

Supplementary Material 9: Extended narrative synthesis, Level 3

Evidence of effectiveness: pharmacological interventions delivered by consultant-led teams (Level 3)

What is the effect of botulinum toxin?

(Related studies n = 5; Retrospective cohort studies: Low ROB¹, High ROB^{2, 3}; Controlled before and after study: Moderate ROB^{4, 5}).

Ahmadi 2013⁴ reported on a before and after study which investigated the effect of Intrasphincteric Botulinum Toxin injection in the treatment of children, aged 2-12 years, with refractory constipation (n=40). The percentage of children experiencing symptoms decreased significantly for painful defecation (88% pre-injection to 15% 6-month post-injection), hard stools (80% to 28%) and soiling (62% to 8%) and defecating interval of more than 3 days (100% to 15%). Hameed 2018⁵ used the same intervention protocol as Ahmadi 2013⁴. This case control study included fifty children (20 cases and 30 control) ranging between 2 and 8 years. The percentage of children experiencing symptoms significantly decreased from pre-injection to 6-month post-injection for painful defecation (85% to 20%), hard stools (80% to 25%), soiling (65% to 10%), and defecation interval of more than 3 days (100% to 15%). No adverse effects were recorded. The authors of both studies concluded that injection of botulinum toxin into the internal anal sphincter is a safe modality for the treatment of chronic idiopathic constipation in children^{4, 5}.

Zar-Kessler 2018¹ conducted a cohort study which assessed the response to botulinum toxin in 141 children with severe constipation (median age 7.3 years). Painful defecation reduced in 62 patients (44%). Defecation frequency increased in 70 patients (60%). Overall, 98 patients (70%) had a positive response (defined as a decrease in defecatory pain or an increase in frequency of stool passage) to BT. Forty-seven (33%) of the children had a response lasting between 6 and 12 months, and 24 (17%) had a response that lasted longer than one year. Out of the 203 separate injections given, 28 (16%) patients reported a side-effect to an injection, the majority of which resolved within one week. The authors concluded that of botulinum toxin injections should be considered for children persistent chronic constipation, particularly early in the disease process, but that randomised studies are needed. Two retrospective cohort studies explored the effect of botulinum injections^{2, 3}. Basson 2014² evaluated success outcomes of intrasphincteric botulinum injection in children with

intractable constipation (n=29) however the results also included children with organic causes of constipation. No side effects post-procedure were recorded in the case-notes for any children. Results relating to other outcomes of interest for this review were not reported in this paper. Hallagan 2019³ reported improvements in clinical outcomes following anal sphincter botulinum toxin injection in children with various anorectal and colonic disorders (n=303); however, only 37% of the sample had CFC and sub-group analysis was not reported. This study was reported in an abstract only, limiting interpretation.

In summary: There is very low quality evidence that botulinum toxin injection for chronic constipation may be an effective method in managing children with functional constipation. Due to methodological limitations and limitations in the reporting of these studies we have very low confidence in this finding. High quality RCTs examining the use of botulinum toxin, and details relating to the delivery of the intervention, are required in order to provide a strong evidence base for its safety and effectiveness.

Evidence of effectiveness: surgical interventions delivered by consultant-led teams

(Level 3)

What is the effect of sacral neuro-modulation?

(Related studies n=9; Prospective cohort studies: Low ROB⁶⁻⁸; Moderate ROB⁹; High ROB¹⁰; Retrospective cohort studies: Low ROB¹¹⁻¹³; Moderate ROB¹⁴).

Peeters 2011¹⁴ provides an abstract reporting on short term results of conducting sacral neuromodulation (SNM) therapy in adolescents with CFC. In this retrospective cohort study 13 female patient records were examined with age ranging from 10-18 years. 11 out of 12 patients had spontaneous and regular defecation and had less abdominal pain in the 6 months follow up period post SNM impact. One lead revision and two pacemaker relocations were required.

Sulkowski 2015¹² performed a retrospective cohort study to identify the short-term impact of SNM on management of children with bowel and bladder dysfunction. Twenty-nine patients (median age 12.1 years) received the intervention. Median follow up period was 17.7 weeks. Five patients required reoperation due to a complication with battery placement. 55% of patients with a pre- SNM cecostomy tube no longer required an antegrade bowel regimen (due to return of voluntary bowel movements).

Van der wilt 2016⁸ performed a prospective cohort study examining the short-term effects of SNM in 27 female children (mean age of 16 years) with long term constipation. During the treatment, defecation frequency increased ($p < 0.001$), abdominal pain decreased ($p < 0.001$) with continuous improvement in symptoms observed during the follow-up period.

