rectal examination (58% of patients continued with their preevaluation laxative during whole study period) Intervention: Glucomannan B: capsule containing glucomannan, a polysaccharide of d-glucose and d-mannose, equal to 450 mg of alimentary fibre. Comparison: Glucomannan A: capsule containing maltodextrins as placebo. Group 1: placebo first and then glucomannan Group 2:	Duration of treatment 2 treatment periods of 4 weeks each Assessment point (s): At 4 and 8 weeks Follow-up period: No follow-up conducted after treatment finished Outcome Measures: -efficacy: changes in frequency of bowel movements (BMs) soiling frequency -successful treatment -parents' global assessment -overall	Children with <3 BMs/week (%) Placebo (n= 31): 52% Fibre (n= 31): 19% P<0.05 Stool consistency Initial (n= 31): 0.3 ± 0.9 Placebo (n= 31): 1.2 ± 0.9 Fibre (n= 31): 1.5 ±0.9 P<0.05 as compared to initial data Children with encopresis Initial (n= 31): 58% Placebo (n= 31): 48% Fibre (n= 31): 42% Frequency of soiling episodes/wk (n=18) Initial (n=18): 9.9 ± 12.3 Placebo (n= 18): 4.2 ± 4.8 Fibre (n= 18): 4.0 ± 6.3 P<0.05 as compared to initial data Successful treatment Placebo (n= 31): 13% Fibre (n= 31): 45% P<0.05 as compared to placebo treatment	Additional information from study: Constipation defined as a delay or difficulty in defecation, present for >2 weeks, and sufficient to cause significant distress to child Encopresis defined as the involuntary loss of formed, semiformed, or liquid stool into the child's underwear in the presence of functional constipation after the child has reached the age of 4 years It had been previously calculated that at α=0.05; 26 subjects would allow a power of approximately 0.95 to detect a difference of 0.7 versus 0.2 in achieving normal bowel patterns in the crossover design Patients randomized by envelope into 1 of 2 treatment arms. Blinding done by having the medication labelled glucomannan A and glucomannan B with the code kept by the company until study was completed and analyzed. Glucomannan A was a capsule containing maltodextrins as placebo. Glucomannan B was a capsule containing glucomannan, a polysaccharide of d-glucose and d-mannose, =450 mg of alimentary fibre Patients and their parents kept diary sheets during the 8 weeks of study. They recorded daily each BM, soiling episode, abdominal pain episode, and

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				glucomannan first and then placebo -Placebo and glucomannan doses: 100 mg/kg body weight daily (maximal 5 g/day), rounded to the nearest 500 mg, because each capsule contained 500 mg. Each capsule either opened and sprinkled on food given with 50 mL of fluid per capsule; given as a solution, whereby the content of each 500-mg capsule was mixed with 50 mL of fluid of the child's choice; or swallowed as a capsule with 50 mL of fluid for each capsule. In addition, parents instructed to have the child sit on the toilet 4 times daily after meals and to keep	tolerance and palatability -safety: side effects	<u>Improved (parent rating)</u> Placebo (n= 31): 13% Fibre (n= 31): 68% P<0.05 as compared to placebo treatment <u>Outcomes controlled for confounders</u> -successful treatment (physician rating) and improvement (parent rating)independent of low or acceptable fibre intake (P>0.6) - more children with encopresis in the laxative group (78% vs. 31%; P<0 .02), and significantly more children in the laxative group were treated successfully with fibre than with placebo (P <0 .01) - Children with constipation only were significantly more likely to be treated successfully with fibre (69%) than those with constipation and encopresis (28%;	medication used and reported at the end of each treatment period the associated subjective symptoms such as stool consistency, new occurrence of abdominal pain, bloating, abdominal distension, excessive gas, or diarrhoea. Stool consistency was assessed rating the stool consistency as hard like rocks, pellets= 0, firm = 1, soft like banana = 2, loose like milkshake = 3, and watery = 4 Successful treatment rated by physician and defined as ≥ 3 bowel movements per week and ≤ 1 soiling episode in the last 3 weeks with no abdominal pain. Parents' global assessments: whether they believed that the child was better during the first or second treatment period No significant differences in baseline characteristics between the 2 groups 46 children originally recruited. 13 children did not show up for the 4-week follow-up: 7 children randomized to placebo first and 6 children randomized to fibre first. 2 constipated girls completed the first 4 weeks of the study only: 1 received placebo and 1 received fibre; both recovered from chronic constipation and abdominal pain during the first 4 weeks of treatment and did not return for the 8-week visit. Data from the 13 children who entered the study and were randomized but did not come for follow-up and the 2 children who did not complete the study were excluded

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				a stool diary. No enemas given during each treatment period, unless rectal disimpaction felt during rectal examination at assessment visits		P<0.04) <u>Safety</u> No significant side effects such as new onset of abdominal pain, bloating, abdominal distension, excessive gas, diarrhoea, or anaphylactic symptoms reported	from the analysis. Initial data of these 15 children not significantly different from the data of the 31 children who completed the study, except soiling frequency per week was significantly less (4.0 ± 1.4; P<0 .001). Data analysis includes 31 children with functional constipation with or without encopresis <u>Reviewer comments:</u> No definition of soiling given. Unclear how different this would be from the authors' definition of encopresis High dropout rate: 28%. ITT analysis not performed <u>Source of funding:</u> DicoFarm (Rome, Italy) provided research support and the medications for the study

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Castillejo 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. 2006. Pediatrics 118[3], e641-e648	Study Type: Double-blind RCT (pilot study) Evidence level: 1+ Study aim: to evaluate the effect of a palatable cocoa husk supplement that is rich in fibre on intestinal transit time and other indices of constipation in children with idiopathic chronic constipation	56 children Inclusion criteria: Children aged 3 to 10 years referred to pediatric gastroenterology outpatients' clinic between January 2004 and April 2005 with chronic constipation Exclusion criteria: presence of fecal impaction that required enema in the 7 days before the start of the study, treatment with dietary fibre, bulk-forming agents, or laxatives in the 2 weeks before the start of the study,	56 children 22 boys Mean age 6.3 ± 2.2 years Country: Spain	Intervention: cocoa husk supplement rich in dietary fibre + standardized toilet training procedures 1 sachet (5.2 g): 4 g cocoa husk + 1 g betafructosans (53.2 g of fibre (39.6 g of total fibre and 13.6 g of betafructosans) per 100 g of product. Insoluble fibre 37.2% and soluble fibre 2.4% of total fibre Cellulose and uronic acids the main type of insoluble fibre and soluble fibre, respectively) Comparison: placebo + standardized toilet training procedures 1 sachet (5.2 g): glucose, cocoa flavouring, and	Duration of treatment 4 weeks Assessment point (s): Immediately after treatment finished Follow-up period: No follow-up made after treatment finished Outcome Measures: -number of bowel movements per week -stool consistency -pain with defecation -safety	No. of bowel movements per week (mean ± SD) Difference (95% CI): 0.67 (-0.76 to 2.10) p=0.780 -Cocoa husk group Basal (*n*=24): 3.86 ±2.05 Final (*n*=24): 6.16 ±3.35 Difference (95% CI): 2.40±3.16 -Placebo group Basal (*n*=24): 3.18± 1.93 Final (*n*=24): 5.08 ±2.10 Difference (95% CI): 1.73 ±1.73 Hard stool consistency (% children) -Cocoa husk group Basal (*n*=24): 95.8 Final (*n*=24): 41.7 -Placebo group Basal (*n*=24): 95.8 Final (*n*=24): 75.0 P=0.017 Subjective improvement in stool	Additional information from study: Chronic functional constipation defined in accordance with Rome II diagnostic criteria, by the presence, for at least 12 (not necessarily consecutive) weeks in the preceding 12 months, of at least 2 of the following symptoms: straining in >25% of defecations; lumpy or hard stools in >25% of defecations; a sensation of incomplete evacuation in >25% of defecations; a sensation of anorectal obstruction/blockage in >25% of defecations; a need for manual maneuvres to facilitate >25% of defecations (e.g., digital evacuation, support of the pelvic floor); and <3 defecations per week Treatment was blinded to both patients and investigator until the study was completed and analyzed. Patients randomly assigned to treatment 1 or 2 in a ratio of 1:1. A randomization list was designed by the manufacturers of the supplement and the placebo (Madaus SA) using a computer random-number generator in 20 blocks of 4 patients each. The details of the randomization codes were kept in sealed envelopes away from the investigators. Only in cases of the utmost necessity (eg, serious adverse events) did the coordinator of the study allow the investigator to know the treatment assigned to the patient Because of lack of previous studies and

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		constipation attributable to organic or anatomic causes (Hirschsprung's disease, hypothyroidism, mental deficiency, psychiatric illnesses, chronic debilitating diseases, neurologic abnormalities, or previous surgery of the colon or anus), renal insufficiency, hypocalcemia, hyperkalemia, or any other metabolic diseases at the start of the study; long-term use of drugs that affect gastrointestinal motility (eg, imipramine, iron or calcium		excipients -doses for both products: Children aged 3 to 6 years: 1 sachet before lunch and 1 sachet before dinner Children aged 7 to 10 years: 2 sachets before lunch and dinner Parents instructed to dissolve content of the sachets in 200 mL of whole milk before ingestion		<u>consistency (n children)</u> P=0.039 Cocoa husk group (*n*=24) Improvement : 14 No Improvement: 10 Placebo group (*n*=24) Improvement : 6 No Improvement: 18 <u>Subjective improvement in pain</u> P=0.109 Cocoa husk group (*n*=24) Improvement : 16 No Improvement: 8 Placebo group (*n=24*) Improvement : 11 No Improvement: 13 <u>Safety</u> No significant adverse effects, such as a new onset of abdominal pain, bloating, abdominal distension, excessive gas, diarrhoea, or anaphylactic symptoms, reported during the 4-week period with either treatment No significant	likelihood of methodological difficulties (in the evaluation of the main parameters) in carrying out a study on this kind of population, authors designed a pilot study with a minimum sample from the statistical point of view Fibre supplement and placebo administered as a soluble powder in sachets of identical weight (5.2 g) and presentation At baseline and after 4 weeks of treatment, investigators evaluated bowel movement habits and stool consistency using a diary completed by patients' parents; and received a subjective evaluation from the parents regarding the efficacy of the treatment. Adherence to the intervention evaluated by the same investigator using a visual analogical scale (in the case of standardized toilet training procedures) and counting the empty sachets that were returned No significant differences in baseline characteristics between the 2 groups 8 children withdrew from study before its completion (5 children discontinued study because of the difficulty of the protocol, and 3 were excluded because of the presence of positive antigliadin and antiendomysium antibodies). Data refer only to 48 participants who completed the study

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		supplements, anticonvulsants), inability to adhere to the study's medications or procedures				changes between groups in relation to hemoglobin concentrations; hematocrit; serum ferritin; or plasma levels of zinc, iron, or calcium	Reviewer comments: Study not controlled for potential confounders ITT analysis not performed Source of funding: Study supported by Madaus, SA, and by grants from the Instituto de Salud Carlos III, Red de Centros RCMN (C03/08), and Red de Grupos (G03/140), Madrid, Spain. One author had received consulting or lecture fees from Madaus Laboratories and another one belonged to Madaus Laboratory

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Staiano et al. Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. 2000. Journal of Pediatrics 136[1], 41-45	Study Type: Case series Evidence level: 3 Study aim: To evaluate the efficacy of glucomannan as a treatment for chronic constipation in children with severe neurologic damage	20 children Inclusion criteria: Severe neurologic damage, constipation of at least 12 months. In most patients evacuation not possible without enema. All patients had severe /profound mental retardation (IQ level < 35) and exhibited severe clinical manifestations of brain damage etiologically related to prenatal or perinatal hypoxia: 12 patients had classical tetraplegia, 6 severe spastic diplegia, 2 persistent	20 children 14 boys mean age 5.7 ± 4.2 years Country: Italy	General: Disimpaction with enemas for 2 or 3 days (not clear what medication used) Intervention: Glucomannan 100mg/kg 2 times a day Comparison: Placebo 100mg/kg 2 times a day Both glucomannan and placebo consisted of a 500-mg capsule. Oral dose given by mixing the contents of one capsule with 100 mL of water	Duration of treatment 12 weeks Assessment point (s): At 4, 8 and 12 weeks Follow-up period: No follow-up conducted after treatment finished Outcome Measures: Stool frequency Stool consistency Presence of painful defecation Laxative use	Number of stools per week (mean ± SD) -at 4 weeks Glucomannan (n=9): 4.0 ± 1.3 Placebo (n=10): 1.1 ± 0.2 -at 8 weeks Glucomannan (n=9): 3.3 ± 1.0 Placebo (n=10): 2.5 ± 1.2 -at 12 weeks Glucomannan (n=9): 3.8 ± 0.9 Placebo (n=10): 2.0 ± 0.6 p<0.01 for glucomannan group at all periods as compared to baseline Stool consistency score (mean ± SD) -at 4 weeks Glucomannan (n=9): 2.4 ± 0.5 Placebo (n=10): 1.3 ± 0.6 -at 8 weeks Glucomannan (n=9): 2.8 ± 0.7 Placebo (n=10): 1.3 ± 0.5	Additional information from study: Children fed by mouth with semi-liquid diet including formula and pureed food No significant differences in baseline characteristics between 2 groups 1 patient receiving glucomannan withdrawn from study after 3 weeks of treatment because of concomitant increase in seizure frequency associated with blood level of Phenobarbital below the therapeutic range During study period a daily diary card was completed for recording symptoms, dietary fibre intake, number of bowel movements per week, stool consistency, presence of painful defecation and use of laxative (lactulose 1g/kg/dose) or glycerol suppository. Arbitrary scoring system used for assessment of symptoms: -stool consistency: 1, pellets; 2, hard; 3, soft; 4, loose; 5, liquid -presence of painful defecation: 1, often; 2, occasionally; 3, none Reviewer comments No definition of constipation given Very small sample size. Sample size calculation not performed Randomisation and allocation concealment methods not described

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		hypotonia <u>Exclusion criteria</u>: unclear				-at 12 weeks Glucomannan (n=9): 2.7 ± 0.7 Placebo (n=10): 1.4 ± 0.7 p<0.01 for glucomannan group at all periods as compared to baseline <u>Painful defecation score(mean ± SD)</u> -at 4 weeks Glucomannan (n=9): 1.4 ± 1.1 (N.S as compared to baseline) Placebo (n=10): 0.9 ± 0.8 -at 8 weeks Glucomannan (n=9): 1.7 ± 1.4 (N.S as compared to baseline) Placebo (n=10): 1.2 ± 0.8 -at 12 weeks Glucomannan (n=9): 1.9 ± 1.2 Placebo (n=10): 1.2 ± 0.9 p<0.01 for glucomannan group as compared to	Blinding procedures poorly described Unclear who measured study outcomes Study not controlled for potential confounders <u>Source of funding:</u> One of the authors supported by a grant from Dicofarm, Italy. No other details provided

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						baseline <u>Laxative use (number per week, (mean ± SD)</u> -at 4 weeks Glucomannan (n=9): 0.3 ± 0.8 Placebo (n=10): 2.0 ± 0.6 p<0.01 for glucomannan group as compared to baseline -at 8 weeks Glucomannan (n=9): 0.5 ± 0.8 (N.S as compared to baseline) Placebo (n=10): 1.8 ± 1.6 -at 12 weeks Glucomannan (n=9): 0.3 ± 0.5 Placebo (n=10): 2.1 ± 0.4 p<0.01 for glucomannan group as compared to baseline All outcomes for placebo group at all points were N.S as	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						compared to baseline	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Tse et al. Dietary fibre intake and constipation in children with severe developmental disabilities. 2000. Journal of Paediatrics and Child Health 36[3], 236-239Australia.	Study Type: Prospective case series (pilot study) Evidence level: 3 Study aim: To evaluate fibre intake of severe developmentally disabled children living in a residential institution and the possibility of reducing the use of laxatives by increasing their fibre intake	20 children Inclusion criteria: severe developmentally disabled children able to take oral feeding and medically stable Exclusion criteria: Not stated	20 children age range 3 to 17 years gender not reported Country: Hong Kong	Intervention: Fibre supplementation: wheat bran (All Bran ® , Kellogg) added in breakfast -Stage 1: 15 g added to each serving of breakfast (total fibre intake, 17g) -Stage 2: 19 g added to each serving of breakfast (total fibre intake, 21g) Comparison: N.A	Duration of treatment - supplementation stage 1: 20 days -normal diet, no supplementation:10 days - supplementation stage 2: 6 weeks Assessment point (s): At the end of stages 1 and 2 Follow-up period: No follow-up conducted after treatment finished Outcome Measures: -bowel motions -use of laxatives	Number of laxatives per week -at baseline: 1.22 (SD 0.36) -at end of stage 1: 0.9 (SD 0.75) $p<0.05$ as compared to baseline -at end of stage 2: 0.7 (SD 0.40) $p<0.01$ as compared to baseline N.S comparing stage 1 and 2	Additional information from study: Definition of constipation: in the centre where the study was conducted if a child does not have a spontaneous bowel movement for 2 consecutive days a laxative is administered. Those who need more than 1 laxative per week are defined as having constipation Baseline fibre intake around 2g/day Reviewer comments: Unclear who measured study outcomes and how Outcomes for bowel movements not reported in paper Source of funding: Study sponsored by the Society for Relief of Disabled Children, Pokfulam, Hong Kong. 'All Bran' ® sponsored by Kellogg's Asia Ltd Wanchai, Hong Kong

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
MAFFIA. Treatment of functional constipation with prune-malt. 1955. Archives of Pediatrics 72[10], 341-346	Study Type: Open label non-RCT Evidence level: 1- Study aim: To evaluate the effectiveness in the treatment of functional constipation in infants and children of a palatable mixture containing prune and fig concentrate and non-diastatic malt syrup neutralised with potassium carbonate	200 children Inclusion criteria: Infants and children aged 3 months to 8 years with functional constipation Exclusion criteria: Organic constipation ruled out clinically and if necessary, after laboratory and radiologic studies	200 children age range: 3 months to 8 years gender not reported Country: USA	Intervention: Prune-Malt ® added to diet -Infants 3 weeks to 1 year old: 2 tablespoonfuls daily added to milk or juice -children 1 to 4 years: 3 tablespoonfuls daily added to milk or food -children 4 to 8 years: 4 tablespoonfuls daily added to milk or food (no changes made in usual diet, no drugs given) Comparison: No intervention	Duration of treatment 3 weeks Assessment point (s): Immediately after treatment completed Follow-up period: No follow-up made after treatment finished Outcome Measures: -improvement / no improvement / return to normality -acceptability	Returned to normality (number of children) Prune-Malt ®: 28 Controls: 16 Improved (number of children) Prune-Malt ®: 51 Controls: 25 Not improved (number of children) Prune-Malt ®: 21 Controls: 59 Acceptability (number of parents) Good: 132 Fair: 47 Poor: 21	Additional information from study: Diagnosis of constipation made on the following: 1) decreases in frequency of stools as compared to the child's usual bowel habits, 2) passage of hard, dry stools Wherever possible, cases of equal severity and ages were equally divided between the 2 groups All mothers given a card to record daily number and description of stools, all associated findings if any and acceptability of Prune Malt by the child Reviewer comments: No sample size calculation performed No comparison made between baseline characteristics No definitions/scoring system given for: "improvement", "no improvement", "return to normality", "good", "fair" and "poor" No dropouts/lost to follow-up children reported Study not controlled for potential confounders Source of funding: Prune-Malt provided by the Benson-Nuen Laboratories Inc., New York No other details provided

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Bu et al. Lactobacillus casei rhamnosus Lcr35 in children with chronic constipation. 2007. Pediatrics International 49[4], 485-490	Study Type: double-blind RCT Evidence level: 1+ Study aim: to investigate the effect of Probiotics (Lactobacillus case rhamnosus, Lcr35) alone in the treatment of chronic constipation in children and to compare the effect with magnesium oxide (MgO) and placebo, respectively	45 children Inclusion criteria: children under 10 years old with chronic constipation Exclusion criteria: organic causes of constipation like Hirschsprung's disease, spina bifida (occulta), hypothyroidism, or other metabolic/renal abnormalities, drugs influencing gastrointestinal function other than laxatives (calcium channel blockers, antidysrythmic agents, anticonvulsivants,	45 children 23 male Age (months, mean, SD) -MgO group 32.4 ± 13.9 -Probiotic group 36.7 ± 14.5 -Placebo group 35 ± 14.7 Country: Taiwan	Intervention: MgO 50 mg/kg per day, twice a day Comparison 1: Lcr35 8 X 10^8 c.f.u/day (Antiobiophilus 250 mg, 2 capsules, twice a day) Comparison 2: Placebo (starch in content) Lactulose use (1mL/kg/day) allowed when no stool passage noted for 3 days. Glycerin enema used only when no defecation for >5days or abdominal pain suffered due to stool impaction	Duration of treatment: 4 weeks Assessment point (s): Immediately after treatment completed Follow-up period: No follow up made after treatment finished Outcome Measures: -frequency of defecation -consistency of stools -episodes of soiling -episodes of abdominal pain -use of lactulose or enema	Defecation frequency (times/day) -MgO (n=18) 0.55 ± 0.13 -probiotic (n=18) 0.57 ± 0.17 -placebo (n=9) 0.37 ± 0.10 MgO vs. probiotic NS Placebo vs. probiotic P=0.006 MgO vs. placebo p=0.01 Hard stool (%) -MgO (n=18) 23.5 ± 7.9 -probiotic (n=18) 22.4 ± 14.7 -placebo (n=9) 75.5 ± 6.1 MgO vs. probiotic NS Placebo vs. probiotic p=0.02 MgO vs. placebo p=0.03 Abdominal pain (times) -MgO (n=18) 4.8 ± 3.7	Additional information from study: Chronic constipation defined as a stool frequency of <3 times/week for >2 months and at least 1 of the following minor criteria: anal fissures with bleeding due to constipation, faecal soiling or passage of large and hard stool Children randomly assigned into the 3 groups according to a computer - generated randomisation list Blinding achieved by the use of 3 interventions with similar appearances and placed into identical capsules, which were either swallowed o as a whole or opened and the contents of the capsule administered in milk or fluid Throughout the duration of study all investigators, participants and data analysts were blinded to the assigned treatment Sample size determined by doing primary trial with 9 patients using non-inferiority to test. Equivalent margin chosen with reference to effect of active control in the data of preliminary trial. Unbalance design of allocation number used for more interest in the new drug (Lcr35): allocation rate set at 2:2:1. One sided significance level set at 0.05 and power was 80%. Under these assumptions the smallest sample size was 45 and the sample size of MgO, Lcr35 and placebo was 18, 18 and 9