Van Wunnik 2012¹³ conducted a retrospective cohort study to examine the short term results of conducting SNM in adolescents with CFC. 12 female children, mean age 15.2 years, received a permanent implant. 10 children during follow up had spontaneous and regular defecation, without medication, felt the urge to defecate, and perceived less abdominal pain without relapse of symptoms until 6 months after implantation.

Janssen 2018¹¹ conducted a retrospective cohort study to compare long-term results of SNM between children and adults. 38 children, mean age 15.8 years, 6.7% male, received permanent SNM. Mean follow up period was 47 months. Defaecation frequency increased in both groups after SNM (frequency was higher in adults) for the duration of the follow-up period. QoL of children was impaired compared with the Dutch population with regard to bodily pain, general health and vitality.

Lu 2017⁶ conducted a prospective cohort study examining the use of SNM for children with constipation severe enough to be treated with ACE. 22 patients underwent the SNM procedure, with average age 12 years, 55% male. The median ACE frequency decreased from 7 per week to 1 per week (after follow up at 12 months). Ten children had their cecostomy/appendicostomy closed. Laxative use remained the same and 6 children experienced complications after SNM requiring further surgery.

Lu 2016⁷ provided an abstract reporting on a prospective study examining long-term outcomes for SNM treatment of constipation in children. 25 children's records were examined (17 with CFC), mean age 14 years, 52% male. Follow-up period was 2 years. Use of laxatives and ACE reduced, 62% of patients had their cocostomy/appendicostomy closed. 6 patients had complications requiring surgery. Overall, SNM led to continued symptomatic improvement in children with constipation 2 years after treatment initiation. Despite a 24% complication rate requiring additional surgery, nearly all parents reported health-related benefit and would recommend SNM to others.

Van der Wilt 2017⁹ conducted a prospective cohort study to examine the cost effectiveness of SNM compared to other treatments. 30 female participants were recruited to the study with mean age of 16 years. Using a Markov probabilistic model, the costs of SNM and conservative treatment were compared. Authors concluded that SNM is a potentially cost-

effective option for children and adolescents with chronic constipation refractory to conservative treatment.

Van der Wilt 2014¹⁰ is an abstract reporting on a cohort study (high risk of bias) examining the effectiveness of SNM on children with CFC. 33 patients (1 male) were included in the study, aged 10-20 years. Three patients showed no improvement and the electrode was removed. Mean defecation frequency increased from baseline to 3 weeks (during the test phase). Twelve patients still needed additional laxatives or bowel irrigation.

In summary: There is very low quality evidence that sacral neuro-modulation may be effective in treating the symptoms of CFC. Aspects commonly reported across studies include less abdominal pain, improvement in symptoms, complications.

What is the effect of anorectal myectomy?

(Related studies n = 4; Retrospective cohort studies: high ROB¹⁵. Prospective cohort studies: Moderate ROB¹⁶; High ROB^{17, 18}).

Peyvasteh 2015¹⁷ reported outcomes of children (n=48) who had undergone anorectal myectomy (mean age 4.4 years) for refractory constipation non-responsive to diet, laxative or enema treatment. Results based on child and parent subjective reporting showed that straining on defecation, defecation frequency and stool consistency significantly improved at 1-year follow-up (p<0.001).

Mousavi 2014¹⁸ reported outcomes of children (n=44) who had undergone anorectal myectomy (median age 4.6 years) for refractory constipation non-responsive to diet, laxative or enema treatment. Outcomes were measured through questionnaires however it is not clear what questionnaires were used or who completed them. Defecation frequency improvement was reported at short-term follow-up in 35 patients (79.5%). There was an overall improvement in 68.2% of the patients after 6 month's follow-up. One patient experienced complications of rectal bleeding which spontaneously stopped after 12 hours. The authors claimed that anorectal myectomy is an effective and technically simple procedure in selected patients with severe idiopathic constipation.

Redkar 2012¹⁵ conducted a retrospective cohort study investigating the effectiveness of anorectal myectomy in children (11 months – 9 years old) with chronic refractory constipation (n=28). Twenty-two of the 28 patients (93%) were reported to be relieved completely of symptoms, with another 4 children showing partial improvement requiring laxative therapy for maintaining regular bowel movements. There were no immediate post-operative complications recorded, however 1 patient developed faecal incontinence at longer

follow-up which was resolved over a 6-week period. The same authors conducted a similar, but prospective, cohort study investigating the effectiveness of anorectal myectomy in children with chronic refractory constipation (n=99 at follow-up)¹⁶. In this study, the mean age of patients at surgery was 4.1 years. Myomectomy was defined as successful based on daily and complete defecation without the need for medication or enemas. Of the 37 patients who had normal histology, 32 (86.5%) did not require any medication or enemas postoperatively.

In summary: There is some very low quality evidence that suggests anorectal myectomy may be effective at treating CFC, in children who have not responded to medical treatment. However, due to methodological limitations and low number of studies, the evidence is insufficient to support generalisable conclusions. It should be noted that these studies were conducted prior to the availability of botulinum toxin, which may provide a non-surgical alternative.

What is the effect of antegrade continence enema (ACE)/ Malone antegrade continence enema (MACE)?

(Related studies n = 17; Retrospective cohort studies: Low ROB¹⁹⁻²⁷; Moderate ROB^{28, 29}; High ROB^{30, 31}. Prospective cohort studies:; High ROB^{32, 33}. Survey: Low ROB³⁴, Mixed ROB^{35, 36}).

Basson 2014a²⁸ conducted a retrospective cohort study to evaluate outcomes after ACE procedure in children, aged 2 months to 16 years, with intractable constipation (total n=111, patients with CFC n=68). Complications occurred in 19% of patients with CFC including: stomal stenosis (n=9); granulation tissue (n=3); local infection/leakage (n=3); stoma leakage (n=1); stoma prolapse (n=1); creation of false passage (n=1), and incisional hernia (n=1). The authors state that “the majority of these complications were minor” but highlight the need to provide relevant information about risk. The ACE procedure was successful in almost 80% (n=54) of patients with CFC, defined as being totally clean or experience of occasional leak. The authors conclude that the ACE stoma is safe and effective in the management of children with faecal incontinence and constipation.

Dolejs 2017²¹ conducted a retrospective cohort study including 93 patients (median age 10 years) who had ACE for unremitting constipation and faecal incontinence. Bowel function had improved in 95% of patients (83% had normal bowel function) and encopresis was no longer present in 86% of patients at final follow-up (median time 26 months). A high overall

morbidity was present following ACE (55%). The authors suggest that effectiveness of ACE must be balanced with high morbidity rates.

Khoo 2017²³ conducted a retrospective cohort study including 84 children (median age 9 years) who had ACE performed for intractable idiopathic constipation. The ACE was considered successful if the child achieved continence (never or only rarely soiling). Twenty-nine of 83 (35%) children had their ACE closed; 21/83 (25%) of the closures occurred for resolution (success) whereas 8/83 children had their ACE closed due to failure of ACE. There were several complications following ACE formation including: ACE stenosis (n=10), ACE granulation (n=5), intolerance to intermittent catheterisation (n=11). The authors concluded that “whilst up to a third of patients can expect their intractable constipation to resolve, the majority of patients will remain reliant on their ACE. This group, clean but not cured, would benefit from improved management and novel treatments directed at restoring spontaneous defaecation”.

Mugie 2012³¹ conducted a retrospective cohort study including 99 patients (median age 8 years) who had ACE performed for chronic constipation, faecal incontinence or both. Only 35% of patients had functional constipation, whereas the remaining patients had organic causes of constipation. At a mean follow-up of 46 months (range 2 to 125 months) 71% of the children met the criteria for ‘success’ and were symptom-free. In 20% of the patients, symptoms improved significantly, but they experienced occasional faecal incontinence. The use of ACE failed in 7 patients. Complications were reported in 60% (n=59) of patients, with 12 of these patients experiencing a major complication that required hospital admission or surgical intervention. The authors conclude that ACE are “a successful and relatively safe therapeutic option”.

Siddiqui 2011²⁶ evaluated the long-term bowel management success of ACE in a retrospective cohort study including 117 paediatric patients (median age 11.1 years). Of the 105 patients (30 with CFC), 69% were reported to achieve successful long-term bowel management after ACE. Children with CFC significantly improved from baseline (pre-procedure) to final assessment (post procedure) ($p < 0.01$). ACE related complications were experienced in 74 (63%) patients with several patients experiencing more than 1 complication, however most complications were regarded as minor. Complications were most frequent in children who received percutaneous ACE. Thirty-nine (33%) required surgical revision of their stoma. The authors concluded that patients generally experience improvement in bowel management after an ACE procedure but there is a high incidence of minor complications and a frequent need for surgical intervention.