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		antidepressants, anticholinergic agents)				-probiotic (n=18) 1.9 ± 1.6 -placebo (n=9) 6.7 ± 3.3 MgO vs. probiotic p=0.04 Placebo vs. probiotic p=0.01 MgO vs. placebo NS <u>Use of glycerine enema (times)</u> -MgO (n=18) 1.3 ± 1.9 -probiotic (n=18) 1.6 ± 1.9 -placebo (n=9) 4.0 ± 2.1 MgO vs. probiotic NS Placebo vs. probiotic p=0.04 MgO vs. placebo p=0.03 No significant differences regarding use of lactulose and faecal soiling amongst 3 groups <u>Patients with treatment success (%)</u> -MgO (n=18): 72.2	respectively No significant differences at baseline amongst the 3 group regarding: sex, age of enrolment, age of onset of constipation, duration of constipation, previous treatment, defecation period, stool consistency, abdominal pain, faecal soiling, bleeding during defecation, use of enema, taking fruit or vegetable daily Patients asked to discontinue any laxatives previously prescribed 3 days before entering protocol, and also asked to avoid any other probiotics, yogurt or beverage containing probiotics for at least 2 weeks before treatment and during therapy All outcomes measures recorded by parents in a stool diary 4 patients discontinued medication during study period: 2 in MgO, 1 in probiotic, 1 in placebo group (2 patients suffered from acute gastroenteritis and 2 patients lost to follow-up) <u>Reviewer comments:</u> Allocation concealment not described Not clear whether the 2 patients who suffered from acute gastroenteritis had it as consequence of the study medication Study not controlled for potential confounders

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						-probiotic (n=18): 77.8 -placebo (n=9): 11.1 MgO vs. probiotic NS Placebo vs. probiotic p=0.01 MgO vs. placebo p=0.01 no adverse effects noted in probiotic and placebo groups, only 1 patient in the MgO group suffered from mild diarrhoea	Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Banaszkiewicz et al. Ineffectiveness of Lactobacillus GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. 2005. Journal of Pediatrics 146[3], 364-369	Study Type: Triple-blind RCT Evidence level: 1+ Study aim: To assess the effectiveness of *lactobacillus rhamnosus* GG (LGG) as and adjunct to lactulose in the treatment of constipation in children	84 children Inclusion criteria: Children aged 2 to 16 years with constipation defined as < 3 bowel movements per week for at least 12 weeks Exclusion criteria: Constipation caused by neuromuscular, anatomic or metabolic diseases (as established by medical history , an abnormal thyroid hormone level or prior anorectal manometry, barium or ionogram examination)	84 children mean age (months) -lactulose + LGG group 79 ± 47 -lactulose + placebo group 65 ± 36 gender not reported Country: Poland	General: Rectal disimpaction with phosphate and saline enema in all patients before study treatment Intervention: Lactulose 70%, 1 mL/kg/day (in 2 divided doses) + 10^9 colony forming units (CFU) of *lactobacillus rhamnosus* GG (LGG) Comparison: Lactulose 70%, 1 mL/kg/day (in 2 divided doses) + placebo	Duration of treatment 12 weeks (from weeks 13 to 24, patients instructed to continue the use of lactulose or other laxatives as needed Assessment point (s): At 4, 8, 12 Follow-up period: At 24 weeks after study treatment finished Outcome Measures: -primary outcome: treatment success -secondary outcomes: number of bowel	Treatment success (%) -At 12 weeks: LGG (n=43): 72 Placebo (n=41): 68 N.S -At 24 weeks: LGG (n=43): 64 Placebo (n=41): 65 N.S Spontaneous bowel movements per week (mean± SD) -At 4 weeks LGG (n=43): 5.9 ± 2.3 Placebo (n=41): 7.7 ± 5.4 N.S -At 8 weeks LGG (n=43): 6.1 ± 2.3 Placebo (n=41): 7.2 ± 3.8 N.S -At 12 weeks LGG (n=43): 6.1 ± 1.8 Placebo (n=41): 6.8 ± 3.1 N.S Episodes of faecal soiling per week	Additional information from study: Allocation sequence and randomisation list computer generated by investigators Blinding achieved by the use of study products with similar appearances and tastes, packed identically and indistinguishable from each other. Throughout duration of study all investigators, participants, outcomes assessors and data analysts were blinded to the assigned treatment No significant differences in baseline characteristics between the 2 groups All patients received stool diaries to record frequency of daily bowel movements, faecal soling, straining, stool consistency as well as any symptoms they consider important (e.g. abdominal pain, bloating, diarrhoea) Treatment success defined as ≥3 spontaneous bowel movements per week with no episodes of faecal soiling 5 children in LGG group discontinued intervention (4 clinical improvement, 1 abdominal pain) vs. 3 patients in placebo group (2 refused to participate, 1 provided other reason) Reviewer comments: Sample size calculation not performed Study not controlled for potential confounders

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
					movements per week number of episodes of faecal soiling per week stool consistency straining frequency per week percentage of patients using laxatives adverse events	<u>(mean± SD)</u> -At 4 weeks LGG (n=43): 0.9 ± 2.1 Placebo (n=41): 0.7 ± 1.5 N.S -At 8 weeks LGG (n=43): 0.8 ± 2.2 Placebo (n=41): 0.3 ± 0.8 N.S -At 12 weeks LGG (n=43): 0.8 ± 1.8 Placebo (n=41): 0.3 ± 0.9 N.S <u>Straining frequency per week (mean± SD)</u> -At 4 weeks LGG (n=43): 1.6 ± 1.9 Placebo (n=41): 1.4 ± 1.9 N.S -At 8 weeks LGG (n=43): 1.4 ± 1.7 Placebo (n=41): 1.4 ± 1.8 N.S	ITT analysis performed Outcomes for stool consistency not reported <u>Source of funding:</u> Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						-At 12 weeks LGG (n=43): 1.3 ± 1.5 Placebo (n=41): 1.6 ± 1.8 N.S <u>Patients using laxatives (%)</u> -At 24 weeks: LGG (n=43): 44 Placebo (n=41): 43 N.S <u>Adverse effects (% patients)</u> LGG (n=43): 9 Placebo (n=41): 14.6 N.S LGG well tolerated. Side effects profile of LGG similar to that of placebo: 3 patients in LGG group vs. 5 patients in placebo group developed abdominal pain. 1 patients in LGG group developed vomiting and 1 in the placebo group experienced headache	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Bekkali et al. The role of a probiotics mixture in the treatment of childhood constipation: a pilot study. 2007. Nutrition Journal 6, 17	Study Type: Prospective case series (pilot study) Evidence level: 3 Study aim: to determine the therapeutic effect of a combination of probiotics strains, containing the bifidobacteria *B. bifidus*, *B. infantis* and *B. longum and the lactobacilli L. casei, L. plantarum* and *L. rhamnosus*, on childhood constipation	20 children Inclusion criteria: Children between 4 to 16 years of age referred to outpatient clinic with constipation Exclusion criteria: use of any oral laxative < 4 weeks before intake, mental retardation, metabolic disease, functional non-retentive incontinence, and a history of gastro-intestinal surgery	20 children 10 boys Median age: 8 years (4 to 16) Country: The Netherlands	General: Disimpaction: rectal enema (Klyx: sodium-dioctylsulfosuccinate and sorbitol) once daily for 3 days Intervention: Daily probiotics mixture of 4 × 109 colony forming units (CFU), containing *Bifidobacteria (B.) bifidum, B. infantis, B. longum, Lactobacilli (L.) casei, L. plantarum* and *L. rhamnosus* Comparison: N.A	Duration of treatment 4 weeks Assessment point (s): At 2 and 4 weeks Follow-up period: No follow-up conducted after treatment finished Outcome Measures: Primary outcomes: -frequency of bowel movements per week -stool consistency Secondary outcomes: -number of faecal incontinence episodes per week	Frequency of bowel movements (BMs) per week, total sample -Baseline: 2.0 (1.0 to 5.0) -Week 2: 4.2 (0.0 to 16.0) p = 0.10 -Week 4: and 3.8 (2.1 to 7.0) p = 0.13 Frequency of bowel movements (BMs) per week in 12 children presenting with <3 BMs per week at baseline: -Baseline: 1.0 (0.0 to 2.0) -Week 2: 3.0 (0.0 to 7.0) p = 0.01 -Week 4: 3.0 (0.0 to 10.0) p = 0.009 Stool consistency Hard stools (n children): -Baseline: 7 -Week 2 : 4	Additional information from study: Constipation defined by Rome III criteria as having at least 2 out of 6 of the following symptoms: bowel movements <3 times/week; faecal incontinence >2 times/week; large amounts of stools obstructing the toilet once in 10 days; painful defecation; withholding behaviour; palpable abdominal or rectal mass on physical examination 7 days prior to baseline assessment and during treatment period all children recorded frequency of bowel movements, number of faecal incontinence episodes, stool consistency, abdominal pain, flatulence and pain during defecation as well as adverse effects such as vomiting and diarrhoea in a standardized bowel diary Stool consistency rated by patients as hard, normal or watery During treatment period children instructed to start toilet training. Toilet training consisted of sitting on the toilet 3 times per day for 5 minutes after each meal with the intention of trying to defecate. Use of laxatives not allowed during treatment period Reviewer comments: No dropouts/lost to follow-up children were reported Source of funding:

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					-incidence of adverse effects such as vomiting and diarrhoea	p = 0.23 -Week 4: 6 p = 1.00 At week 4, hard stools appeared in 5 children who also had hard stools at baseline. 1 child with normal stools at baseline, reported hard stools only at the end of the study. 2 of the 7 children who presented with hard stools, reported normal stools at the end of the study <u>Number of faecal incontinence episodes per week</u> Baseline: 4.0 (0.0 to 35.0) Week 2: 1.5 (0.0 to 14.0) p = 0.007 Week 4: 0.3 (0.0 to 7.0) p = 0.001 <u>Side effects</u> There were no side	Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						effects such as vomiting, bloating and increased flatulence during the study period	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Young et al. Increasing oral fluids in chronic constipation in children. 1998. Gastroenterology Nursing 21[4], 156-161	Study Type: Open label RCT Evidence level: 1- Study aim: To determine whether or not increasing liquid intake by either excess water intake or excess hyperosmolar liquid intake would significantly alter the course of simple constipation in children	108 children Inclusion criteria: Prepubertal children with moderate to severe simple constipation as assessed by the Constipation Assessment Score Exclusion criteria: Post pubertal children, hypercalcemia, Hirschsprung's disease, hypothyroidism, cardiac or renal disorders, children receiving specialised diets, malnourished children already receiving stool softeners or laxative	90 children 31 boys (47.46%) mean age 7.5 years (range 2.5 to 12.5 years) Country: USA	Intervention: Increased water intake: group instructed to increase water intake by 50% on the basis of total measured oral liquid intake during1st baseline week Comparison 1: Hyperosmolar liquids: group administered supplemental liquid in the form of Kool-Aid, juice, soda pop or other liquids know to contain more than 600 mOsm/L Comparison 2: Control group: no intervention	Duration of treatment 2 weeks Assessment point (s): At week 2 and 3 Follow-up period: No follow-up made after treatment finished Outcome Measures: -stool frequency -stool consistency -difficulty of stool passage	Stool frequency (mean) H2O (water) HiOsm (high osmolality) -baseline: Control: 3.45 H2O: 3.52 HiOsm: 3.75 -week 2: Control: 4.05 H2O: 3.57 HiOsm: 4.31 -week 3: Control: 3.40 H2O: 3.70 HiOsm: 3.44 Stool consistency (mean) -baseline: Control: 6.30 H2O: 6.13 -week 2: Control: 6.33 H2O: 5.99 -week 3: Control: 6.30 H2O: 5.79 Difficulty of stool passage (mean) -baseline:	Additional information from study: Constipation Assessment Score based on 8 variables assessed during the past 3 days: abdominal distension or bloating, change in amount of gas passed rectally, less frequent bowel movements, oozing liquid stools, rectal fullness or pressure, rectal pain with bowel movement, smaller stool size, urge but inability to pass stool. Each variable scored as 0, no problem; 1, some problem and 2, severe problem. A gift certificate to a toy store was used as incentive to return data collection forms The concentration of 600 mOsm/L chosen because it was considered to be a level above which a significant osmotic load in the small bowel would result in significant plasma to lumen flux. The 50% increase arbitrarily chosen as being feasible , >50% considered potentially burdensome for children/caregiver and probably not therapeutically obtainable under normal situations Stool frequency, consistency and difficulty with passage assessed daily by parents using a simple form. The Stool Consistency Continuum previously developed by Bergstrom chosen to evaluate stool form. Difficulty of passage scored as: 0, no problem; 1, some problem; 2 severe problem A second round of analysis excluded all

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		preparations, children who were physically or intellectually challenging (?) or who had an underlying central nervous system disease				Control: 0.96 H2O: 0.78 HiOsm: 0.77 -week 2: Control: 0.95 H2O: 0.84 HiOsm: 0.74 -week 3: Control: 1.06 H2O: 0.87 HiOsm: 0.62 Neither increasing water intake nor increasing hyperosmolar liquid intake significantly increased stool frequency or decreased stool consistency or difficulty with stool passage within groups when comparisons were made with previous weeks, or between the 3 groups during the same week	subjects who failed to comply with at least 75% of assigned intervention, and this did not change the study outcomes <u>Reviewer comments:</u> Sample size calculated on the basis of preliminary power analysis but no details provided. Non probability convenience sample was used No comparison made of baseline characteristics Methods of randomisation and allocation concealment not described 108 children originally included, but only 90 completed the entire study as assigned. 18 children failed to comply with 75% of the intervention, but there are no clear explanations as to why that happened Outcomes for stool consistency in the HiOsm group not reported Study not controlled for potential confounders <u>Source of funding:</u> Not clearly stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Eisenberg et al. Contribution of stepping while standing to function and secondary conditions among children with cerebral palsy. 2009. Pediatric Physical Therapy 21[1], 79-85 Einsberg et al. 2009	Study Type: Non-RCT Evidence level: 1- Study aim: To explore the feasibility and efficacy of stepping while standing and its effect on function and the prevalence of secondary conditions among children with severe cerebral palsy (CP)	22 children Inclusion criteria: Aged between 3.5 and 10 years at first visit, CP spastic quadriplegia with gross motor function classification system (GMFCS) level 4 or 5, inability to stand and walk with traditional walker/rollator due to insufficient upper extremity control, attempts steps when in a supported standing position, flexion contractures of the hips and knees of less than 30°	22 children Intervention group (n=11): 6 males mean age (yr) 6.1±2.1 Controls (n=11): 6 males mean age (yr) 6.7±1.6 Country: Israel	Intervention: Trial of David Hart Walker (HW) device (to encourage active stepping while standing) in addition to physical therapy sessions. Beginning with 30 minute sessions 4 times a week, parents and children encouraged to use device at home Comparison: Program in standing frame (SF) (passive standing) as part of physical therapy session. 30-minute sessions 4 times a week, parents and children encouraged to use SF at home	Duration of treatment 6 months Assessment point (s): at 6 months after treatment initiated Follow-up period: None after intervention period finished Outcome Measures: Prevalence of constipation	Prevalence of constipation (number, % of children) -At entry: HW: 6 (54.5) SF: 6 (54.5) NS -at 6 months: HW: 1 (9.1) SF: 6 (54.5) p = 0.02	Additional information from study: Intervention and control children matched for age and sex HW device – The David Hart Walker (HW) Orthosis, a hands free walker provides weight-bearing support and leg alignment while allowing upper extremity freedom, aiming to allow the action of stepping while standing Constipation defined as 2 bowel movements per week, or 2 of the following on more than 1 of 4 occasions: straining, hard stools and a feeling of incomplete evacuation Diary of bowel function kept by parent and/or the physical therapist and maintained throughout follow-up period used to assess for constipation At baseline children in the HW group had higher significant mean scores in the self-care and social function domain of the Paediatric Evaluation of Disability Inventory (PEDI) score than children in the SF group Reviewer comments Very small study population No dropouts/loss to follow-up reported PEDI scores may have confounded the effects of the intervention and this was not accounted for

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		Exclusion criteria: Not stated					Source of funding: Not stated

Effectiveness of excluding Cow's Milk from the Diet in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Iacono et al. Intolerance of cow's milk and chronic constipation in children. 1998. New England Journal of Medicine 339[16], 1100-1104United States.	Study Type: Cross over randomised controlled trial Evidence level: 1+	65 patients 33 patients received cow's milk and 32 soy milk during the fist study period 32 patients received cow's milk and 33 soy milk during the second study period Inclusion criteria: consecutive children referred by family paediatricians to a paediatric gastroenterology clinic diagnosed with chronic constipation. Chronic constipation defined as chronic faecal retention (one	Age (mo) 34.6+-17.1 Sex M/F 29/36	Intervention: Excluding cow's milk and its derivatives from the diet of children with constipation Comparison: Cow's milk vs. soy milk Weeks 1-2: observation period all medication stopped Weeks 3-4: one group received cow's milk and unrestricted diet and the other had cow's milk and its derivatives excluded from diet and received soy milk instead Week 5: washout period for both groups, unrestricted diet and intake of soy or cow's milk and its derivatives	Follow-up period: Mean: 10 months (range 3 to 20) Outcome Measures: Number of bowels movements Children with eight or more bowel movements during a treatment period were considered to have a response Qualitative faecal score 1: mushy or liquid stool 2: soft faeces and no pain in passing stools 3: hard faeces and difficulty and pain on passing stools Both Number of bowels movements and	Observation period (n=65) Number of bowel movements: 4 Median: 3-5 25th to 75th percentile Qualitative faecal score 1: 0 2: 0 3: 65 Weeks 3-4 and 6-7 -Cow's milk group: Number of bowel movements: Median: 4 25th to 75th percentile: 3-5 Qualitative faecal score 1: 0 2: 0 3: 65 -Soy milk group: Number of bowel movements Median: 10 25th to 75th	The order of treatment was randomly assigned by a computer-generated method with the individual patient as the unit of randomisation. The researchers were unaware of the order of the treatment. At baseline and end of two study periods children were examined by a researcher who was unaware of laboratory test results and histological findings To ensure that children did not receive any other kind of milk-containing food during the study periods parents were given a list of most common milk-containing food to be avoided 6 patients were withdrawn from the study during the cow's-milk study period (on days 9-12) because of the reappearance of constipation and other related disorders. For these children the number of bowel movements per period was prorated. Intention to treat analysis was used The mean (±SD) daily consumption was 450±120 ml of soy milk and 470±135 ml of cow's milk. Analysis of the main constituents of the diet (proteins, carbohydrates and fibres) did not show any qualitative or quantitative variation during the study period (data not shown). Patients were highly selected and this might have led to overestimate the

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		bowel movement every 3 to 15 days) often associated with abdominal symptoms (abdominal pain, painful defecation and so forth) <u>Exclusion criteria:</u> Anatomical causes (Hirschsprung's disease, spinal disease) another disorder (hypothyroidism, psychomotor retardation), prior anal surgery, medication that can cause constipation (chlorpromazine) and referral for other reasons		Week 6-7: patients switched to the other type of milk Total amount of milk given to the patient during the two weeks: 5-10 litres Bottles coded A or B by hospital dispensary Infants < 15 months age: formula based on cow's milk (Transilat, Plasmon, Milan, Italy) or formula based on soy (Plasmonsoy, Plasmon). Children > 15 months age: commercially available whole cow's milk or soy milk After the two study periods children with a response to cow's-milk free diet were given the soy-milk diet	qualitative faecal score were recorded by parents	percentile: 4-12 Qualitative faecal score 1: 2 2: 42 3: 21 p values were < 0.001 for all variables <u>Challenge with cow's milk (n=44)</u> -Placebo group (soy milk): 0 clinical reactions -Cow's milk group: 0 acute reaction, but in all patients constipation associated with hard stools and discomfort on defecation reappeared after 5-10 days on the diet. Cow's-milk-free diet was recommenced, with a consequent normalisation of bowel movements in all patients <u>Follow-up:</u> 0 children with response had	frequency of cow's milk intolerance as a cause of constipation. Paediatricians who referred the patients may have preselected them having being the centre where the study was conducted experience in the treatment of food allergies. The inclusion of patients with no response to laxatives may have also contributed to this issue.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				for another month and then underwent a 2-week double-blind challenge with cow's milk at hospital. Children were randomly assigned to receive cow's milk or a placebo containing soy milk. If no clinical reactions were observed within 12 hours, patients were discharged and the challenge continued at home with bottles coded A or B by the hospital dispensary. Challenge was stopped when a clinical reaction occurred, in particular when there were not bowel movements for 72 hours and the patient had abdominal pain, perianal lessons or both.		constipation Cow's milk reintroduced into the diets of 15 children after 8-12 of cow's milk-free diet and in all cases constipation returned within 5-10 days Children with no response to soy-milk diet were treated with high doses of laxatives, with subsequent improvement in stool frequency. In all cases symptoms returned once treatment with laxatives was stopped	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Carroccio et al. Chronic constipation and food intolerance: A model of proctitis causing constipation. 2005. Scandinavian Journal of Gastroenterology 40[1], 33-42Norway.	Study Type: Case series and embedded randomised controlled challenge Evidence level: 3	52 consecutive infants and children with chronic constipation unresponsive to previous treatments examined at the outpatients clinic of a hospital. Chronic constipation defined as chronic faecal retention (one bowel movement every 3 days or more) with painful elimination of hard stools associated with abdominal pain Inclusion criteria: -a history of chronic constipation lasting at least 6	Age (months) : 51.2±18 Sex (M/F): 22/30	Intervention: Cow's milk-free diet, with the exclusion of cow's milk and all its derivatives Comparisons: 1. Cow's milk-free diet vs. soy milk 2. Cow's milk vs. ass's milk 1. Cow's milk-free diet vs. soy milk -2 weeks observation period: all medications stopped and at the end a clean-out with single dose of polyethylene glycol 4000 (0.75g/kg). Normal diet, no restrictions -4 weeks of cow's milk free diet (without cow's milk derivatives too) Infants < 15	Follow-up period: None reported Outcome Measures: Number of bowels movements/week Qualitative faecal score 1: mushy or liquid stool 2: soft faeces and no pain in passing stools 3: hard faeces and difficulty and pain on passing stools both number of bowels movements/week and qualitative faecal score were recorded by parents Children with eight or more bowel movements during a treatment	Observation period: -Patients with food intolerance (n=30) Number of bowel movements/week: Median: 1.5 25th to 75th percentile: 1-2 Qualitative faecal score 1: 0 2: 0 3: 30 - Patients with constipation unrelated to food intolerance (n=22): Number of bowel movements/week: Median: 1.5 25th to 75th percentile: 1-2 Qualitative faecal score 1: 0 2: 0 3: 22 Elimination diet period: -Patients with food	Qualitative faecal score previously validated according to authors Randomisation method used during the cow's milk challenge not described To ensure that children did not receive any other kind of milk-containing food during the study periods parents were given a list of most common milk-containing food to be avoided. Furthermore, they were asked to record the amount and type of food their children had eaten every day. Frequent telephone contacts helped to ensure adherence to the diet Patients with chronic constipation caused by food intolerance showed at baseline a higher frequency of a personal history of previous food intolerance (p=0.02) and concomitant signs of food intolerance (bronchospasm five cases, rhinitis four cases, dermatitis two cases) (p=0.03) than patients with constipation unrelated to food intolerance. No difference was observed between the 24 patients with CM intolerance and the 6 patients with multiple food intolerance for outcome measures considered (number of bowel movements and qualitative faecal score), either at baseline or on elimination diet. However in comparison with patients intolerant to CM alone, patients suffering from multiple food intolerance were older (p=0/04) and had a higher frequency of family history of atopic disease (p=0.03) Analysis of the main constituents of the

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		months -lack of response to a previous increase in dietary fibre intake and/or to laxative treatment (milk of magnesia 1-2 ml per kg bodyweight, polyethylene glycol 4000 mean dose 0.75 g per kg daily) attempted for at least one month -regular dietary intake of cow's milk and derivatives <u>Exclusion criteria:</u> -prior anal surgery -use of medication that can cause constipation -referral for reasons other than chronic		months age: soy-based (Nutrilon-soya, Nutricia, Milan, Italy) Children > 15 months age: commercially available soy milk Patients unresponsive to CM-free diet placed on oligoantigenic diet 4 weeks (also excluding cow's milk): exclusively rice, lamb, carrots, ass's milk, olive oil and sugar 2. Cow's milk vs. ass's milk Double-blind placebo-controlled challenge with cow's milk, after 12 weeks, to all patients cured on CM-free or oligoantigenic diet. Placebo: ass's milk If no clinical	period were considered to have a response Normalised stools habits: bowel frequency of at least five evacuations/week with the elimination of soft stools, without painful defecation	intolerance (n=30) Number of bowel movements/week: Median: 5 25th to 75th percentile: 4-7 Qualitative faecal score 1: 2 2: 28 3: 0 - Patients with constipation unrelated to food intolerance (n=22): Number of bowel movements/week: Median: 1.5 25th to 75th percentile: 1-2 Qualitative faecal score 1: 0 2: 0 3: 22 <u>Cow's milk challenge:</u> No specific data are reported apart from saying that in all cases cow's milk readministration caused the	diet (proteins, carbohydrates and fibres) did not show any qualitative or quantitative variation during the study period (data not shown) Patients with food intolerance (to CM only or multiple) were treated as a group for the purpose of analysing the data, therefore it is not possible to offer specific data for the CM group only The high frequency of chronic constipation owing to food intolerance likely due to a selection bias, as mainly food-intolerant patients are treated at the centre where study was conducted. <u>Funding source:</u> partly supported by a grant from MURST and from the MiPAF (progetto "ALICE", D.D. n 86 dated 30.01.2002)

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		constipation -anatomical /neurological causes of constipation (Hirschsprung's disease, spinal disease, psychomotor retardation) -another disease causing constipation (hypothyroidism, coeliac disease)		reactions after 12 hours, patients were discharged and challenge continued at home with bottles coded A or B. Challenge was stopped when a clinical reaction occurred		reappearance of constipation within 5 days after commencing the challenge (median 2 days, range 1-5 days)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Iacono et al. Chronic constipation as a symptom of cow milk allergy. 1995. Journal of Pediatrics 126[1], 34-39	Study Type: Case series Evidence level: 3	27 infants Inclusion criteria: referred to a paediatric gastroenterology clinic during the 12 months preceding the study and considered to have idiopathic constipation. Diagnosis of constipation made on the basis of a history of reduced frequency of stools (one evacuation every 3 to 7 days- and on pain in the passage of hard stools. In all patients the frequency of stools per day was lower than the 3rd percentile of the values observed in a	15 boys Mean age: 20.6 +- 13.4 months (range 5 to 36 months)	Intervention: Excluding cow's milk and its derivatives from the diet of children with chronic constipation Comparisons: 1. Cow's milk-free diet vs. soy milk/ ass's milk 2. Cow's milk vs. ass's milk 1. Cow's milk-free diet vs. soy milk/ ass's milk -First 7 days: All patients were being fed the same diet as at the time of diagnosis: various form of commercial formula derived from cow milk or whole cow milk and its derivatives -For the next month: all patients started a cow's milk protein-free diet. Three patients aged <	Follow-up period: monthly for a mean period of 18 months (range 10 to 30 months) Outcome Measures: -Number of stools/day -Description of stools + Difficulty in passing them = Qualitative score Qualitative score: 3: hard faeces, difficulty and pain in passing stools 2: soft faeces, no pain 1: mushy or liquid stool During the various study periods (as recorded by parents):	Mean number (+-SD) of stools per day during unrestricted diet (UD) and during CMP-free diet Stools from patients on CMP-free diet -Cured (n=21) a. UD: 0.24+-0.10 b. 1rst CMP-free diet: 1.04+-0.12 c. 1rst CMP challenge: 031+-0.14 d. 2nd CMP-free diet: 1.05+-0.11 Significance: b and d vs. a and c, p<0.0005 -Unimproved (n=6) UD: 0.18+-0.12 1rst CMP-free diet: 0.20+-0.13 CMP challenge: - CMP-free diet: - Qualitative score: -Cured (n=21) a. UD: 2.85+-0.05 b. 1rst CMP-free diet: 1.90+-0.08 c. 1rst CMP challenge: 2.75+-0.11	Analysis of the patient's dietary diaries did not show any significant variations in daily fibre and liquid intake during the various study periods It is not reported whether any medication was stopped at the beginning of the study Funding: not reported

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		large population of healthy subject participating in an Italian multicentre study Exclusion criteria: Hirschsprung's disease, mental retardation		12 months were fed a formula containing soy protein and the others received soy milk or ass's milk (eight cases) and all milk derivatives were excluded After a month: -Patients whose symptoms abated: cow milk challenge. Cow milk given for a maximum of 10 days, again an exclusion diet for 1 month and then a second cow milk challenge. All challenges were performed in hospital. Before the challenge a prick test was performed with CMP. In patients with a negative result, the challenge was performed by giving whole cow milk in a singles feeding; if there were no clinical		d. 2nd CMP-free diet: 1.85+-0.10 (p<0.001) -Unimproved (n=6) UD: 3 1rst CMP-free diet: 3 CMP challenge: - CMP-free diet: - Difficulty in passing stools: -Cured (n=21) a. UD: B. 1rst CMP-free diet: none had difficulty c. 1rst CMP challenge: Painful d. 2nd CMP-free diet: none had difficulty During the second challenge symptoms reappeared within 24 to 48 h: all 21 patients had painful passage of stools and for this reason challenge was suspended on the third day -Unimproved (n=6)	

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				reactions, the same food was given the following days. In patients with a positive test result, the challenge was performed by giving a formula containing CMP, beginning with an initial quantity of 10 ml and gradually increasing the amount to reach the dose equivalent to a full feeding after 48 hours. No other change in diet was made. Reintroduction of cow milk cautiously attempted in 16 children 6-9 months after the diagnosis of CMPA-dependant constipation -Patients with no abatement in symptoms: permanently given		Control: ? 1rst CMP-free diet: no changes CMP challenge: - CMP-free diet: - <u>Follow-up period:</u> Reintroduction of cow milk was cautiously attempted in 16 children 6-9 months after the diagnosis of CMPA-dependant constipation. In eight children CMP did not cause the onset of any problems and it was reintroduced on a permanent basis; in eight patients CMP led to the reappearance of constipation within 2 to 3 days after introduction, and these infants were still following CMP-free diet at the time the paper was written.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				an unrestricted diet, except for one infant who had episodes of recurrent bronchospasm related to ingestion of cow milk			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Iacono et al. Food intolerance and chronic constipation: manometry and histology study. 2006. European Journal of Gastroenterology and Hepatology 18[2], 143-150	Study Type: Case series and embedded randomised controlled challenge Evidence level: 3	36 consecutive infants and children with chronic constipation unresponsive to previous treatments, examined at the outpatient clinic of a hospital Paediatric Gastroenterology Division. Chronic constipation defined as less than 3 bowel movements/r week with painful elimination of hard stools Inclusion criteria: - a history of chronic constipation lasting at least 3 months -lack of response to a previous	20 females Aged 9 months to 10 years (median 3.6 years)	Intervention: Cow's milk-free diet, with the exclusion of cow's milk and all its derivatives Comparisons: 1. Cow's milk-free diet vs. soy milk 2. Cow's milk vs. ass's milk 1. Cow's milk-free diet vs. soy milk: 2-week observation period: all medications stopped 4 weeks: all patients on cow's milk free diet. Infants < 15 months old received a formula based on soy (Nutrilon-soya, Nutricia, Milan, Italy), children>15 months old a commercially available soy milk. Patients	Follow-up period: Not reported Outcome Measures: Number of bowel movements/week Appearance of stools + child's degree of difficulty in passing stools = Qualitative faecal score: 1. Mushy or liquid stools 2. Soft faeces and no pain in passing stools 3. Hard stools and difficulty and pain on passing stools (All outcomes measures were recorded by parents) Normalised stool habits: a bowel frequency of at	Observation period: -Patients with food intolerance (n=17) Number of bowel movements/week: Median: 1.5 25th to 75th percentile: 1-2 Qualitative faecal score 1: 0 2: 0 3: 17 - Patients with constipation unrelated to food intolerance (n=19): Number of bowel movements/week: Median: 1.5 25th to 75th percentile: 1-2 Qualitative faecal score 1: 0 2: 0 3: 19 Elimination diet period: -Patients with food	To ensure that all children observed a correct elimination diet, parents were asked to record the amount and type of food their children had eaten each day. These diaries were analysed at the end of the study to evaluate adherence to the diet and the quantity of milk consumed Neither the parents nor the children were able to distinguish whether the bottles contained asses' or cows' milk. According to the authors the qualitative faecal score had been previously validated Randomisation method used during the cow's milk challenge not described Specific data related to number of bowel movements and qualitative faecal score were not reported for the challenge period. Analysis of the main constituents of the diet (proteins, carbohydrates and fibres) did not show any qualitative or quantitative variation during the study period (data not shown) Patients with food intolerance (to CM only or multiple) were treated as a group for the purpose of analysing the data, therefore it is not possible to offer specific data for the CM group only Funding: partly supported by a grant from MIUR and MiPAF: project "Alimetazione e celiachia (ALICE)", D.D. n 86 dated 30.01.2002)

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		increase in dietary fibre intake or to laxative treatment (milk of magnesia 1-2 ml/ kg of body weight) -a regular dietary intake of cow's milk and derivatives <u>Exclusion criteria:</u> -previous evaluation for chronic constipation -anatomical /neurological causes (Hirschsprung's disease, psychomotor retardation) -another disease (coeliac disease, hypothyroidism) -previous anal surgery -use of medication		unresponsive to CM-free diet placed on oligoantigenic diet 4 weeks (also excluding cow's milk): exclusively rice, lamb, carrots, ass's milk, olive oil and sugar 2. Cow's milk vs. ass's milk: After 12 weeks: patients cured on cow's milk-free diet and oligoantigenic underwent a 2-week double-blind placebo-controlled challenge with cow's milk. Asses' milk was used as placebo. If no clinical reactions after 12 hours, patients were discharged and challenge continued at home with bottles coded A or B. Challenge was stopped when a clinical reaction	least three evacuations per week, with the elimination of soft stools, without painful defecation	intolerance (n=17) Number of bowel movements/week: Median: 5 25th to 75th percentile: 3-7 Qualitative faecal score 1: 1 2: 16 3: 0 - Patients with constipation unrelated to food intolerance (n=19): Number of bowel movements/week: Median: 1.5 25th to 75th percentile: 1-2 Qualitative faecal score 1: 0 2: 0 3: 19 <u>Cow's milk challenge period</u> Reappearance of constipation in all cases (n=17), very often associated with	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		that causes constipation -referral for reasons other than constipation		occurred		painful defecation, within 5 days after the commencement of the challenge (median 2 days, range 1-5 days).	

Psychological/Behavioural Interventions for Ongoing Treatment/Maintenance in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Loening-Baucke. Modulation of abnormal defecation dynamics by biofeedback treatment in chronically constipated children with encopresis. 1990. Journal of Pediatrics 116[2], 214-222	Study Type: Parallel-RCT Evidence level: 1+ Study aim: To determine whether outcome in chronically constipated and encopretic children with abnormal defecation dynamics could be improved with biofeedback training	43 children Inclusion criteria: Children 5 to 16 years with chronic constipation and encopresis and abnormal defecation dynamics Exclusion criteria: Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating diseases, neurologic abnormalities, previous surgery of the colon	43 children 33 boys Mean age: 8.9 years (range 5 to 16) Country: USA	Intervention: Conventional treatment alone (CT) CT: use of laxatives, increase of dietary fibre and scheduled toileting Disimpaction with enemas (type and dose not reported) Maintenance: milk of magnesia ~ 2ml/kg body weight daily to induce at least 1 bowel movement daily and prevent faecal retention. Doses decrease gradually to maintain daily bowel movement and prevent faecal retention and soiling Patients instructed to discontinue laxative therapy at	Duration of treatment 6-month protocol. Assessment point (s) and follow-up period: 7 & 12 months Outcome Measures: Recovery rate	Recovery rate (number recovered, %) -at 7 months: CT (n=19): 1(5) BF (n=22): 12 (55) P<0.001 Recovery rates did not differ between boys and girls in general and within the biofeedback group in particular. Prior unsuccessful treatment no related to treatment outcome in either group Patients with an initial abdominal faecal mass (severe constipation) significantly more likely to recover with BF training than with CT alone (46% vs. 0%, p<0.02) -at 12 months : CT (n=19): 3 (16)	Additional information from study: Constipation and encopresis defined as having ≥ 2 soiling episodes/week and evidence of a huge amount of faecal material in the rectal ampulla at rectal examination. In many patients stool evacuation was incomplete as evidenced by periodic passage of very large amounts of stools (every 7 to 30 days), often clogging the toilet Abnormal defecation dynamics defined as abnormal contraction of the external anal sphincter and pelvic floor during defecation attempts, as determined by anorectal manometry Sample size and calculation: 2 pairs of subjects would be needed per group to allow a power of approximately 0.9 to detect a difference of 0.7 vs. 0.2 in achieving normal bowel habits (recovery from constipation and encopresis) Sealed envelopes with cards indicating either conventional therapy alone or conventional therapy with biofeedback training used for randomisation 1 boy in the conventional treatment group was lost to follow-up 1 month after treatment began. At that visit he was taking milk of magnesia and his soiling had resolved. 1 boy was lost to follow-up in the biofeedback group after the first biofeedback session

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				6 ± 0.5 months after initiation of therapy <u>Comparison</u>: Conventional treatment (CT) + biofeedback (BF) Up to 6 sessions of biofeedback therapy 7 +/- 2 days apart. 1 session included approximately 30 to 35 defecation trials and lasted approximately 45 minutes Patients instructed to discontinue laxative therapy at 6 ± 0.5 months after initiation of therapy		BF (n=22): 11 (50) P<0.05 A 14-yeor old boy in the BF group had a relapse. He had severe faecal impaction with enormous abdominal distension initially. Faecal impaction recurred 4 months after successful discontinuation of milk of magnesia. at time study was written he had no soiling but required intermittent treatment for constipation	Baseline characteristics not significantly different between both groups apart from gender: more girl in the BF group than in the CT group (41% vs. 5%, p<0.02). During initial evaluation the following significantly more frequent in girls than in boys: severe constipation (an abdominal faecal mass present) (90% vs. 48%, p<0.03), daytime urinary incontinence (70% vs. 23%, p<0.02) and a history of previous urinary tract infection (60% vs. 6%, p<0.001) Patients considered to have recovered if they had ≥3 bowel movements/week and soiling ≤ 2 episodes/month while not receiving laxatives for 4 weeks. Patients considered not to have recovered if they had <3 bowel movements/week or were soiling >2 times/month or had been started on a regime of laxatives again Re-evaluation of patients included review of last month's stool, soiling and medication dairy. Follow-up interview by questionnaire at 12 months <u>Reviewer comments:</u> Not completely clear who measured outcomes and how, and whether questionnaires were piloted ITT analysis not performed <u>Source of funding:</u> Supported by grant No. M01-RR-00059 from the General Clinical Research

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							Centre Program,, Division of Research Resources, National Institute of Health; the Children's Miracle Network Telethon and the Spelman-Rockefeller Child and Parenting Seed Grant

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
van der Plas et al. Biofeedback training in treatment of childhood constipation: a randomised controlled study. 1996. Lancet 348[9030], 776-780	Study Type: Parallel-RCT Evidence level: 1+ Study aim: To evaluate the effect of biofeedback training and conventional treatment on defaecation dynamics and outcome in chronically constipated children	192 children Inclusion criteria: Patients with paediatric constipation who fulfilled at least 2 of these 4 criteria: stool frequency <3 per week, ≥2 soiling and/or encopresis episodes per week, periodic passage of very large amounts of stool at least once every 7–30 days, or a palpable abdominal or rectal mass. Children needed to be at least 5 years old to understand the manometric procedures and instructions	192 children 126 boys -age range (total population): 5 to 16 years -median age for both groups: 8 years Country: The Netherlands	Intervention: Conventional laxative treatment (CT) 5 outpatient visits lasting approximately 30 min during which laxative treatment and information from a diary containing defaecation frequency and encopresis and/or soiling episodes were discussed High-fibre diet advised but additional fibre supplements not prescribed Patients instructed to try to defecate on the toilet for 5 min immediately after each meal During the first 3 days patients were to use daily enemas (120 mL sodiumdioctylsulfosuccinate, 1 mg	Duration of intervention 6 weeks Assessment point (s) and follow-up period: after the last visit of the intervention period at 6 weeks, then at 6 months, 1 year, and 1 ½ years Outcome Measures: Treatment success	Treatment success (number of children cured, %) -at 6 weeks CT (n=94): 31/94 (33%) CT+BF (n=98): 31/98 (32%) NS -at 6 months CT (n=94): 48/93 (52%) CT+BF (n=98): 44/94 (47%) NS -at 1 year CT (n=94): 54/92 (59%) CT+BF (n=98): 46/92 (50%) NS -at 1 ½ year CT (n=94): 52/92 (57%) CT+BF (n=98): 44/92 (48%)	Additional information from study: A faecal mass defined as a large hard or soft stool in the rectum which completely filled the rectal vault. Soiling defined as loss of loose stools in underwear. Encopresis defined as voluntary or involuntary passage of a quantitatively normal bowel movement in underwear in children over the age of 4, occurring on a regular basis without any organic cause. A large amount of stool was estimated to be twice the standard shown in a clay model High percentage of non compliance reported by parents if the child was asked to attempt toilet training 15–30 min after the meal to profit from the gastro—colic reflex Treatment was considered successful if the patients achieved ≥3 bowel movements per week and < 2 soiling or encopresis episodes per month while not receiving laxatives for 4 weeks It was estimated that a sample of 180 patients would be adequate to show a difference of at least 70% success at 6 months for CT+BF compared to 45% success using CT with a two-tailed alfa 2 of 0·05 with a power of 90% At baseline patients were comparable for gender, age, and frequency of gastrointestinal complaints, and urinary problems

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		and had to have had treatment with laxatives for a minimum of 1 month before randomisation Exclusion criteria: Hirschsprung's disease, spina bifida occulta, hypothyroidism or other metabolic or renal abnormalities, mental retardation, and children using drugs influencing gastrointestinal function other than laxatives		sorbitol, 250 mg per mL, Klyx) at home. If, on day 3, enemas still resulted in large amounts of stool, enemas were continued for a maximum of 7 days. After the initial 3-day enema treatment, patients started oral laxatives with Importal (lactitol betagalactoside sorbitol, 1 sachet of 5 g/10 kg body weight per day divided in 2 doses). Enemas given whenever spontaneous defaecation was delayed for more than three days. Motivation enhanced by praise and small gifts Comparison: 5 outpatient visits, including the same conventional treatment as			At 6 months, 5 patients were lost (4 patients in the CT+BF and 1 patient in the CT group), and at 1 year 8 patients were lost to follow up (another 2 in the CT+BF and 1 in the CT group). Patients lost to follow up were withdrawn from further analysis During the intervention period, 3 patients in the CT group refused manometry at the end of the treatment period: 1 patient was successfully treated and the parents refused permission for manometry; 1 patient was unsuccessfully treated and refused manometry; and 1 patient was lost to follow-up after two visits. 2 patients of the CT+BF group discontinued treatment: one 5-year-old patient did not cooperate and another patient discontinued treatment because his parents could not afford the cost of transport. At the beginning and end of the 6-week treatment period, each patient had a detailed medical history, abdominal and rectal examination, and anorectal manometry. The child and parents were asked about bowel function, frequency of defaecation soiling and/or encopresis, consistency and size of stool, pain during defaecation, and associated symptoms such as abdominal pain, appetite, and enuresis. Follow up done either during a clinical visit using a standard questionnaire or by telephone

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				described above, in combination with 5 biofeedback training sessions. As far as possible, both groups received equal attention.			Because other studies have selected patients for evaluation according to the presence of abnormal defaecation dynamics at the start of the study, authors compared defaecation dynamics at randomisation and after treatment, and found no correlation between achievement of normal defaecation dynamics and success. Analysis of all patients showed no relationship between post-treatment defaecation dynamics and success. Log-linear modelling showed significant relationships between pre-treatment and post-treatment defaecation dynamics (x2= 13·91, p<0·001) and between treatment and post-treatment defaecation dynamics (x2=28·38, p<0·001). There was no association between post-treatment defaecation dynamics and treatment success after 6 weeks (x2=2·41, p=0·12). The results at 6 months and 1 year were similar <u>Reviewer comments:</u> Randomisation and allocation concealment methods not reported Not completely clear who measured outcomes and how ITT analysis not performed <u>Source of funding:</u> Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Nolan et al. Randomised controlled trial of biofeedback training in persistent encopresis with anismus. 1998. Archives of Disease in Childhood 79[2], 131-135United Kingdom.	Study Type: Parallel-RCT Evidence level: 1+ Study aim: To determine whether surface electromyographic (EMG) biofeedback training produces sustained faecal continence in medical treatment resistant and/or treatment dependent children with anismus	29 children Inclusion criteria: Children aged ≥4 years, judged to be of adequate maturity to cooperate with biofeedback treatment and had received 3 months or more of conventional multimodal therapy; had continuing soiling with or without laxative treatment (more than once a month) or had achieved remission from soiling but could not sustain continence without continued laxative treatment; and had	29 children 24 boys age range: 4.8 to 14.9 years -mean age (years) (SD): BFT+CT : 9.2 (2.7) CT: 8.4 (2.3) Country: Australia	Intervention: EMG biofeedback training and conventional medical treatment (BFT+CT) Up to 4 sessions at weekly intervals conducted for each patient, each session consisting of ~ 30–35 defecation attempts. Aim was to achieve 10 relaxations of the external anal sphincter without visual feedback in 2 successive sessions. If this occurred in less than 4 sessions then biofeedback was discontinued. At completion of training, subjects followed at monthly intervals by a single paediatrician, who gave verbal reinforcement of the skills learned during training	Duration of treatment CT: Unclear BFT: up to 4 weeks Assessment point (s): 6 months Follow-up period: None Outcome Measures: Treatment success	Treatment outcome -Full remission: BFT+CT (n=14): 2 (14%) CT (n=15): 2 (13%) 95% CI on difference, −24% to 26% -Improved: BFT+CT (n=14): 2 (14%) CT (n=15): 4 (27%) p = 0.7; 95%CI on difference, −46% to 23% (for remission and improvement combined) -No improvement: BFT+CT (n=14): 10 (71%) CT (n=15): 9 (60%) 3/14 patients in the BFT group completed the training in 3 sessions, and the remainder underwent 4 sessions. Only 1	Additional information from study: Originally, it was planned to recruit 25 subjects into each group, which would mean that, at the alfa = 0.05 level (one tailed), there would be 80% power to detect at least a 38% point advantage of biofeedback (32% against 70% or better) in the comparison group. An interim analysis conducted when it became clear that successful and sustained biofeedback outcomes were not occurring. A revised sample size calculation was based on argument that if no successful outcomes were to be achieved in 15 subjects randomised to biofeedback, there would be a 95% confidence that the true rate of successful outcome could not be greater than 18%. The precision of the final result was expressed in the confidence interval (CI) around the difference in remission rates Procedure to determine whether anismus was present involved the use of a balloon filled with 50 ml warm water. After a tuition period to explain what was required to achieve correct straining and squeezing, patient asked to make 5 alternating attempts each to squeeze and strain. Normal strain response defined as a persistent decrease in external anal sphincter activity (measured by a decrease in amplitude of the electromyographic recording and an increase in rectal pressure of at least 50 mm Hg) in at least 3 of 5 attempts. A persistent increase in external anal

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		anismus on EMG during anorectal manometry Exclusion criteria: known structural congenital or postoperative anatomical defect (such as spina bifida or anorectal malformation), or Hirschsprung's disease (excluded by rectal biopsy only if clinically indicated)		Comparison: Conventional medical treatment alone (CT) -Laxative therapy in 2 phases: 1. Initial disimpaction phase: 3-day cycles of 5 mL 'Microlax' enemas (sodium citrate) on day 1, one 5 mg bisacodyl tablet after school and 1 in evening of day 2. Up to 4 cycles (12 days) undertaken. Further cycles prescribed if later evidence of stool reaccumulation 2. Maintenance phase: liquid paraffin 5 to 30 ml once or twice a day, senna granules and or bisacodyl tablets. Medication use decreased to a level consistent with		patient was unable to demonstrate relaxation of the external anal sphincter with attempted defecation. Only 1 patient (same one) was unable to defecate the biofeedback balloon by the time of their final session. All complied well with instructions and procedures involved in the training. 2 complained of transient discomfort when the biofeedback apparatus was inserted. No other adverse effects seen or reported	sphincter activity with a corresponding increase in rectal pressure in at least four of five attempts were deemed as indicating anismus Randomisation carried out using a stratified, blocked schedule, with subjects stratified on the basis of whether they were soiling or were in laxative dependent remission. Each treatment allocation was recorded on a card in an opaque numbered and sealed envelope and stored sequentially. An individual not connected with the clinic or the study carried out the randomisation plan Full remission defined as no medication and no soiling for at least 4 weeks; full remission on medication was defined as on medication and no soiling for at least 4 weeks; partial remission defined as soiling no more than once a week, regardless of medication used. The use of medication was attempted by all those not in full remission, not only those who were worse or not improved. The remainder were those who were soiling more than once a week, regardless of medication use. Improvement defined as progression by at least one level from baseline status, but without achieving full remission Presence or absence of continued soiling ascertained on the basis of parental report, assisted by daily diary

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				maintenance of continence as monitored by bowel diary -Standard paediatric behaviour modification: clarification during joint parent-child interview of the postulates underlying physiological basis for encopresis. Bowel training programme used positive reinforcement for successful defection in toilet and additional reinforcement for each 24h without soiling. Reinforcement consisted of parental praise and use of start-chart diary (fitness training card) to indicate soiling-free days. Regular sitting programme of 5 to 10 minutes			record. Patient data recorded prospectively in a relational database was also used for appointment scheduling and data quality control At baseline there were slightly more subjects with primary encopresis in the biofeedback group than in the control group <u>Reviewer comments:</u> No definition of constipation given Small sample size Unclear how the use of medication was measured No dropouts/lost to follow up reported Results not controlled for potential confounders <u>Source of funding:</u> grants from the National Health and Medical Research Council (grant 910621) and the Royal Children's Hospital Research Foundation

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				toilet-time within 30 minutes of each meal was basis of the programme. -Dietary advice, general counselling and support provided by paediatrician. Psychiatric assessment or treatment initiated when indicated clinically			

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Borowitz et al. Treatment of childhood encopresis: A randomized trial comparing three treatment protocols. 2002. Journal of Pediatric Gastroenterology and Nutrition 34[4], 378-384United States.	Study Type: Parallel-RCT Evidence level: 1+ Study aim: To compare short- and long-term effectiveness of three additive treatment protocols in children experiencing chronic encopresis	87 children Inclusion criteria: Children aged between 5 and 15 years of age who had experienced encopresis for a minimum of 6 months, defined as at least weekly episodes of faecal soiling for at least 6 months Exclusion criteria: any chronic underlying medical conditions or developmental disabilities	87 children 72 boys Mean age at time of enrollment: 8.6 ± 2.0 years (range, 5 to 13 years) Country: USA	Intervention: Intensive medical therapy (IMT) 1 of 2 paediatric gastroenterologists directed treatment: colonic disimpaction with a series of enemas followed by sufficient laxative therapy to produce at least 1 soft stool each day without associated pain. Laxatives prescribed: Milk of Magnesia and/or senna (Senokot, Ex-Lax, or Fletcher Castoria). Laxative dosages adjusted regularly to produce 1 to 3 soft bowel movements daily. An enema or suppository administered if child had not produced a bowel movement during a 48-hour period. No specific dietary recommendations	Duration of treatment Unclear Assessment point (s) and follow-up period When subjects had been enrolled in the study, data concerning toileting habits were collected for 14 consecutive days before and after the initial outpatient visit, and again at 3 months, 6 months, and 12 months after initiation of therapy Outcome Measures: -soling frequency -improvement rate -cure rate -number of	Soling frequency(mean, SD) -at 3 months: IMT: 0.54 (0.68) ETT: 0.22 (0.21) BF: 0.34 (0.51) -at 6 months: IMT:0.44 (0.52) ETT: 0.38 (0.45) BF:0.20 (0.26) -at 12 months: IMT:0.33 (0.48) ETT: 0.36 (0.53; 95% confidence interval, 0.05 to 0.47) BF:0.27 (0.37) NS among the 3 groups at any time Improvement rate (% children) -at 2 weeks: IMT: 41 ETT: 48 BF: 62 NS between 3 groups	Additional information from study: Using a random number generator, blocks of six consecutive children were randomly assigned to one of 3 treatment groups All data were collected using the Automated Patient Symptom Monitor system, a computerized voice-mail system that telephones the families each day. With each telephone call, the computer asked parents the same 8 pre-recorded questions relating to bowel habits during the previous 24 hours. After parents had answered all questions, the computer checked responses to ensure all items were answered and that responses were within acceptable ranges. If the computer detected an error, the questionnaire was repeated No significant differences in baseline clinical or demographics characteristics between the 3 groups Treatment considered successful if the child experienced no episodes of faecal soiling during the 2-week assessment 12 months after initiation of therapy Reviewer comments: No definition of constipation given No sample size calculation performed Method of allocation concealment not reported

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				or manipulations undertaken. Families received specific instructions and written brochure detailing treatment protocol and need for children to attend the toilet at least twice dally, preferably after breakfast and supper <u>Comparison 1</u>: Intensive medical therapy + enhanced toilet training (ETT) Similar enema and laxative therapy, with 1 clinical psychologist adjusting laxative dose. Only difference from previous therapy was that laxative therapy was decreased gradually when children demonstrated stable bowel	bowel movements passed in the toilet each day -self-initiated toileting each day -laxative use	-at 3 months: IMT: 45 ETT: 85 BF: 61 -at 6 months: IMT: 41 ETT: 74 BF: 58 -at 12 months: IMT: 41 ETT: 78 BF: 61 At 3 months, 6 months, and 12 months, the number of children who responded in the ETT group was significantly greater than in either the IMT or the BF group ($P < 0.05$), and these results were very stable over time ($P < 0.001$). With all 3 regimens, response to treatment during the first 2 weeks of	No drop outs/lost to follow up children reported <u>Source of funding:</u> supported by National Institutes of Health grant RO1 HD 28160

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				frequency with no soiling episodes. As long as child had daily bowel movements of normal size for a week, laxative dose was decrease by one quarter. This process was continued until laxative therapy was discontinued. If child did not pass daily bowel movements of normal size, laxative dose was increased. Parents and child instructed on the psychophysiology of constipation and encopresis, and how responding to early rectal distention cues along with regular toileting was critical to avoid reimpaction and to establish regular bowel habits. Various incentive programs		therapy strongly correlated with response to treatment at 3, 6, and 12 months ($r > 0.90$, $P < 0.0001$ in all cases). Of those children who had significant improvement after 2 weeks of therapy, 86 continued to improve at 3 months, 83 at 6 months, and 81 at 12 months <u>Cure rate (number of children cured)</u> -at 12 months: IMT: 10/29 (34.5%) ETT: 12/27 (44.4%) BF: 11/31 (35.5%) chisquare=0.9488 p=0.7005 <u>Number of bowel movements passed in the toilet each day (mean, SD)</u> -at 3 months: IMT:1.44 (0.57) ETT: 1.21 (0.49)	

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				established, depending on the developmental age and the motivation of the child. Target behaviours: spontaneous trips to the toilet and clean pants. Toilet training was "enhanced" because instructions were given on the role of paradoxic constriction of the external anal sphincter, and because appropriate defecation straining was modeled. The therapist sat on a portable toilet and demonstrated how to relax the legs and feet, how to take in a deep breath and hold it while sitting up straight, and how to push down with the held breath and pull in from the lower abdomen (rectus		BF: 1.25 (0.64) -at 6 months: IMT:1.36 (0.61) ETT:1.31 (0.63) BF:1.12 (0.60) -at 12 months: IMT:1.30 (0.61) ETT:1.01 (0.51) BF:1.16 (0.67) NS among the 3 groups at any time <u>Self-initiated toileting each day (times/day, mean, SD)</u> -at 3 months: IMT: 1.53 (0.77) ETT: 1.62 (0.82) BF:1.40 (0.71) -at 6 months: IMT:1.49 (0.60) ETT:1.67 (0.95) BF:1.34 (0.72) -at 12 months:	

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				abdominous muscle) to propel out a stool. The child then replicated this while sitting on a portable toilet. The child received “hand feedback” by placing one hand on the abdomen just below the navel to feel the abdomen move out when the breath was pushed down, and placing the second hand just below the first to feel inward movement with contraction of the rectus abdominous. Parents instructed to prompt these behaviours at home. Additionally, 8 to 12 minutes of “toilet time” was scheduled daily, beginning 15 to 30 minutes after the same two meals.		IMT:1.40 (0.76) ETT:1.31 (0.83) BF:1.31 (0.69) NS among the 3 groups at any time <u>Laxative use (number of children using)</u> -at 12 months: IMT: 17/29 (58.6%) ETT: 9/27 (33.3%) BF: 17/31 (54.8%) (chi-square= 4.1414, P= 0.1261)	

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				During these times, children were instructed to practice tensing and relaxing the external anal sphincter for the first 4 minutes, with the objective of localizing control of and fatiguing the external anal sphincter, and to mechanically stimulate the rectum. To desensitize children to toilet sitting, the second 4 minutes were spent “having fun” while being read to or playing games. During the final 4 minutes, the child was to strain and attempt to have a bowel movement while relaxing his or her legs and feet. This routine toilet sitting was discontinued 2 weeks after the last scheduled treatment session			

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				<u>Comparison 2:</u> Intensive medical therapy + enhanced toilet training + anal sphincter biofeedback (BF) Same instructions that previous 2 groups and simultaneously received surface electromyographic biofeedback training. Same 2 psychologists who worked with the ETT group also worked with the BF group			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Sunic-Omejc et al. Efficiency of biofeedback therapy for chronic constipation in children. 2002. Collegium Antropologicum 26 Suppl, 93-101	Study Type: Parallel-RCT Evidence level: 1+ Study aim: To asses the success of biofeedback method vs. conventional method in the treatment of chronic constipation in childhood over a 12-week period and to follow-up the effect of biofeedback treatment on defecation dynamics and other anorectal manometric parameters	49 children Inclusion criteria: Children aged >5 years who met at least 2 of the following criteria fro chronic constipation: defecation frequency < 3 times/week, ≥ 2 episodes of soiling and/or encopresis /week, periodic evacuation of large volume stools at least once every 7 to 30 days and palpable abdominal or faecal mass Exclusion criteria: Hirschsprung's disease, spina bifida, hypothyroidism, metabolic or renal disorders,	49 children 27 male Mean age (CON): 94 ± 33 months Mean age (BFB): 92 ± 35 months Country: Croatia	Intervention: Conventional treatment (CON) Per oral administration of Portalak (lactulosis, 240 mg/day or 10 mL syrup) with dose titration for the patient to have at least 3 stools/week. When spontaneous defecation failed to occur for > 3 days in spite of appropriate therapy an enema was used. In addition a fibre-rich diet and attempting defecation after meal were advised Comparison: Conventional treatment (CON, as previous) + Biofeedback (BFB) Pressure technique.	Duration of treatment 12 weeks Assessment point (s): At 12 weeks Follow-up period: None Outcome Measures: Therapeutic success	Therapeutic success (number of children cured) -CON: 15/24 (62.5%) -BFB: 21/25 (84%) P<0.05	Additional information from study: Treatment considered successful if a frequency of ≥ 3 stools /week and < 2 episodes of soling or encopresis per month were achieved without laxatives Therapeutic success evaluated by use of questionnaires distributed on weekly visits No significant differences in baseline characteristics between 2 groups All children completed treatment Reviewer comments: Small sample size, no sample size calculation Randomisation and allocation concealment methods not described Insufficient details on who measured outcomes and how Results not controlled for potential confounders Source of funding: Not stated

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		mental retardation, taking drugs for		Child and parents instructed on how to perform Kegel exercises at home. Exercises include alternating 10-second contraction and relaxation of sphincter and pubo-rectal muscle, performed 5 times a day in 20 cycles			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Loening-Baucke. Biofeedback treatment for chronic constipation and encopresis in childhood: long-term outcome. 1995. Pediatrics 96[1 Pt 1], 105-110	Study Type: Retrospective cohort Evidence level: 2+ Study aim: To evaluate if patients who received biofeedback treatment (BF) continued with improved outcome compared with patients who received conventional treatment alone (CT)	129 children Inclusion criteria: Children 5 to 18 years with chronic constipation and encopresis (≥1 soiling episode per week) Exclusion criteria: Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating diseases, neurologic abnormalities, previous surgery of the colon	129 children 97 boys Mean age (years): -CT group Initial: 9.1 ± 3.3 Follow-up: 13.4 ± 3.3 -BF group Initial: 10.4 ± 3.2 Follow-up: 14.5 ± 3.3 Country: USA	Intervention: Conventional treatment (CT) + biofeedback (BF) At least 2 and up to 6 weekly training sessions given. 1 session included approximately 30 to 35 defecation trials and lasted approximately 45 to 60 minutes. Number of training sessions given depended on how soon child learned to relax external sphincter. Sessions stopped after 10 relaxations of the external sphincter without visual feedback could be accomplished in each of 2 successive training sessions Comparison: Conventional treatment alone (CT) CT: use of	Duration of treatment BF: between 2 and 6 weeks CT: unclear Follow-up period: -CT group: 4.2 ± 2.5 years -BF group: 4.1 ± 2.4 years Outcome Measures: -stool frequency -presence of soiling -soiling frequency -recovery rate -laxative use	Stool frequency/week (mean ± SD) BF (n=63): 5 ± 3 CT (n=66): 6 ± 3 N.S % of children soiling BF (n=63): 35 CT (n=66): 24 N.S Soiling frequency/week (mean ± SD) BF (n=63):1 ± 2 CT (n=66):1 ± 2 N.S Recovery rate (number of children, %) BF (n=63): 28 (44) CT (n=66): 41 (62) N.S Laxative use (% children using laxatives) BF (n=63): 25 CT (n=66): 18 N.S	Additional information from study: Parents and children instructed to keep diary of bowel movements, faecal soiling and medication used Of 64 patients who originally received biofeedback 1 patient did not return after the first unsuccessful biofeedback session and was lost to follow-up. The 63 patients included in the biofeedback group were combined from 2 studies (clinical characteristics of both groups were similar): 21 patients from an RCT (included already in this review, see Loening-Baucke, 1990) and 42 patients who had not recovered after at least 6 months of conventional treatment. Patients were charged for this service. Because of cost, inability to return for weekly biofeedback training or parent's and children's satisfaction with the marked improvement of constipation and encopresis with conventional treatment these patients chose to continue with conventional treatment. 23 patients have been originally included in the RCT but 1 boy was lost to follow-up after the first biofeedback session and a second patient received a central nervous system shunt during the follow-up period and was exclude from analysis In May 1993 parents requested by email to fill out with the help of their children a structured questionnaire eliciting information on the presence of soiling and frequency and amount of soiling per

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				laxatives, increase of dietary fibre and scheduled toileting (child instructed to defecate fro 5 minutes after each meal and after returning from school for the initial months, and try to defecate at least daily once they could recognise the urge to defecate Disimpaction with enemas (type and dose not reported) Maintenance: milk of magnesia ~ 2ml/kg body weight daily to induce at least 1 bowel movement daily and prevent faecal retention. Doses decreased gradually to maintain daily bowel movement and prevent faecal retention and soiling.			week, the frequency and size of bowel movements per week and the use of laxatives. In December 1993 questionnaires again were mailed to non responders and to those families evaluated between January and May 1993. non responders were contacted by telephone Patients considered to have recovered if they had ≥3 bowel movements/week and soiling ≤ 2 episodes/month while off laxatives for at least 1 month. Patients considered not to have recovered if they had <3 bowel movements/week or were soiling >2 times/month or had been started on a regime of laxatives again Baseline characteristics were comparable between both groups except for the presence of an abdominal faecal mass (number of children, BF: 60 vs. CT: 41; $p<0.05$) Age and follow-up age were not related to outcome in either group. The length of follow-up was significantly related to recovery for the biofeedback group ($p<0.02$) and for all patients ($p<0.01$) but showed no relationship for the conventionally treated group <u>Reviewer comments:</u> No clear definition of constipation given <u>Source of funding:</u> Supported by grant No. M01-RR-00059 from the General Clinical Research

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				Occasionally mineral oil or senna used instead of milk of magnesia			Centre Program,, Division of Research Resources, National Institute of Health; the Children's Miracle Network Telethon and the Spelman-Rockefeller Child and Parenting Seed Grant

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van Dijk et al. Behavioral therapy for childhood constipation: a randomized, controlled trial. 2008. Pediatrics 121[5], e1334-e1341	Study Type: Parallel-RCT Evidence level: 1+ Study aim: To evaluate the clinical effectiveness of behavioural therapy with laxatives compared with conventional treatment in treating functional constipation in childhood	134 children Inclusion criteria: Children with functional constipation aged 4 to 18 years referred to the gastrointestinal outpatient clinic at the Emma Children's Hospital between 11/ 2002 and August 2004 Exclusion criteria: Having received a comprehensive BT in the previous 12 months, use of drugs influencing gastrointestinal function other than laxatives, organic causes for defecation disorders, e.g	134 children 76 boys age range: 4 to 18 years -mean age: CT group: 6.5 (2.1) BT group: 6.9 (2.5) Country: The Netherlands	General: -Disimpaction: daily Klyx enemas (sodium-dioctylsulfosuccinate and sorbitol; 60 mL/day for children ≤ 6 years of age; 120 mL/day for children > 6 years of age) for 3 consecutive days was prescribed by paediatric gastroenterologists before starting treatment -Maintenance: polyethylene glycol 3350, 1 sachet (10 g) per day, and if treatment considered to have insufficient effect dose increased by 1 sachet. If spontaneous defecation delayed for >3 days, parents advised to give an enema or bisacodyl suppository of 5	Intervention period: For both CT and BT 12 visits during 22 weeks with similar intervals between treatment sessions Assessment point (s) & follow-up period: At the last visit (posttreatment time point) and 6 months after the 22-week treatment ended (follow-up). Time between baseline assessment and follow-up: ~1 year Outcome Measures: -Primary outcomes a. defecation frequency	IRR: incidence rate ratio RR: relative risk CT (n=67) BT (n=67) Defecation frequency per week, mean (95% CI) -Post-treatment CT: 7.2 (6.1 to 8.5) BT: 5.4 (4.3 to 6.7) -Follow-up CT: 6.6 (5.0 to 8.8) BT: 5.3 (4.4–6.3) *Group (main effect of BT):* IRR=0.75 (0.59 to 0.96) p=0.021 *Group x time (interaction effect of BT with measurement at follow up):* IRR= 1.06 (0.75 to 1.50) p=0.758 Faecal incontinence per week, mean (95% CI)	Additional information from study: At entry, patients had to meet at least 2 of 4 criteria: defecation frequency< 3 times per week, faecal incontinence ≥ 2 times per week, passage of large amounts of stool at least once every 7 to 30 days (large enough to clog the toilet), or a palpable abdominal or rectal faecal mass After baseline measurement and if written informed consent was given, a research assistant performed a telephone call to a randomization centre and revealed the allocation to parents immediately. A computer-based system used to generate a sequence of random group assignment for consecutive patients. Random assignment stratified by age (4 to 8 years or ≥8 years) and gender. Within 2 weeks after random assignment, patients received their 1rst treatment session Sample size calculated to allow detection of a 25% difference in the proportion of success between BT and CT. It was estimated that CT reached success in 35% of the children at follow-up. Under the additional assumption of a significance level of .05, a power of .80, and 2-sided hypothesis testing, a minimal sample size of 124 with 62 children in each group was determined During treatment 2 (3.1%) of 64 in the CT group and 9 (13.8%) of 65 in the BT group discontinued intervention

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		Hirschsprung's disease, spina bifida occulta, hypothyroidism, or other metabolic or renal abnormalities		mg. In BT preferred to give oral bisacodyl tablets of 5 mg instead of rectal laxatives. During BT, paediatric psychologists adjusted laxative dose and consulted paediatric gastroenterologist when necessary. In both treatment groups, patients kept a bowel diary <u>Intervention:</u> Protocolised behavioural therapy (BT) -developed by paediatric psychologists of the psychosocial department of our hospital. Basic assumption that phobic reactions related to defecation can be reduced and that adequate toileting behaviour and appropriate defecation	per week b. faecal incontinence frequency per week c. successful treatment -Secondary outcomes: a. stool withholding behaviour	-Post-treatment CT: 2.1 (0.8 to 5.8) BT: 5.0 (2.1 to 12.0) -Follow-up CT: 6.4 (3.5 to 11.7) BT: 8.6 (4.0 to 18.3) *Group (main effect of BT):* IRR=2.36 (0.77 to 7.31) p=0.135 *Group x time (interaction effect of BT with measurement at follow up):* IRR= 0.57 (0.12 to 2.61) p=0.467 <u>Success, % (95% CI)</u> -Post-treatment CT: 62.3 (51.1 to 76.1) BT: 51.5 (39.7 to 66.9) RR= 0.83 (0.60 to 1.14) p=0.249 -Follow-up CT: 57.3 (46.6 to 70.4) BT: 42.3 (31.8 to 56.4)	(P=0.054). At follow-up, 4 patients dropped out in CT. There was 1 loss of contact, and 3 children were referred for BT directly after CT, making them unsuitable for follow-up measurements. Questionnaires were not returned by 3 patients in both intervention arms at posttreatment and by 9 patients (CT: 6; BT: 3) at follow-up Except for painful defecation (65.0% CT vs. 43.1% BT, P=0 .014), no significant differences between the 2 groups in baseline sociodemographic factors or for clinical characteristics Intent-to-treat analyses conducted. Because of withdrawal before treatment start, dropouts during the study, failure to fill out questionnaires, or research procedure violations, missing data occurred. Imputation of missing values used to make intent-to-treat analyses feasible Treatment considered successful if patients achieved a defecation frequency of ≥3 times per week and a faecal incontinence frequency of ≤1 times per 2 weeks, irrespective of laxative use <u>Reviewer comments:</u> Insufficient details on how outcomes were measured Results controlled for confounders

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				straining can be (re)acquired by teaching parents behavioural procedures and by behavioural play therapy with the child in presence of his or her parents. The protocol consists of 2 age-related modules: a module for children aged 4 to 8 years and a module for children aged ≥8 years. Learning process for child and parents: 5 sequential steps (know, dare can, will, and do). This approach is derived from a multidisciplinary BT to treat children with defecation disorders. For all involved psychologists, a detailed manual for both age-related modules available to ensure a standard		RR= 0.74 (0.52 to 1.05) p=0.095 <u>Stool withholding behaviour at follow-up (% children with behaviour)</u> CT: 13.8 BT: 10.6 NS	<u>Source of funding:</u> funded in part by the Dutch Digestive Disease Foundation (SWO 02-16)

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				delivery of therapy. Visits lasted ~45 minutes <u>Comparison</u>: Conventional treatment (CT) -conducted by paediatric gastroenterologists, visits lasted ~20 to 30 minutes, laxative treatment and bowel diary discussed. Patients and their parents received education to explain that symptoms are not harmful and are common in children with functional constipation and that a positive, non-accusatory approach is essential. Children instructed not to withhold stool when they feel urge to defecate. Motivation enhanced by			

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				praise and small gifts from the paediatric gastroenterologists			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Ritterband et al. An Internet intervention as adjunctive therapy for pediatric encopresis. 2003. Journal of Consulting and Clinical Psychology 71[5], 910-917	Study Type: Parallel-RCT (multicentre) Evidence level: 1+ Study aim: To examine the utility and effectiveness of an Internet-based version of enhanced toilet training	24 children Inclusion /exclusion criteria: Children aged between 6 and 12 years, soling at least once a week and have no medical diagnosis other than constipation that could explain their faecal incontinence	24 children 19 boys mean age: 8.46 years (SD1.81) -Web group: 12 children (10 boys) -No-Web group: 12 children (9 boys) Country: USA	Intervention: Laxatives + Web intervention Comparison: Laxatives only Laxatives: all children instructed to start with a basic regime of one square of Ex-Lax (senna), twice a day -The Web site: Web-based program for the treatment of paediatric encopresis (U-CAN-POOP-TOO Child-focused programme, targets primarily 5 to 10 years old children but was designed to be used by child and parent (s) together 3 core modules take 60 to 90 minutes to complete, all users instructed to	Duration of intervention: 3 weeks Assessment point (s): 3 weeks after initial home visit Follow-up period: None Outcome Measures: -number of faecal accidents per week -number of bowel movements (BM) passed in the toilet per week - bathroom use without prompts -bathroom use with prompts -internet use (most/least useful aspect of the programme; preference questions	**Percentage change from pre- to post-assessment** Number of faecal accidents per week (mean, SD) -Web group: 0.50 (.85) -No-Web group: 8.27 (13.83) Number of bowel movements (BM) passed in the toilet per week -Web group: +152% -No-Web group: -16% p=0.001 Bathroom use without prompts -Web group: +109% -No-Web group: -37% p=0.021 Bathroom use with prompts -Web group: +47% -No-Web group: -45% NS Internet use (Web	Additional information from study: Computer and internet access provided to all families who contacted the research centre and met the inclusion criteria Participants received a $25 gift certificate to a local toy sore for completing the pre-treatment assessment and another $25 gift certificate for completing the post-treatment assessment Information regarding BM assessed by parent report on the Child Information Form. Question regarding child's bowel habits included such as number of BMs in toilet and use of toilet with / without parental prompts. Questions regarding use of internet programme also included in post-treatment form for the intervention group. The Virginia Encopresis/Constipation Apperception Test (VECAT) also administered. It assesses bowel specific problems related to the process of encopresis, such as avoidance of the toilet, non responsiveness to rectal distension cues and fear of defecation pain. A generic subscale included as a comparison measure, addresses problem behaviours not related to bowel issues. The VECAT consists of 18 pairs of drawings (9 pairs bowel-specific and 9 parallel generic events) and child selects the picture in each pair that best describes him/herself

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				review them during the first week: 1. The body (anatomy, physiology and pathophysiology of digestion) 2. How to poop (behavioural techniques for treatment of encopresis) 3. Medication (clean-out and laxative treatment) New modules assigned each week based on a follow-up assessment the user completes about their child's status. Not all modules necessarily used by all users, only those modules identified as relevant are assigned and reviewed. However all modules can be viewed by all users. Follow-up	regarding individual cores an modules)	<u>group only)</u> 1. Most useful aspect of the programme: -the step by step program to get the child regulated -understanding why his body does what it needs to do everyday-and what happens when he doesn't have a BM and health consequences…information was tremendously useful -developing a feeling that he can control his own body -realising that he's not the only child with this problem…that was reassuring 2. Least useful aspect of the programme -difficulty with connections -modules regarding fear of toilet and "monsters" -art work of the body did not print out -Miralax should have been included (as a choice of laxative)	No significant differences in baseline characteristics between the 2 groups (age, gender, race, stage of bowel movement training, length of current laxative regime or any of the outcomes measured) CM1: anatomy and pathophisiology CM2: medication (enemas/laxatives) CM3: behavioural intervention <u>Reviewer comments:</u> No definition of constipation / soling given Small sample size, no sample size calculation Randomisation and allocation concealment method not described No dropouts/lost to follow up reported Results not controlled for potential confounders <u>Source of funding:</u> National Institutes of Health Grant RO1 HD28160

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				comprised of 17 to 20 questions, depending on the week. System contains a total o 22 modules, each takes 5 to 10 minutes to review		-nutrition portion was too limited <u>Internet experience: parents' views / satisfaction</u> -found material understandable (mean 5.00, SD 0.00, N = 20) -found it easy to use (mean 4.62, SD 0.74, N = 21) -believed their child liked the program (mean 4.05, SD 1.28, N = 21) - believed their child found it understandable (mean 4.32, SD 0.89, N = 19) - believed their child found it easy to use (mean 4.47, SD 0.77, N = 19) 3. Preference regarding cores modules (CM) (mean,	

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						SD) (score 0 to 4) a. How useful: CM1: 3.84 (0.38) CM2: 3.94 (0.24) CM3: 4.00 (0.00) b. How well did you understand the material CM1: 3.89 (0.32) CM2: 3.89 (0.32) CM3: 3.92 (0.28) c. how well did your child understand the material CM1: 3.53 (0.61) CM2: 3.28 (1.07) CM3: 3.54 (1.13) d. How much did you enjoy using the module CM1: 3.68 (0.48) CM2: 3.67 (0.49) CM3: 3.69 (0.48) e. How much did your child enjoy using the module CM1: 3.63 (0.76) CM2: 3.61 (0.98) CM3: 3.46 (1.13)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Taitz et al. Factors associated with outcome in management of defecation disorders. 1986. Archives of Disease in Childhood 61[5], 472-477	Study Type: Quasi-RCT Evidence level: 1+ Study aim: To report our experience with children who presented with faecal soiling, with or without constipation, who were treated by incentive based behavioural modification, plus or minus psychotherapy, and consider factors that might predict the outcome for a non-intensive approach and in particular, to draw attention to social background	47 children Inclusion criteria: children who presented with faecal soiling, with or without constipation Exclusion criteria: identified organic bowel disease or neurological handicaps	47 children 26 boys age not reported Country: UK	General In cases where constipation was severe with large faecal masses children initially admitted to the ward for defecation was made impossible by severe impaction. They were then continued on whatever laxative they had been on before referral. Where no laxative had previously been used the child was offered a twice daily dose of lactulose. If no accumulation of faeces no laxatives prescribed. No other laxatives used in this study, and in general their use was minimised, with the parents encouraged to stop the treatment with laxatives as	Duration of treatment -BhM: 6 weekly intervals for between 3 months and 1 year Assessment point (s): 1 year after initiating treatment Follow-up period: None Outcome Measures: Treatment success	Treatment success did not differed between both groups. It is not possible to report the figures here, as they were only analysed by the authors according to compliance with treatment and with children social class, but not according to treatment groups	Additional information from study: One year after the beginning of treatment parents sent a postal questionnaire, which sought to elicit the response to treatment. This survey included all patients who 'dropped out' of this study at any stage. They were asked whether they considered the child cured, improved, or unchanged and asked how often the child defecated; whether and how often soiling occurred; and whether and how often laxatives were needed. These answers were made as objective as possible by requesting parents to place ticks in appropriate boxes. This response was then graded into three categories-cured, improved, and no response, on the basis of the parents' answers to the questionnaire, compared with the clinical assessment before allocation to treatment groups. Assessment of results were thus made by the parents at home and not by the professionals involved Criteria for the classification of the results of treatment: (1) Cured. At least 5 normal stools each week without soiling. Only occasional use of laxatives (less than once a week) (2) Improved. At least three stools each week and soiling less than once a week (3) Non-responders. Less than three stools each week or soiling more than once a week. These children were considered as failing to improve, despite the fact that in most cases there was less soiling than at the beginning of

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
	as a prognostic indicator			soon as a regular bowel habit established. In none of the children were suppositories used at any time. All the children were encouraged to take a high residue diet and in particular were asked to take bran with their breakfast cereal <u>Intervention:</u> Behaviour modification (BhM) Carried out by paediatrician. All children placed on a star chart regimen. Children offered varying coloured stars for 'sitting on the toilet' and 'remaining unsoiled for a full day'. In some cases stars awarded to encourage			treatment 4 children dropped out from the study and 13 failed to keep adequate 'star charts'. The 'drop outs' occurred at 1, 2, 3, and 4 months. 2 children were subsequently found to be cured <u>Reviewer comments:</u> No definition of constipation given Small sample size, no sample size calculation Baseline characteristics not compared Randomisation and allocation concealment methods not reported ITT analysis not performed <u>Source of funding:</u> Grants from the Hawley Trust, National Health Service Locally Organised Research Grant (Trent RHA) and CHRIS Fund, Children's Hospital

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				children who were reluctant to take bran in their diet. Contract negotiated between child and parent (usually father) for an award to be made at the discretion of the paediatrician. Child was to understand that the giving of the award would depend on response to treatment. 'Demystification', alleviation of guilt, and use of explanatory diagrams generally followed the lines recommended by Levine and Bakow. Children seen at 6 weekly intervals by paediatrician for between 3 months and 1 year and subjected to shows of affection and interest,			

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				which included careful and serious inspection of the charts. Failure to keep a star chart on 2 successive visits resulted in firm statement of displeasure. 2 further failures at 6 week intervals led to the stopping of treatment and discharge with the option of psychiatric referral. Discharge of cured patients was at discretion of the parents <u>Comparison</u>: Behaviour modification (as previous) + psychotherapy (BhM +Psy) -Psychotherapy: children seen by the child psychiatrist at roughly monthly intervals for periods between			

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				two and 12 months. Treatment was organised along the following lines: (1) At each appointment mother (and also father in 4 cases) seen for 15-30 minutes to explore her feelings in respect of the child's bowel problem and its effect on the family and her own relationship with the child. Whenever possible mother's own history explored and other emotional problems discussed where relevant e.g. expressions of grief, anger, depression, etc. (2) Child seen for between 15-30 minutes for play, including picture drawing, games, and sharing of their own toys and belongings. Their			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				feelings concerning their problem also explored. Behavioural star chart also often brought, and reviewed and child praised and encouraged according to progress (3) Mother and child seen together sometimes early in treatment, sometimes later, depending on their relationship and success with management of the problems to assess to overall progress			

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Silver et al. Family therapy and soiling: An audit of externalizing and other approaches. 1998. Journal of Family Therapy 20[4], 413-422	Study Type: Retrospective audit Evidence level: 3 Study aim: To asses the effectiveness of Externalizing Treatment EXT) as compared to traditional treatments in children with soiling problems	108 children and their families Inclusion criteria: Children treated for soiling problems. Referrals included 'faecal soiling', 'encopresis', 'psychological soiling', 'failed toileting', 'constipation with overflow' and 'deliberate soiling'. Exclusion criteria: Families who failed to attend or cancelled their first appointment, the problem had been resolved, the children were put into care or sent to	108 children 3 to 5 years: 45 >6 years: 63 mean age (years): -EXT: 6.98 -OTH: 6.68 Country: UK	Intervention: *Externalizing Treatment (EXT)* Families were only included if the approach included: 1 Externalizing the poo from the first interview with the child and family (based on White, 1984 and White and Epston, 1990) 2 Developing a narrative with the child and family where they could see themselves as capable, skilful and determined to teach the poo a lesson, outwit the poo or defeat the poo 3 Not using rewards, interpretation, confrontation or paradoxical interventions as therapeutic manoeuvres.	Duration of treatment (mean, months) -EXT: 7.8 -OTH: 6.6 Assessment point (s) & follow-up period At a minimum of 6 months (mean 28 months) after treatment Ended Outcome Measures: -Parent assessment of usefulness of treatment -Soiling presence /frequency (parents' assessment /GP assessment /paediatric notes -Number of appointments	EXT (n=54) OTH (n=54) Not all children assessed for all outcomes Parent assessment of treatment (number of parents) -EXT: Helpful: 24 Unhelpful: 5 -OTH: Helpful: 10 Unhelpful: 20 p = 0.0001 End of treatment outcome (from notes) -EXT: No soiling/improved: 42 Soiling: 5 -OTH: No soiling/improved: 30 Soiling: 13 p = 0.02 GP follow-up -EXT: No soiling: 29 Soiling: 8	Additional information from study: 162 sets of notes of all referrals for soiling over a four-year period were audited Some children clearly diagnosed in the referral letter as 'constipated' or 'not constipated', but in some referral letters it was not stated whether the referring doctor had checked for constipation The treatment given depended only on the current approach of the therapist who received the referral. All the families had received either 'externalizing' or 'other treatments' No significant differences between the groups on baseline variables At a minimum of 6 months' follow-up (mean 23 months), all parents (including those who dropped out) sent a questionnaire with a letter from the secretary, explaining that we could learn a great deal from their responses, whether negative or positive, with no names being recorded. Parents asked whether there had been any further soiling incidents since they were last seen and frequency of these incidents in the past month. Parents asked whether they had found their treatment helpful or unhelpful and what was helpful or unhelpful and to offer other comments. Where children had returned for paediatric consultation, frequency of soiling stated in paediatric

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		boarding school very early in treatment or the soiling had a medical cause (Hirschsprung's disease). Children who had full control, but would insist on a nappy for a bowel movement. 3 more families where a therapist who usually used externalizing switched to a behavioural approach in a systems context in the belief that externalizing would not work. Within the remaining families in the audit there was no known selection for a		4 Attempting to see the whole family at least once. <u>Comparison</u>: *Other Treatments (OTH)* Mixed group of traditional treatments with predominantly (but not only) a behavioural approach in a family systems context. There were no elements of externalizing in any OTH sessions		-OTH: No soiling: 24 Soiling: 18 p = 0.045 <u>Parent follow-up</u> -EXT: No soiling/stains: 24 Soiling: 14 -OTH: No soiling/stains: 13 Soiling: 22 p = 0.026 <u>Number of appointments (mean)</u> -EXT: 8.2 -OTH: 10 NS Externalizing proved to be superior for boys, for children aged ≥ 6 years, for those with frequent soiling at the outset, for those with over 2 years' continuous soiling and those diagnosed as constipated on referral	notes was recorded even if parents did not reply to the audit. GPs asked whether they were aware of any further soiling after treatment had ended <u>Reviewer comments:</u> No definition of constipation given Unclear exactly how many children dropped out/ were lost to follow up <u>Source of funding:</u> Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
		particular therapy					

Complementary Therapies for Ongoing Treatment/Maintenance in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Bishop et al. Reflexology in the management of encopresis and chronic constipation. 2003. Paediatric Nursing 15[3], 20-21	Study Type: Prospective case series Evidence level: 3 Study aim: To investigate the efficacy of treating patients with encopresis and chronic constipation with reflexology	50 children Inclusion criteria: Children diagnosed with encopresis / chronic constipation Exclusion criteria: Not stated	50 children age range 3 to 14 years 64% boys Country: UK	Intervention: Reflexology: 6 sessions , 30 minutes each at weekly intervals (no other details provided) Comparison: N.A	Duration of treatment 6 weeks Assessment point (s): Immediately after treatment was completed Follow-up period: No follow-up made after treatment finished Outcome Measures: -soiling frequency -frequency of bowel movements (BM) -parents' attitude towards reflexology	Soiling frequency (n=48) % children -Before: at least daily: 78 1 to 3 times/week: 16 no soiling/week: 6 -After: at least daily: 20 1 to 3 times/week: 30 no soiling/week: 48 p<0.05 (unclear for which comparisons) Frequency of bowel movements (BM)(n=48) % children -Before: No BM/week: 36 1 to 4 BMs/week: 46 daily BMs: 18 -After: No BM/week: 2 1 to 4 BMs/week: 72	Additional information from study: With the help of their parents, children completed questionnaires on bowel motions and soling patterns before, during and after treatment Parents completed questionnaires on their attitude towards reflexology Existing medications were unaltered 2 children only attended the first session Reviewer comments: No definition of constipation/encopresis given Questionnaire not reported as piloted Results not controlled for potential confounders Baseline outcomes for the 2 children who only attended the first session were reported but it is unclear whether they were included in the analysis Source of funding: Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						daily BMs: 24 p<0.05 (unclear for which comparisons) <u>Parents' attitude towards reflexology</u> 70% parents keen to try treatment, 72% satisfied with outcome	

Surgical Interventions for Maintenance: Effectiveness of the ACE procedure in Children with Chronic Idiopathic Constipation

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
King et al. The antegrade continence enema successfully treats idiopathic slow-transit constipation. 2005. Journal of Pediatric Surgery 40[12], 1935-1940	Study Type: Retrospective cohort Evidence level: 2+ Study aim: to determine whether ACE are successful for idiopathic paediatric slow transit constipation (STC)	56 children Inclusion criteria: patients with appendicostomy for idiopathic constipation formed between Jan/95 and Oct/04, who satisfied Rome II criteria for functional constipation, with/without faecal incontinence and had undergone a prolonged period of unsuccessful medical management Exclusion criteria: not stated	42 children 31 boys mean age at interview: 13.1 years (median 12.4; range 6.9 to 25.0) mean age at procedure: 9.1 years (median 7.8, range 3.1 to 18.5) -recurrent soiling: 29/42 (69%) -inability to adequately pass stool: 7/42 (17%) -recurrent hospital admissions for nasogatric washouts: 6/42 (14%) Country: Australia	Intervention: appendicostomy (ACE): laparoscopy or mini-laparotomy Comparison: none Enemas: -median initial regimes used: Golytely (PEG 3350 and electrolytes): 250 to 500 ml every second day, infused over 20 to 30 mins for 1 to 3 months Liquorice , 250 to 500 ml daily, infused over 10 to 20 mins infused over 10 to 20 mins for 1 to 3 months -median regime at time of interview: Golytely (PEG 3350 and electrolytes): 500	Follow-up period: Mean: 48 months (median 39, range 3 to 118) Outcome Measures: -ACE usage -ACE efficacy -ACE complications	ACE usage a. ACE regimes -median initial regimes used (% children): Golytely (79) Liquorice (12) Water (2) Other (7) -outcome (% children): Excellent (29) Good (36) Average (7) Poor (28) -median regime at time of interview: Golytely: (how many children?): Defecation occurred 20 to 30 mins after ACE finished, with 20 to 30 mins spent on toilet Majority of patients (25/42, 60%) either using the initial regime or had tried one regimen change. No correlation	Additional information from study: Independent investigator conducted confidential telephone interviews using a modified questionnaire Continence score: modified Holschneider (maximum score 12). Modification required because the criterion of “frequency of defecation” not appropriate for the cohort Quality of life score: modified Templeton and Toogood Frequency score used for all frequency measures: daily=6, 3 to 6 d/wk=5, 1 to 2 d/wk=4, 1 to 2 d/fortnight=3, 1 to 2 d/mo=2, once every 2 to 3 months=1 and never=0) Reviewer comments: Originally 56 children met the inclusion criteria, but only 42 (75% of the families) were interviewed without a clear explanation for that Source of funding: Dr. King funded by scholarships from the NHMRC (Australia) and the Royal Australian College of Surgeons

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				to 750 ml every second day, infused over 10 to 20 mins with no need for disimpaction		between numbers of ACE regimens tried, patient satisfaction or length of ACE usage. Many families believed regimes changes were a necessary response to increased tolerance to a particular ACE solution b. patient input into ACE regimen (n children) -completely independent: 7 (all older 10 years) -requiring supervision only: 5 -needing help setting up and cleaning up: 15 -completely dependent: 15 c. patients satisfaction with ACE (n children) -very satisfied or satisfied: 37 (88%) -families would recommend ACE to other children: 41 (98%	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						-families felt significant improvement in quality of child's life: 39 (93%) -mean optimal age for appendicostomy formation, as felt by families: 4.9 years (median 4, range 2 to 12) d. effectiveness -effective: 41 (98%) e. symptoms resolution (n patients) -ceased ACE: 15 (36%): in 7 symptoms resolved, in 4 a colostomy was formed, in 2 an ileostomy was formed and 2 patients returned to conservative management -successful ACE: 34 (81%) <u>ACE efficacy (mean, median and range):</u> -continence score: pre-ACE: 2.5 (2; 0 to 8)	

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						post-ACE:: 5.2 (5; 1 to 12) p<0.0001 -quality of life score: pre-ACE: 1.4 (1.5; 0.5 to 3.0) post-ACE: 2.2 (2.5; 0.5 to 3.0) p<0.0001 -soiling frequency score: pre-ACE: 5.7 (6; 0 to 6) post-ACE: 3.0 (3; 0 to 6) p<0.0001 -abdominal pain severity score: pre-ACE: 7.4 (8; 0 to 10) post-ACE: 3.0 (3; 0 to 8) p<0.0001 -abdominal pain frequency score: pre-ACE: 5 (6; 0-6 to 3-6 d/week) post-ACE: 2.5 (2.5; 0-6 to 1-2 d/month) p<0.0001 <u>ACE complications</u>: a. symptoms at some	

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						stage of treatment: Total: 30/42 (71%) cramping: 18/30 nausea: 17/30 vomiting: 7/30 sweating: 14/30 dizziness: 10/30 pallor: 10/30 (3 or more symptoms present in 12/30 patients) b. Long-term complications (n, %), N=42: -granulation tissue: 33 (79), unresolved: 15% -anxiety about ACE: 21 (50), unresolved: 29% -stomal infection: 18 (43), unresolved: 11% -stomal leakage (ACE days): 16 (38), unresolved:13% -embarrassment about device: 16 (36), unresolved: 87% -dislikes device: 12 (29), unresolved: 58% -stomal leakage (non ACE days): 12 (29), unresolved: 8% -stomal pain: 11 (26),	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						unresolved: 45% -stomal stenosis: 8 (19), unresolved: 0 -new behavioural disturbance: 7 (17), unresolved: 72% -stomal prolapse: 6 (14), unresolved: 33% -stomal bleeding: 6 (14), unresolved: 0 -limited activity: 4 (10), unresolved: 75% -weight loss: 2 (5), unresolved: 0 -perforation: 2 (5), unresolved: 0	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Cascio et al. MACE or caecostomy button for idiopathic constipation in children: a comparison of complications and outcomes. 2004. Pediatric Surgery International 20[7], 484-487	Study Type: Retrospective cohort Evidence level: 2+ Study aim: to compare the results complications and outcomes of the Malone antegrade enema (MACE) with the caecostomy button (CB) in children with intractable constipation	49 children Inclusion criteria: children who underwent MACE or CB between June 1998 and August 2002 for intractable idiopathic constipation and faecal soiling that had failed conventional treatment Exclusion criteria: not clearly stated, but all rectal biopsies were aganglionic.	49 children 15 boys -MACE: 37 children 15 boys -CB: 12 children 9 boys Country: UK	Intervention: Malone antegrade enema (MACE) Antegrade enemas started on the 4th postoperative day and Foley catheter left in appendicostomy for 6 weeks Comparison: Caecostomy button (CB) Enemas started on 4th postoperative day and MIC-KEY gastrostomy tube changed to standard gastrostomy button after 6 weeks Enemas performed by administering saline (20ml/kg) to empty the entire colon at a convenient time for patient. Children not	Follow-up period: Mean, 18 months Outcome Measures: -Soiling -Failure -Surgical complications	Soiling (n children in which stopped completely) MACE (n=37): 30 (81%) CB (12): 9 (75%) Occasional soiling still present in 1 child with MACE and 2 with CB. 1 child with CB resumed regular activity and CB was removed Failure -MACE (n=37): 6 (16.2%) 4 patients' colonic washouts ineffective. 1 patient: colonic washout associated with abdominal pain during enema. 1 patient required revision for perforation of appendicostomy and the fibrotic-ischaemic appendix was replaced with a CB -CB (12): 1 (8.3%) Reason for failure was leaking faecal content around the	Additional information from study: One patient with CB and one with MACE moved to another region and were lost to follow-up Success criteria: -full: totally clean or minor or minor rectal leakage on the night of the washout; -partial: clean, but significant stomal or rectal leakage, occasional major leak, still wearing protection but perceived by the child or parent to be an improvement -failure: regular soiling or constipation persisted , no perceived improvements, procedure abandoned usually to a colostomy Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				responding to saline wash-out used Klean-Prep. Frequency and volume of enemas individualised to each patient to achieve cleanliness and stop soiling		button, converted to MACE after 20 months P >0.05 <u>Surgical complications %):</u> a. requiring operative intervention MACE (n=37) -total: 9 (24%) -stoma stenosis: 11% -iatrogenic perforation appendicostomy: 5% -difficult catheterization: 5% -adhesive obstruction: 3% CB (n=12) -total: 0 -adhesive obstruction: 0 Others N.A P=0.009 for total b. not requiring operative intervention MACE (n=37) -total: 7 (19%) -pain/difficult catheterisation: 11% -stoma granulosa: 5% -stoma stenosis: 3% -faecal leakage: 0 -pain around button:	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						N.A CB (n=12) -total: 11 (92%) -pain/difficult catheterisation: N.A -stoma granulosa: (33%) -stoma stenosis: N.A -faecal leakage: 42% -pain around button: 92% p<0.001 for total	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Mousa et al. Cecostomy in children with defecation disorders. 2006. Digestive Diseases and Sciences 51[1], 154-160	Study Type: Retrospective cohort Evidence level: 2+ Study aim: To report authors' 4-year experience with 2 different techniques of the caecostomy procedure and to compare the clinical outcome of caecostomy in children with defection disorders secondary to functional constipation, imperforate anus and spinal abnormalities	31 children Inclusion criteria: Children who received a caecostomy fro constipation, faecal soiling or a combination of both. Underlying conditions included functional constipation, Hirschsprung's disease, imperforate anus, imperforated anus combined with tethered spinal cord syndrome and spinal abnormalities Exclusion criteria: Not stated	-total population 31 children 58% boys -9 children with functional constipation median age at time of caecostomy: 12 years old (range 3 to 16) Country: USA	Intervention: Caecostomy performed percutaneously by interventional radiologist Comparison: Caecostomy performed by open surgical approach	Duration of study period: 4 years Follow-up period: Median 11 months (range 1 to 45) after caecostomy Outcome Measures: -type of antegrade enemas used -bowel movement frequency -soiling frequency -number of medications -number of physician visits related to defecation problems -number of hospital admissions for disimpaction	(all values are median) Type of antegrade enemas used No subgroup analysis performed Bowel movement frequency (n=9) Pre: <5/week Post: 5/week to 3/day P<0.01 Soiling frequency (n=9) Pre: constant Post: none P=0.01 Number of medications (n=9) Pre: 4 Post: 1 P=0.01 Number of physician visits related to defecation problems (n=9) Pre: 6 Post: 2 P<0.01 Number of hospital admissions for disimpaction (n=9) Pre: 4	Additional information from study: Standardised questionnaire used to obtain data on outcomes measured Frequency of bowel movements scored as: 1, <5 bowel movements/week; 2, 5/week to 3/day; 3, 3/day Soling frequency scoring: 1, none; 2, occasional, 3, few episodes/week; 4. few episodes/week to daily; 5, constantly Quality of life assessed by scoring limitations of activity (none, mild, moderate and severe), global health score, and global emotional score (poor, fair, good, very good and excellent) Reviewer comments: Not clear who interviewed the parents Source of funding: study supported in part by the Ter Meulen Fund, Royal Netherlands Academy of Arts and Sciences

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
					-number of missed school days per month -quality of life -complications	Post: 0 P<0.01 <u>Number of missed school days per month (n=9)</u> NS <u>Global health score (n=9)</u> Pre: poor Post: good P=0.01 <u>Global emotional score (n=9)</u> Pre: poor Post: good P=0.01 <u>Limitations of activity (n=9)</u> Pre: moderate Post: mild P<0.01 <u>Complications</u> No major complications like perforation, stoma stenosis, or stoma prolapse. No difference found in occurrence of number of complications between different procedures/techniques	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						Other outcomes not reported here as no subgroup analysis performed	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Jaffray. What happens to children with idiopathic constipation who receive an antegrade continent enema?. An actuarial analysis of 80 consecutive cases. 2009. Journal of Pediatric Surgery 44[2], 404-407United States.	Study Type: Prospective case series Evidence level: 3 Study aim: to perform an actuarial analysis of the outcomes of antegrade continent enema (ACE) procedure in children who have idiopathic constipation and who did not respond to 3 years of medically supervised conservative management	80 children Inclusion criteria: All children with idiopathic constipation undergoing ACE surgery by 1 surgeon. In all children symptoms had persisted despite medical management supervised by paediatrician for at least 3 years Exclusion criteria: Hirschsprung's disease (excluded by rectal biopsy in all cases)	80 children 44 boys median age at surgery: 9.6 years (range 3.4 to 18.7 years) Country: UK	Intervention: Antegrade continent enema (ACE) procedure Children followed up in a nurse-led continence clinic Lavage regime was supervised by specialist nurses and used a solution of saline prepared by parents at a volume of 20mL/kg body weight Comparison: N.A	Follow-up period: 6 months to 10 years (median 6.2 years) Outcome Measures: -Ongoing lavage -Failure: either the parents have stopped using the technique because colonic lavage has not been found to improve the child's bowel habit or the child's colon had not proved to be lavageable and symptoms had deteriorated -Cure: the appendicostomy was closed/reversed because the child achieved normal bowel	53 children: conventional ACE 27 children: laparoscopic ACE - ACE lavage failed in 12 children: 4 children were identified where the appendicostomy was not being used. Although these children could be lavaged, parent's had not found it to be of help in the child's bowel management and had ceased use In 8 children, deterioration of symptoms occurred despite ACE lavage and required alternative treatment of symptoms. These children could not be lavaged Kaplan Meier probability of an ACE failing: 0.3 at 8.5	Additional information from study: In the first 32 cases the diagnosis was confirmed by the use of marker studies using an established protocol. However because the marker studies did not alter treatment decisions and to avoid unnecessary radiation exposure, this practice was stopped Previous treatment was heterogeneous and had always included prolonged treatment with laxatives, usually with periods of in-patient administration of surgical bowel cleansing solutions, frequent manual disimpaction and often involvement of a clinical psychology service In calculating the Kaplan Meier probability of an ACE being reversed or failing, the following times were calculated: -ongoing lavage: length of follow up calculated as time from the date of formation of ACE to current date -time to failure calculated as the time from creation of the ACE to the clinic letter stating that the parents had ceased using the ACE, or the date of commencement of alternative treatment -cure: the date of the operation to

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
					habit	years; estimated mean failure time: 8.6 years (95% CI 7.9 to 9.2) -12 children had normal bowel habit, no longer performed colonic lavage and underwent closure of appendicostomy. The Kaplan Meier probability of an ACE being reversed was 0.2 at 6.2 years, estimated mean time to reversal (9.1 years (95% CI: 8.4 to 9.7) -56 children currently performing colonic lavage Colonic transit time (CTT), age at surgery and duration of follow-up were not significantly associated with ACE failure, but sex was (p=0.04) the higher failure rate amongst girls was significant (p=0.02) CTT significant factor in predicting failure in	reverse the ACE was used as the censoring time A minimum of 6 months follow-up judged to be appropriate because a decision regarding “cure” would take no less than 6 months to determine Children who could not be lavaged defined as those having failed too have a bowel evacuation despite an appropriate volume of lavage fluid. These children were assessed by performing continuous lavage though the appendicostomy over several days while in hospital. Typically such children accommodate very large volumes of fluid in their colon, often in excess of 10 L without bowel evacuation Criteria for ACE reversal: for at least the previous 6 months, child had stopped using their ACE, was stooling spontaneously at least every other day, was not requiring laxative therapy and was not soiling. ACE reversed by dissecting the appendix to the caecal wall and ligating and removing it No patient was discharged, and none was lost to follow up <u>Source of funding:</u> Not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						children who accommodated very large volume of lavage fluid (>10 L) in their colon without bowel evacuation. Median CTT for this subset significantly longer than for children who could be lavaged (141 h (SD 30) vs. 73 h (SD 17); 95% CI difference 9 to 74 h; p=0.01)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Youssef et al. Management of intractable constipation with antegrade enemas in neurologically intact children. 2002. Journal of Pediatric Gastroenterology and Nutrition 34[4], 402-405	Study Type: Retrospective case series Evidence level: 3 Study aim: to assess the benefit of antegrade colonic enemas through caecostomy catheters in children with severe constipation who were referred to a tertiary care centre	12 children Inclusion criteria: children referred to a tertiary care motility centre for further evaluation of intractable constipation, who had undergone caecostomy placement for administration of antegrade enemas Exclusion criteria: neurologic handicap and other organic causes of constipation	12 children 9 boys mean age: 8.7 ± 4.4 years Country: USA	Intervention: Caecostomy (surgically and by interventional radiology) Comparison: none Choice of irrigation solution used after caecostomy varied, based on preference of treating physician. Most patients began with low volume infusions of solution, which were increased according to therapeutic response. 67% of patients used 200 mL to 1,000 mL (mean 478 mL ± 262 mL) polyethylene glycol irrigation solution, daily to every other day. 25% of patients used a combination of saline and	Follow-up period: 13.5 ± 8.5 months Outcome Measures: -Bowel movements/week -Soiling episodes/week -Number of medications used for constipation -Episodes of abdominal pain/week -Missed school days/month -Emotional health -Overall health -Physician office visits/year	Bowel movements/week before: 1.4 ± 0.7 after: 7.1 ± 3.8 p<0.005 Soiling episodes/week before: 4.7 ± 3.2 after: 1.0 ± 1.4 p<0.01 Number of medications used for constipation before: 4.0 ± 1.0 after: 0.8 ± 0.6 p<0.005 Abdominal pain score: before: 2.9 ± 1.6 after: 0.9 ± 1.0 p<0.005 Missed school (days/month) before: 7.5 ± 6.9 after: 1.5 ± 2.5 p<0.02 Emotional health score before: 1.9 ± 0.8 after: 3.6 ±1.1 p<0.005 Overall health score:	Additional information from study: A questionnaire used to interview caregivers 13.5 ± 8.5 months after caecostomy placement. No caregiver refused to participate in interview Scoring for episodes of abdominal pain: 0 = none, 1=once or twice, 2=a few times, 3=fairly often, 4=very often, 5= everyday Scoring for overall health and emotional state: 1=poor, 2=fair, 3=good, 4=very good, 5=excellent Reviewer comments: Very small sample Not clear who performed the review of the clinical records Not clear who interviewed the parents Researchers not reported blinded Questionnaire not reported piloted/validated Source of funding: not stated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				glycerin, mixing 60 mL to 75 mL of glycerin in 240 mL to 300 mL of saline. 1 patient received 90 mL phosphate soda solution followed by 300 mL of saline. Evacuation occurred within 1 hour of enema administration in 7 children and occurred within 3 hours in the other 5 children.		before: 1.7 ± 0.9 after: 3.6 ± 0.9 p<0.005 <u>Physician office visits/year</u> before: 24.0 ± 19.1 after: 9.2 ± 14.2 p<0.05 No acute adverse events <u>Postoperative adverse events (n children):</u> -skin breakdown and development of granulation tissue: 1 -leakage of irrigation solution: 1 -accidental removal of the catheter with subsequent easy catheter replacement by the interventional radiologist: 2 No adverse event led to discontinuation of antegrade enema use. No child has required admission to a hospital because of faecal impaction since starting antegrade enemas. 5 patients	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						discontinued antegrade enemas with removal of the caecostomy at a mean of 14.6 ± 9.1 months after beginning treatment. None has redeveloped problems with constipation or faecal soiling.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Curry et al. The MACE procedure: experience in the United Kingdom. 1999. Journal of Pediatric Surgery 34[2], 338-340	Study Type: Retrospective survey Evidence level: 3 Study aim: to find out the current status of the Malone Antegrade Continence Enema (MACE)	273 children Inclusion criteria: MACE procedures performed by UK members of the British Association of Paediatric Surgeons (or their units) up to the end of 1996 Exclusion criteria: not clearly stated	273 children Mean age: 12.3 years Country: UK	Intervention: Malone Antegrade Continence Enema (MACE) Comparison: None	Follow-up period: Mean 2.4 years (range 0.3 to 6) Outcome Measures: -children diagnoses -success rate -complications encountered	Overall success rate Including both full and partial): 79% Success rate based on diagnosis (%): Constipation (n=23) Full: 52 Partial: 10 Failure: 38 Unknown: 1	Additional information from study: Results included figures from authors' previous study, reported figures from one other UK centre and replies to proformas sent by authors to BAPS members 102 proformas sent, 58 returned Success criteria: -full: totally clean or minor or minor rectal leakage on the night of the washout; -partial: clean, but significant stomal or rectal leakage, occasional major leak, still wearing protection but perceived by the child or parent to be an improvement -failure: regular soiling or constipation persisted , no perceived improvements, procedure abandoned usually to a colostomy Reviewer comments: Retrospective study Low response rate to the proforma Results for patients with diagnoses other than constipation not reported here because they are outside the remit of this review. Main complications not related in paper to the clinical diagnosis and therefore not reported here Source of funding: not stated

Clinic-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Burnett et al. Nurse management of intractable functional constipation: a randomised controlled trial. 2004. Archives of Disease in Childhood 89[8], 717-722	Study Type: RCT Evidence level: 1+ Study aim: To evaluate the effectiveness of a nurse led clinic (NLC) compared with a consultant led paediatric gastroenterology clinic (PGC) in the management of chronic constipation	102 children Inclusion criteria: All children aged 1 to 15 years presenting to the paediatric gastroenterology service at the John Radcliffe Hospital, Oxford, UK with constipation Exclusion criteria: Organic or neurological disease	102 children 55 males median age at study entry: 4.6 (NLC) and 4.8 years (PGC) age range: 13 months to 14.7 years Country: UK	Intervention: Nurse led clinic (NLC) Comparison: Consultant led paediatric gastroenterology clinic (PGC) **-Assessment:** Nurse led clinic designed to be a follow up clinic for children who had undergone a full and detailed medical assessment in the paediatric gastroenterology clinic leading to a diagnosis of idiopathic functional constipation **-Investigations:** Where it was clinically appropriate, an abdominal radiograph obtained at the time of initial	Intervention period: 30 months Assessment point (s): Unclear Follow-up period: Median: 16.6 months for both groups Outcome Measures: 1. Primary outcomes: -Time to cure at last visit or later confirmed by telephone -Time to cure at last visit. -Premature study termination. 2. Secondary outcomes: -number of	**Primary outcomes** Time to cure at last visit or later confirmed by telephone -Number cured, % NLC (n = 52): 34 (65.4%) PGC (n = 50): 25 (50.0%) -Time to event (median (95% CI, months) NLC (n = 52): 18.0 (8.5 to 27.5) PGC (n = 50): 23.2 (17.3 to 29.2) Hazard ratio(one sided 95% CI): 1.332 (0.860 to ∞) Time ratio (one sided 95% CI): 0.816 (0 to 1.032) Time to cure at last visit -Number cured, % NLC (n = 52): 27 (51.9%)	Additional information from study: Constipation defined as (1) decreased frequency of bowel movements (that is, decreased from the individual's previous pattern); and/or (2) harder stool consistency; and/or (3) subjective difficulty, including pain and distress associated with defecation Interpretation of abdominal radiograph obtained at the time of initial assessment made though a validated scoring system (Leech) using scores ranging from 0 (no stool) to 5 (gross faecal loading with bowel dilatation) in three areas of the colon, giving a total severity score ranging from 0 to 15. Using this system a radiographic score of >9 has been shown to have a high specificity and sensitivity in the diagnosis of childhood constipation The primary outcome of cure at last visit or later confirmed by telephone used to assess sample size. For non-inferiority to be concluded between NLC and PGC, 200 patients (100 per arm) would be required for a power of 80% and a one-sided significance level of 0.05, assuming the success rate of the PGC to be 50%. The range of clinical equivalence was defined to be within 15%, therefore non-inferiority was defined as the ruling out of a hazard

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				assessment both as a diagnostic tool and as a semi-quantitative marker of the severity of constipation **-Treatment:** a standardised treatment algorithm (constructed for the study, similar to a number of published guidelines) provided the basis for management decisions in all consultations in both clinics -initial phases: involved child and parent education about diet (fibre and fluid), exercise, toilet training, and the actions of the laxatives prescribed. Laxative therapy comprised a combination of stool softeners	clinic visits -number requiring additional medication/in-patient procedures during the scheduled treatment period	PGC (n = 50): 22 (44.0%) -Time to event (median (95% CI, months) NLC (n = 52): 22.1 (15.1 to 29.2) PGC (n = 50): 25.1 (17.0 to 33.2) Hazard ratio(one sided 95% CI): 1.207 (0.749 to ∞) Time ratio (one sided 95% CI): 0.855 (0 to 1.112) <u>Premature study termination</u> -Number, % NLC (n = 52): 5 (9.6) (2 lost to follow-up, 3 withdrew) PGC (n = 50): 14 (28) (10 lost to follow-up, 4 withdrew) -Time to event (median (95% CI, months) NLC (n = 52): NA	ratio less than 0.85 on the basis of the lower limit of the one sided 95% confidence interval. Conversely, for an outcome where a reduction of events is preferable, non-inferiority is defined as the ruling out of a hazard ratio greater than 1.176 on the basis Allocation concealment facilitated by using sequentially numbered sealed envelopes produced by an external source for consecutive and eligible study patients. Randomisation performed using block randomisation with fixed blocks of size four Time to cure at last visit or later confirmed by telephone relates to all those children confirmed cured either at their last visit, or subsequently, confirmed over the telephone. Children who were close to achieving the definition of ‘‘cured’’ at their last visit but who were still being weaned off medication, were not required to attend for a further follow up appointment but received their follow up via the telephone. Time to cure at last visit relates to only those children confirmed cured at their last visit (a subset of the previous outcome). Premature study termination comprises those patients who were either lost to follow up or withdrawn for whatever reason Baseline demographic and clinical presentation characteristics as well as

Clinic-based Interventions							
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				(for example, lactulose, docusate sodium) and stimulants. Stimulants of different potencies (senna, bisacodyl, sodium picosulphate) were prescribed according to the clinical response as indicated by the bowel diaries. If there was an inadequate clinical response to this initial phase, the patient moved on to an advanced treatment regime which might include, enemas, intestinal lavage, manual removal of faeces under general anaesthesia, or psychological referral as was appropriate in each case **-Monitoring /follow-up:** Bowel		PGC (n = 50): NA Hazard ratio(one sided 95% CI): 0.334 (0 to 0.788) Time ratio (one sided 95% CI): NA **Secondary outcomes** <u>Number of clinic visits</u> -Median number of visits in each clinic: 6.0 -Median number of inter-visit contacts: NLC: 6.0 (range 2 to 16) PGC: 0.0 (range 0.0 to 29) <u>Number requiring additional medication/in-patient procedures during the scheduled treatment period</u> No significant differences between both groups	previous laxative usage well balanced across clinics ITT analysis conducted for all outcomes. Survival analysis conducted for the primary time-to-event outcomes <u>Reviewer comments:</u> Unclear who measured outcomes Results not controlled for potential confounders <u>Source of funding:</u> Research grants from Norgine Ltd and from WellChild

Clinic-based Interventions							
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				diaries, which report the frequency, size, and consistency of stools, presence or absence of soiling, and a record of daily laxative medication, were used in both clinics to monitor progress and response to treatment. Dedicated case report forms were used for each study participant and, together with detailed clinical history (including a detailed dietetic history) and clinical findings on initial assessment, documented details of bowel habit and drug therapy at all subsequent outpatient visits. Any other contact with the families, e.g. on the telephone or a		10 children (5 NLC, 5 PGC) completed study as per the protocol but were not cured (treatment failures): -8/10: formally referred for psychological / psychiatric management -9/10: had documented serious behavioural problems -3/10: also referred for surgical assessment and management A total of 15/102 children still undergoing follow up, as they are not cured. In this group, 7/15 children are followed up in the PGC and 8/ 15 in the NLC. 7/15 children had documented psychosocial problems associated with poor compliance in attending clinic appointments	

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				home visit, was documented using inter-visit contact forms **-Discharge:** Child defined as having been ‘‘cured’’ of their constipation when, for a period of at least 1 month, they had been opening their bowels, producing a normal formed stool without difficulty at least 3 times per week and without any laxative therapy			

Clinic-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Sullivan et al. Parent satisfaction in a nurse led clinic compared with a paediatric gastroenterology clinic for the management of intractable, functional constipation. 2006. Archives of Disease in Childhood 91[6], 499-501	Study Type: Survey-RCT Evidence level: 1+ Study aim: To assess parent's satisfaction with a nurse led clinic (NLC) for children with intractable, functional constipation compared with a consultant led paediatric gastroenterology clinic (PGC)	102 children Inclusion criteria: All children aged 1 to 15 years presenting to the paediatric gastroenterology service at the John Radcliffe Hospital, Oxford, UK with constipation Exclusion criteria: Organic or neurological disease	102 children 55 males median age at study entry: 4.6 (NLC) and 4.8 years (PGC) age range: 13 months to 14.7 years Country: UK	Intervention: Nurse led clinic (NLC) Comparison: Consultant led paediatric gastroenterology clinic (PGC) Intervention as described in previous study	Duration of treatment As previous RCT Assessment point (s): After 12 months' follow-up or before this if the child has been "cured" Outcome Measures: 1. Parent satisfaction, 6 domains: -provision of information -empathy with patient -technical quality and competence -attitude towards the patient -access to and continuity with	Provision of information scores (median) NLC: 8.7 PGC: 7.5 P<0.001 Empathy with patient scores (median) NLC: 9.0 PGC: 7.3 P<0.001 Technical quality and competence scores (median) NLC: 9.1 PGC: 8.0 P<0.001 Attitude towards the patient scores (median) NLC: 8.7 PGC: 7.3 P<0.001 Access to and continuity with the caregiver scores (median) NLC: 8.2 PGC: 6.7 P<0.001 Overall satisfaction scores (median)	Additional information from study: Satisfaction with care defined as "the degree to which parents perceive the needs of their children are met" Parent satisfaction measured using a validated instrument based on the Leeds Satisfaction Questionnaire (LDQ), which has been shown to be easy and quick to complete sensitive to change, reliable and reproducible. Questions in the LDQ were pertinent to a rheumatology clinic and thus adapted for the purposes of this constipation clinic. Questionnaire covered 6 separate domains in 48 statements: provision of information, empathy with the patient, access to and continuity with the caregiver and overall satisfaction. The "overall satisfaction" component was added for the purposes of validation. 5 point Likert scales used fro responses ranging from "strongly agree" to "strongly disagree", stability of the instrument tested using the test-retest method An attempt was made to record all "inter-visit" contacts (by telephone or day ward attendances) made by parents outside their schedules outpatients appointment A total of 90 questionnaires returned from 107 families canvassed (84%); 40/51 (78%) from the PGC and 50/56 (89%) from the NLC. Robustness and high reliability of the questionnaire

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					the caregiver -overall satisfaction 2. Number of inter-visit contacts	NLC: 8.7 PGC: 7.3 P<0.001 Number of inter-visit contacts (mean (SD)) NLC: 2.37 ± 4.17 PGC: 1.70 ± 4.79 NS	demonstrated by calculating the internal consistency for each domain; lowest Cronbach's alpha: 0.81 <u>Reviewer comments:</u> This study is an evaluation of the previous RCT ITT analysis performed for all outcomes <u>Source of funding:</u> Research grant form WellChild

Clinic-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Poenaru et al. The Pediatric Bowel Management Clinic: initial results of a multidisciplinary approach to functional constipation in children. 1997. Journal of Pediatric Surgery 32[6], 843-848	Study Type: Prospective case series Evidence level: 3 Study aim: To present the experience of the first 16 months of a multidisciplinary clinic for the treatment of functional constipation	114 patients Inclusion criteria: Children up to 19 years old referred to the clinic with constipation after a 3-month unsuccessful course of treatment Exclusion criteria: Obvious associated anomalies causing constipation or encopresis	114 patients Mean age: 5.4 ± 3.8 years (range 4 months to 19 years) 51.4% boys Country: Canada	Intervention: Bowel Management Clinic -Clinic staff: a physician (rotating between 2 paediatricians, 1 paediatric gastroenterologist and 1 paediatric general surgeon), a nurse practitioner, a dietician, an enterostomal therapist/nurse educator and a psychosocial nurse specialists -Assessment: new patients always assessed by clinic nurse and physician assessment to identify potential organic causes of constipation and to establish components of individualised management. Further referral to other BMC staff	Duration of treatment Mean time span between first and last visit to clinic: 4.5 months Assessment point (s): 2 and 4 months after initial clinic visit Outcome Measures: -stool frequency per month -stool consistency -occurrence and frequency of symptoms (soiling, rectal pain, rectal bleeding) -satisfaction with care, 5 scales: respectful and supportive care, enabling and partnership,	Stool frequency per month, mean (n=26) 1rst visit: 11.73 last visit:: 29.77 p=0.00026 Stool consistency (n=55) (Unclear whether the following are number of children or %) -liquid 1rst visit: 0 last visit:1 -soft 1rst visit: 4 last visit: 13 -formed 1rst visit: 16 last visit: 13 -hard 1rst visit: 10 last visit: 3 p=0.00004 Occurrence of symptoms (%) -Soiling (n=42) 1rst visit: 57 last visit: 43 NS	Additional information from study: Children considered constipated when they had persistent symptoms (soling, pain, bleeding, etc) related to bowel movements which tend to be infrequent Total number of visits was 257 with average of 6 patients per clinic. 62 patients seen more than once with a mean of 3.1 visits per patient and a mean time span between the first and the last visit to clinic of 4.5 months Sample size varies in each category of symptoms because of incomplete observations and stool frequencies were only included for non-soiling patients 13 children appeared to be lost to follow-up (no return to clinic in over 6 months) and 11 were discharged Among the discharges the mean number of clinics visits was 3.5 Patient data collected prospectively from the families and the clinic staff. .Before initial clinic visit families filled out several mailed questionnaires covering medical, psychological and social issues surrounding the child's problem. These included a medical information questionnaire, a family information questionnaire, the Family Assessment Device (FAD), the Chronic Illness psychosocial Inventory (CI-PSI) and a knowledge quiz. Parents also required to complete a "constipation/soiling diary"

Clinic-based Interventions							
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				as needed -Investigations: only performed if there is suspicion of organic cause of constipation or lack of improvement after adequate intervention (abdominal radiograph with lumbosacral spine, barium enema, anorectal manometry and rectal mucosa biopsy) -Treatment: only compulsory treatment modality is patient education. Enemas only used in initial treatment if faecal impaction, to provide social continence fro children with persistent encopresis and avoid undue rectal distension until laxatives start	providing general information, providing specific information, coordinated and comprehensive care	-Rectal pain (n=51) 1rst visit: 53 last visit: 22 p=0.0003 -Rectal bleeding (n=54) 1rst visit: 26 last visit: 4 p=0.00035 <u>Frequency of symptoms per month</u> Soiling (n=26) 1rst visit: 30.7 last visit: 12.8 p=0.015 Rectal pain (n=23) 1rst visit: 9.5 last visit: 2.0 N.S Rectal bleeding (n=11) 1rst visit: 0.6 last visit: 0.2 N.S <u>Satisfaction with care</u> Results only reported in a graph from which it is difficult to extract estimates Scores were normal	fro one week, detailing the child's stools and symptoms. At the first clinic visit a structured history/physical examination completed by physician. At each follow up families completed a short progress questionnaire and asked to continue diaries throughout. The FAD, CI-PSI questionnaires and knowledge quiz were repeated at 2 and 4 months after initial clinic visit. A Measure of Processes of Care (MOPC) questionnaire was also administered at the 4-month point. MPOC is a self report measure of the parents' perceptions of the extent to which 5 behaviours of health care professionals occur (respectful and supportive care, enabling and partnership, providing general information, providing specific information, coordinated and comprehensive care). The scores from the study group were compared with those from a normative group of 653 patients <u>Source of funding:</u> Educational grant from Janssen Pharmaceutica through Queen's GI Motility Education Centre

Clinic-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
				taking effect. Choice of enemas are phosphate and tap water or saline. High colonic saline irrigations used in severe cases, suppositories not routinely employed. Choice of laxative based on compliance and nature of symptoms. Most patients treated with senna, Docusate sodium and mineral oil. Multiple laxatives avoided. Patient started on recommended dosages, then increased by 50% every 4 to 5 days until symptomatic improvement noted. Individualised dosage then maintained minimum 3 to 6 months, during which dietary and psychosocial issues are dealt		or higher that the norm for: respectful and supportive care, enabling and partnership and coordinated and comprehensive care Scores were lower than the norm for providing general information and providing specific information	

Clinic-based Interventions							
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				with. Patient is then slowly weaned off medications -Follow-up: arranged by each health care professional as needed. Visits used to monitor progress and continue education process. Patients who show no progress are reassessed by physician and may become candidates for diagnostic testing -Discharge: when patient is asymptomatic and off medications. Patient referred back to the referring physician, with information for maintaining healthy bowel routine Comparison: N.A			

Information and Support for Children with Chronic Idiopathic Constipation and their families

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Ritterband et al. An Internet intervention as adjunctive therapy for pediatric encopresis. 2003. Journal of Consulting and Clinical Psychology 71[5], 910-917	Study Type: RCT (multicentre) Evidence level: 1+ Study aim: To examine the utility and effectiveness of an Internet-based version of enhanced toilet training	24 children Inclusion /exclusion criteria: Children aged between 6 and 12 years, soling at least once a week and have no medical diagnosis other than constipation that could explain their faecal incontinence	24 children 19 boys mean age: 8.46 years (SD1.81) -Web group: 12 children (10 boys) -No-Web group: 12 children (9 boys) Country: USA	Intervention: Web intervention Comparison: No-Web intervention -The Web site: Web-based program for the treatment of paediatric encopresis (U-CAN-POOP-TOO (please refer to Ritterband, 2008 for a description of the program)	Duration of intervention: 3 weeks Assessment point (s): 3 weeks after initial home visit Follow-up period: None Outcome Measures: -number of faecal accidents per week -number of bowel movements (BM) passed in the toilet per week - bathroom use without prompts -bathroom use with prompts -internet use (most/least useful aspect of	**Percentage change from pre- to post-assessment** Number of faecal accidents per week (mean, SD) -Web group: 0.50 (.85) -No-Web group: 8.27 (13.83) p=0.18 Number of bowel movements (BM) passed in the toilet per week -Web group: +152% -No-Web group: -16% p=0.001 Bathroom use without prompts -Web group: +109% -No-Web group: -37% p=0.021 Bathroom use with prompts -Web group: +47%	Additional information from study: Computer and internet access provided to all families who contacted the research centre and met the inclusion criteria Participants received a $25 gift certificate to a local toy sore for completing the pre-treatment assessment and another $25 gift certificate for completing the post-treatment assessment Information regarding BM assessed by parent report on the Child Information Form. Question regarding child's bowel habits included such as number of BMs in toilet and use of toilet with / without parental prompts. Questions regarding use of internet programme also included in post-treatment form for the intervention group. The Virginia Encopresis/Constipation Apperception Test (VECAT) also administered. It assesses bowel specific problems related to the process of encopresis, such as avoidance of the toilet, non responsiveness to rectal distension cues and fear of defecation pain. A generic subscale included as a comparison measure, addresses problem behaviours not related to bowel issues. The VECAT consists of 18 pairs of drawings (9 pairs bowel-specific and 9 parallel generic events) and child selects

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
					the programme; preference questions regarding individual cores an modules)	-No-Web group: -45% NS <u>Internet use (Web group only)</u> 1. Most useful aspect of the programme: -the step by step program to get the child regulated -understanding why his body does what it needs to do everyday-and what happens when he doesn't have a BM and health consequences…information was tremendously useful -developing a feeling that he can control his own body -realising that he's not the only child with this problem…that was reassuring 2. Least useful aspect of the programme -difficulty with connections -modules regarding fear of toilet and	the picture in each pair that best describes him/herself No significant differences in baseline characteristics between the 2 groups (age, gender, race, stage of bowel movement training, length of current laxative regime or any of the outcomes measured) CM1: anatomy and pathophisiology CM2: medication (enemas/laxatives) CM3: behavioural intervention <u>Reviewer comments:</u> No definition of constipation / soling given Small sample size, no sample size calculation Randomisation and allocation concealment method not described No dropouts/lost to follow up reported Results not controlled for potential confounders <u>Source of funding:</u> National Institutes of Health Grant RO1 HD28160

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
						"monsters" -art work of the body did not print out -Miralax should have been included (as a choice of laxative) -nutrition portion was too limited <u>Internet experience: parents' views / satisfaction</u> -found material understandable (mean 5.00, SD 0.00, N = 20) -found it easy to use (mean 4.62, SD 0.74, N = 21) -believed their child liked the program (mean 4.05, SD 1.28, N = 21) - believed their child found it understandable (mean 4.32, SD 0.89, N = 19) - believed their child found it easy to use (mean 4.47, SD 0.77, N = 19) 3. Preference regarding cores modules (CM) (mean, SD)	

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
						(score 0 to 4) a. How useful: CM1: 3.84 (0.38) CM2: 3.94 (0.24) CM3: 4.00 (0.00) b. How well did you understand the material CM1: 3.89 (0.32) CM2: 3.89 (0.32) CM3: 3.92 (0.28) c. how well did your child understand the material CM1: 3.53 (0.61) CM2: 3.28 (1.07) CM3: 3.54 (1.13) d. How much did you enjoy using the module CM1: 3.68 (0.48) CM2: 3.67 (0.49) CM3: 3.69 (0.48) e. How much did your child enjoy using the module CM1: 3.63 (0.76) CM2: 3.61 (0.98) CM3: 3.46 (1.13)	

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Ritterband et al. Using the internet to provide information prescriptions. 2005. Pediatrics 116[5], e643-e647	Study Type: RCT-Survey Evidence level: 1+ (RCT component) 3 (survey component) Study aim: To determine if families of children suffering from chronic constipation and/or encopresis will visit an educational Web site that is specifically prescribed by their physician and whether an e-mail reminder increases the likelihood that they will visit the Web site. In addition, barriers to accessing the prescribed	83 patients and their families Inclusion/exclusion criteria: Families with a child who was being seen for the first time in the paediatric gastroenterology clinic at the University of Virginia with a chief complaint of chronic constipation and/or encopresis. To be eligible, families had to have access to the Internet in their home and have an active e-mail account	83 patients and their families -Children's mean age: 7 years 10 months (94 ± 38 months) (range: 25 months to 14.5 years Country: USA	Intervention: E-mail-prompt group (n=43) Comparison: No E-mail-prompt group (n=40) At the conclusion of the patient's clinic visit, 1 of the 2 attending gastroenterologists provided a form with the Web-site address and a log-in identification number. The handout, signed by the physician, stated: "It is important to learn as much as you can about bowel problems and how to manage them. As part of your child's care, I want you to go to this Web site and review the relevant material. This should be beneficial to your	Duration of intervention 1 week Assessment point (s): 1 week Follow-up period: None Outcome Measures: -Number of families who visited the prescribed Web site within 1 week of their clinic visit -Perceived barriers to accessing the Web site	Number of families who visited the prescribed Web site within 1 week of their clinic visit (N=83) 54 (65%) Perceived barriers to accessing the Web site 18 interviewed subjects did not go to the Web site because (n, %): 1. Personal / family / behaviour: -just forgot: 11 (61) -didn't have much time: 11 (61 -lost flyer: 6 (33) -interrupted: 3 (17) -computer in use by another: 2 (11) -did not think it would be useful: 2 (11) -did not want to go: 1 (6) -did not like typing in URLs: 1 (6) -did not know how to type in URLs: 1 (6) -child not	Additional information from study: On the Web page, users read the following instructions: "We hope you find the information in this website to be helpful. Before you can begin, please enter the ID number you were given in the space below, and then click the button to begin." When the "submit" button was clicked, the 2-digit identification number and the date and time were logged in a database. The 2-digit identification number identified the family as a member of the e-mail-prompt group or no-prompt group. This was the only information captured in the database No significant differences between the 2 groups on type and speed of Internet connection, the number of times they reported checking their e-mail, or frequency of using the Internet There were no significant differences in the ages of the children between the 2 groups Approximately 1 week after the clinic visit, the study coordinator attempted to contact the primary caretaker of each patient by telephone or e-mail to ask about their experience accessing the Web site. Families who did not access the Web site were encouraged to identify barriers that they may have experienced in accessing the prescribed Web site. They were presented with a

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
	Web site were identified			child's treatment." Families were assigned randomly into a "prompt" group or "no-prompt" group. 2 business days after the clinic visit, an e-mail containing the Web-site address and a reminder to visit the Web site was sent to those in the "prompt"group -The Web site: an abbreviated version of a larger Web-based program for the treatment of paediatric encopresis (U-CAN-POOP-TOO) -3 modules: (1) "How to Strain": reviewed proper defecation dynamics, including proper positioning, straining, and		cooperating: 0 -did not know how to use internet: 0 -family thought it was a bad idea: 0 2. Technical issues/obstacles -computer broken: 4 (22) -internet connection broken: 2 (11) -difficulty logging on: 1 (6) -too long to log on:1 (6) No significant differences in identified obstacles between the families who received the e-mail reminder and those who did not	list of potential barriers and were asked whether the item had been a barrier for them to accessing the Web site. Individuals were able to select multiple barriers, if applicable Of the 83 families, 67 (81%) were contacted by telephone (n= 57) or e-mail (n= 10) No significant differences were found in identified obstacles between the families who received the e-mail reminder and those who did not <u>Reviewer comments:</u> No definition of chronic constipation or encopresis given No sample size calculation performed Randomisation and allocation concealment methods not described Results controlled for potential confounders <u>Source of funding:</u> Partially supported by National Institutes of Health grant RO1 HD28160

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
				muscle control/ strength-building exercises (2) “Giving and Getting Enemas”: reviewed techniques for administering enemas (3) “The SuperCleanout game” : An arcade-style game for children with a learning message. Parents and children were able to view as much of the site as they wanted and could come back as often as they liked			

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Ritterband et al. Examining the added value of audio, graphics, and interactivity in an internet intervention for pediatric encopresis. 2006. Children's Health Care 35[1], 47-59United States.	Study Type: Single sample cross-over RCT Multicentre (and these are the results of 3 individual studies for each component) Evidence level: 1+ Study aim: To determine the usefulness and user preference for audio (use of sound), graphics (use of images) and interactivity (triggering of events by the user causing various actions, i.e. clickable buttons) in a paediatric	49 children and their families Inclusion criteria: Children aged 5 to 12 years who were being see for encopresis at 2 paediatric gastroenterology clinics Exclusion criteria: Not stated	49 children and their families 32 boys mean age: 7.98 years (SD=1.88) Country: USA	Intervention: Modified modules including audio, graphics and interactivity Comparison: Modules without audio, graphics or interactivity 2 modules of the original U-CAN-POOP-TOO intervention were revised: -"Giving and Getting Enemas": reviewed techniques for administering enemas "How to Strain": reviewed proper defecation dynamics, including proper positioning, straining, and muscle control/ strength-building exercises Design was significantly	Duration of intervention Each module with or without each component presented once Assessment point (s): Immediately after each module was presented Follow-up period: None Outcome Measures: -motivation -readiness to change	Motivation scores (lower score reflects more motivation) **-Audio** 1. Audio-computer a. Child Pre: 6.00 Post: 5.13 P≤0.004 b. Parent Pre: 7.56 Post: 6.25 P=0.06 2. Audio-person a. Child Pre: 6.19 Post: 5.63 N.S b. Parent Pre: 8.75 Post: 7.13 P≤0.02 **-Graphics** 1. Graphics + a. Child Pre: 5.69 Post: 5.19	Additional information from study: Families who agreed to participate received a $25 gift certificate forma a local toy store Parents asked to complete the motivation and readiness to change items from their child's perspective: -Motivation: a 3-item parallel drawing selection measure was created in the same manner as the Virginia Encopresis-Constipation Apperception Test for both the enema and proper defecation dynamics modules. Respondents select the image in each pair which they feel is closest to represent how they might act given the scenario presented in the picture (e.g. child does not want an enema vs. child wants an enema, child feels urge to poop but keeps on playing vs. go right away to sit on toilet). Respondents are then asked whether he or she is "a lot like or "a little like" the image selected. Pre-post reliability correlations on the motivation scale for the enemas and dynamic modules were .66 and.83 respectively -Readiness to change: a 1-item scale with4 response options was created to identify the child's stage of change as defined by Prochaska and DiClemente, 1983) with respect to both receiving an enema and proper defecation dynamics

Web-based Interventions							
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	Internet-based health intervention specifically designed for patients with encopresis			improved with special emphasis given to graphical, animation and interactive elements. For each of the 3 studies conducted, the 2 modules were modified to either include the 3 constructs of interest (audio, graphics and interactivity) or not. For the study examining audio both modules were created with and without sound. For the study examining graphics both modules were created with graphics and completely text based; and for the study examining interactivity both modules were created with interaction (use the mouse to click various aspects of		N.S b. Parent Pre: 7.13 Post: 6.06 P≤0.03 2. Graphics - a. Child Pre: 5.75 Post: 5.94 N.S b. Parent Pre: 8.06 Post: 7.19 P=0.06 -Interaction 1. Interaction + a. Child Pre:6.00 Post: 4.71 P=0.03 b. Parent Pre: 8.35 Post: 6.88 NS 2. Interaction - a. Child Pre: 5.18	<u>Reviewer comments:</u> No definition of chronic constipation or encopresis given No sample size calculation Baseline characteristics not compared Randomisation and allocation concealment methods not described No dropouts/lost to follow up reported Results controlled for potential confounders <u>Source of funding:</u> National Institutes of Health grant RO1 HD28160

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
				the screen and navigation) and as a movie (where no interaction was necessary and the participant could just watch the module play from beginning to end		Post: 4.41 P=0.02 b. Parent Pre: 7.76 Post: 7.29 NS <u>Stage of change scores</u> **-Audio** 1. Audio-computer a. Child Pre: 2.88 Post: 3.00 N.S b. Parent Pre: 2.19 Post: 2.69 N.S 2. Audio-person a. Child Pre: 2.69 Post: 2.63 N.S b. Parent Pre: 2.25 Post: 2.75 P=0.04	

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
						-Graphics 1. Graphics + a. Child Pre: 3.38 Post: 3.31 NS b. Parent Pre: 2.44 Post: 2.88 P=0.01 2. Graphics - a. Child Pre: 3.38 Post: 3.25 NS b. Parent Pre: 2.75 Post: 3.13 NS **-Interaction** 1. Interaction + a. Child Pre: 2.47 Post: 2.71 NS	

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
						b. Parent Pre: 2.18 Post: 1.94 NS 2. Interaction - a. Child Pre: 2.53 Post: 2.53 NS b. Parent Pre: 1.82 Post: 1.94 NS	

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Ritterband et al. Real world use of an Internet intervention for pediatric encopresis. 2008. Journal of Medical Internet Research 10[2], e16	Study Type: Prospective case series Evidence level: 3 Study aim: To examine the utility and impact of an Internet intervention for childhood encopresis as part of standard medical care in a "real world" setting	22 children Inclusion criteria: Children with a documented diagnosis of encopresis as noted in their medical records and their families, seen at the Paediatric Gastroenterology Clinic at the University of Virginia Children's Hospital between . all children had been given access to the paediatric encopresis Internet intervention as part of their treatment Exclusion criteria: Not stated	22 children 13 males mean age: 8.10 years (SD 2.3 years) range 5.1 years to 12.11 years Country: USA	Intervention: Internet-based intervention for childhood encopresis: U-CAN-POOP-TOO Child-focused programme, targets primarily 5 to 10 years old children but was designed to be used by child and parent (s) together 3 core modules take 60 to 90 minutes to complete, all users instructed to review them during the first week: 1. The body (anatomy, physiology and pathophysiology of digestion) 2. How to poop (behavioural techniques for treatment of encopresis) 3. Medication (clean-out and	Duration of intervention 2 weeks Assessment point (s) and follow-up period -initial period: 2 weeks before children were enrolled in the program -follow-up period: 2 weeks immediately before phone interview Outcome Measures: -number of faecal accidents over a 2-week period -number of bowel movements (BM) passed in the toilet over a 2-week period -average amount of	Number of faecal accidents over a 2-week period (mean) -initial period: 13.86 (SD 10.40, median 13.00) -follow-up period: 2.14 (SD 2.21, median 1.00) *P* < .001 Number of bowel movements (BM) passed in the toilet over a 2-week period (mean, SD) -initial period (n=21, missing data) 14.62 (10.68) -follow-up period: 14. 82 (8.65) NS Average amount of perianal pain experienced during defection over a 2-week period (mean, SD) -initial period: 0.56 (0.78) (n=18, missing data) -follow-up period:	Additional information from study: Of 46 patients originally provided with the Web-based information prescription 10 could not be reached by phone or email for interview, of the remaining 36 3 did not provide consent, 3 stated that they never received the initial email with their personalised log-in information, 5 never logged on and 3 logged but never viewed any of the intervention material. No subsequent data was collected on these patients Number of faecal accidents, number of bowel movements passed in the toilet and average amount of perianal pain experienced during defection were obtained from children's medical charts and though a phone interview with parents. Interview also included open-ended questions about what the parents believed were the most helpful and least helpful components of the programme. 3 structured questionnaire mostly developed for this interview were also completed: U-CAN-POOP-TOO Utility Questionnaire administered to all parents who had used the program (extent to which the parent and child found program useful, enjoyable, understandable and easy to use); U-CAN-POOP-TOO Impact Questionnaire administered to all parents who had used the program (parents to rate how much they perceived the programme helped their child) and Internet Intervention Adherence Measure

Web-based Interventions							
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				laxative treatment) New modules assigned each week based on a follow-up assessment the user completes about their child's status. Not all modules necessarily used by all users, only those modules identified as relevant are assigned and reviewed. However all modules can be viewed by all users. Follow-up comprised of 17 to 20 questions, depending on the week. System contains a total o 22 modules, each takes 5 to 10 minutes to review <u>Comparison</u>: N.A	perianal pain experienced during defection over a 2-week period -utility and impact of the programme :parents' views/satisfaction -adherence	0.14 (0.47) NS <u>Utility and impact of the programme :parents' views/satisfaction</u> -liked program (mean 4.62, SD 0.50, N = 21) -found it understandable (mean 5.00, SD 0.00, N = 20) -found it easy to use (mean 4.62, SD 0.74, N = 21) -believed their child liked the program (mean 4.05, SD 1.28, N = 21) - believed their child found it understandable (mean 4.32, SD 0.89, N = 19) - believed their child found it easy to use (mean 4.47, SD 0.77, N = 19) -most helpful components of the program: tutorials about anatomy and pathophysiology, liked that the program was geared toward	administered to patients who stopped using the programme for some reason other than that their problem was "resolved". Those who responded "not applicable" to items on the U-CAN-POOP-TOO Utility Questionnaire were not included in the analysis for that item (explaining the varying sample sizes) The U-CAN-POOP-TOO Impact Questionnaire was administered to examine how much the parents believed the program affected outcome. Those who responded "not applicable" were not included in the analysis for that item No significant correlations found between computer/Internet usage and the change from initial to follow-up period for accident frequency (r = .09, P < .69, N = 22), BMs passed in the toilet (r = .38, P < .09, N = 21), or amount of pain associated with defecation (r = .08, P < .76, N = 18). Internet comfort and connection speed were also not significantly correlated to changes in any of the bowel-related outcome variables (r values ranged from −.17 to .27; P values ranged from .25 to .59) Of the 22 patients who used U-CAN-POOP-TOO, 18 (82%) completed all three assigned cores (main treatment components). All 22 patients completed the Anatomy Core; 20 completed the Medication Core; and 18 completed the Behavior Core. A total of 12 patients

Web-based Interventions							
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						the child, but that it was comprehensive and non-judgemental -least helpful components of the program: no clear themes emerged -How much parents believed the program helped them and their children: On average, 19/25 items (76%) rated at least "somewhat helpful," no item described as "not at all helpful." On the 1- to 5-point scale, average responses ranged from a low of 2.33 (the program helped reduce the number of times parents had to remind their child to use the bathroom) to a high of 4.2 (the program helped the child feel more comfortable using the toilet at home). <u>Adherence</u> 16/22 patients examined, stopped using the program for some reason other	(55%) completed one follow-up, four (18%) completed a second and third follow-up, and two of these four (9%) completed more than three follow-ups. Modules were individually assigned based on responses to follow-ups; however, patients had access to all the modules. The average number of modules completed was 7.23 (SD 9.64); 14 patients (64%) completed at least one module <u>Reviewer comments:</u> Unclear how encopresis was defined/diagnosed Small sample size, no sample size calculation Unclear whether questionnaires were piloted <u>Source of funding:</u> Partially supported by NIH grant RO1 HD28160

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
						than that their problem was "resolved." -Obstacles to using the program (only 2 items with a mean score of 2 or greater (on a 1- to 3-point scale)): I just forgot [to go to the website]" (mean 2.00, SD 0.89) "I didn't have time in my schedule" (mean 2.06, SD 0.85)	

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
Borowitz et al. Using the Internet to teach parents and children about constipation and encopresis. 2001. Medical Informatics and the Internet in Medicine 26[4], 283-295	Study Type: Online survey Evidence level: 4 Study aim: To described the feedback received regarding a web-based tutorial about chronic childhood constipation and encopresis during 28 months between January 1998 and April 2000	1142 participants Inclusion criteria: Children and parents who accessed a tutorial about childhood constipation and encopresis, developed and installed on the web pages of the Children's Medical centre at the University of Virginia, and also completed an online feedback form. No internal or external announcement made to communicate the availability of the tutorial, but access to the website was not	1142 participants only 887 (78%) answered the questions categorising the reader: -789 (89%): parents and guardians of a child with constipation or encopresis -44 (5%): grandparent or other family members -30 (3%): teachers -9 (1%): physicians -35 (4%): other healthcare providers Country: USA	Intervention: Multimedia tutorial Directed primarily at parents and older children. Includes information about differential diagnosis, aetiology, treatment and potential side effects, method of follow-up including regular monitoring, natural history and prognosis and a list of references Comparison: N.A	Outcome Measures: -clarity and easiness of information presented in tutorial -usefulness of tutorial: helping parents to understand why children develop constipation and/or encopresis, making parents better able to take care of their child -usefulness of tutorial as a good way to teach people about health problems -questions or comments or suggestions as to how to improve the tutorial	The tutorial received 157 326 successful page requests from 38 012 distinct hosts Was the information presented in the tutorial clear and easy to understand? (N=883) -Very clear: 812 (92%) -Pretty clear: 71 (8% -Nobody chose "not very clear" or "not clear at all" Did the tutorial help you to understand why children develop constipation and/or encopresis? (N=696) -Completely: 174 (25%) -Somewhat: 174 (25%) -A little: 13 (2%) -Not al all: 0 After completing the tutorial, do you think you are better able to take care of a child suffering from constipation and/or	Additional information from study: The tutorial also includes a one-page feedback form comprised of 6 multiple-choice questions and one open-ended comment field. Questions were developed in consultation with the university division of survey research. All completed form were sent via email directly to the main author Responses to multiple-choice questions were tabulated. One author reviewed all free text comments and identified the central them of each comment. Comment were categorised as: -appreciation for making the information available -question (s) about a particular child's symptoms or treatment -a general question not specific to any particular child -a referral request -a request for dietary recommendations -a request for additional online information, such as online forum or a frequently asked questions (FAQ) site -specific recommendations as to how to improve the tutorial Definition of constipation in the tutorial: a child is constipated when he or she passes bowel movements less than every other or every third day and when he or she passes a bowel movement, it often is large and hard and perhaps more important, it hurts"

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
		limited in any way. These pages can be found by a link in the university homepage called "tutorials for families" Exclusion criteria: Not stated				encopresis? (N=696) -Very much: 408 (59%) -Somewhat: 226 (32%) -A little: 42 (6%) -Not at all: 20 (3%) Do you think this type of tutorial is a good way to teach people about health problems? (N=691) -Very good: 599 (87%) -Pretty good: 89 (13%) -Not very good: 0 -Not good at all: 3 (0.4%) Do you have any questions or comments or suggestions as to how to improve the tutorial? (N=845) -appreciation for making the information available: 443 (52%) -question (s) about a particular child's symptoms or treatment: 167 (20%)	Reviewer comments: Not all participants answered all the questions in the feedback form Source of funding: Not stated

Web-based Interventions							
Bibliographic Information	**Study Type & Evidence Level**	**Number of Patients**	**Patient Characteristics**	**Intervention & Comparison**	**Follow-up & Outcome Measures**	**Effect Size**	**Reviewer Comments**
						-a general question not specific to any particular child: 96 (11%) -a referral request: 46 (5%) -a request for dietary recommendations: 34 (4%) -a request for additional online information, such as online forum or a frequently asked questions (FAQ) site: 21 (2%) -specific recommendations as to how to improve the tutorial: 38 (4%)	