Gomez-Suarez 2016²² conducted a retrospective cohort study including 40 patients (median age 9.5 years), of whom 31 had CFC, who had ACE performed. A good outcome was defined as ≤ 1 episodes of soiling per week, a minimum defecation frequency of 4 times per week, and absence of abdominal pain or pain with defecation. Thirty of the 40 patients (75%) reported a good outcome. There was no difference in the outcome in patients with functional constipation compared with organic constipation. Abdominal pain improved post-ACE in 14 of the 24 patients who experienced abdominal pain pre-ACE. Complication that required additional surgery or complex care occurred in 12% and 35% of patients, respectively. Surgical revision was required in 5 patients.

Hoekstra 2011³⁰ conducted a retrospective cohort study including 23 patients (median age 7 years), of whom 15 had CFC, who had MACE performed for intractable constipation and/or faecal incontinence. Improvements were reported for defecation frequency and faecal incontinence after surgical intervention. A non-validated quality of life questionnaire was completed by 22 (96%) patients which showed an 86% satisfaction rate as a result of the Malone stoma. All 23 patients experienced either minor or major postoperative complications with the most commonly reported being: wound infection (52%), faecal leakage (43%) and stomal stenosis (39%). Almost half of the patients still experienced occasional abdominal pain post-MACE. The authors concluded that MACE is an effective alternative treatment option in children with intractable organic or functional constipation and/or faecal incontinence not responding to conventional conservative laxative therapy, although the number of complications was high.

Youssef 2002²⁷ conducted a retrospective cohort study to assess the effect of ACE in 12 otherwise "healthy" children with CFC (mean age 8.7 years). At follow-up after ACE (mean time 13.1 months) there were significant improvements in defecation frequency ($p < 0.005$), faecal incontinence ($p < 0.01$), abdominal pain ($p < 0.005$), school attendance ($p < 0.02$) and emotional health ($p < 0.005$). The number of medications used ($p < 0.005$) and physician visits per year ($p < 0.05$) significantly reduced. Four postoperative adverse events were recorded, although none of these led to discontinuation of ACE use. The authors suggested that ACE should be considered before proceeding with partial or total colectomy, in children with severe CFC.

Randall 2014³³ conducted a cohort study to assess the long-term outcomes of ACE in 203 patients (126 with CFC) aged between 3 and 17 years. At the last follow up (median 5.5 years), 132 patients were still using their ACE, of which ACE was reported to prevent soiling

in 79 patients (75%). Over a quarter of children had reversal of ACE following resolution of symptoms.

Peeraully 2014²⁴ explored the long term (15 year) outcomes of children who underwent MACE procedures. 40 records were analysed, reporting on children with median age of 15.5 years and 72.5% male. Sixteen of 40 children had CFC. 80% of children had at least one complication following the MACE procedure with 25% of children experiencing multiple complications. 32.5% of patients stopped using their MACE (reasons being ineffective (5%), psychological factors (2.5%) and developing spontaneous and regular bowel movement (17.5%). 27.5% of children underwent a MACE reversal procedure during follow-up (reasons being return to spontaneous and regular bowel movement (10%), reversal secondary to stomal problems (10%)). Overall, a high success rate of 92.5% for MACE procedures was observed with a significant proportion of patients having a MACE reversal procedure due to the return of normal bowel habits.

Three small retrospective cohort studies also evaluated longer term outcome of ACE procedures in children^{20, 29, 32}. Within the Chong 2016²⁰ study, Only 14 of the included children, aged 5-12 at the time of the ACE procedure, had CFC; 3 of 14 patients (21%) experienced normal defecation frequency without soiling after ACE formation at 5-year follow-up. Eight of the 14 patients were still using the ACE with good results. Within the Mousa 2006³² study, only nine children (mean age 12 years) had CFC; these children had the ACE procedure through cecostomy. The mean follow-up was 11 months ranging between 1 month and 45 months. The findings were based on parent responses to interview questions. Post-ACE compared to pre-ACE, defecation frequency ($p<0.01$), global health score ($p=0.01$), and soiling ($p=0.01$) significantly improved. School attendance did improve but not to a significant level. Both authors concluded that ACE is safe and helpful in the management of intractable constipation and faecal incontinence in children with different underlying etiologies. Husberg 2011²⁹ report findings in an abstract of a cohort study they conducted to assess the long-term outcome of MACE in children aged 5-21 years ($n=27$). Only two of these patients had CFC. Of the 23 patients who had continued to use their ACE, 17 were reported to be fully continent and 6 had occasional leakage. However, it is unclear whether the 2 patients with CFC continued to use their ACE.

Bellomo-Branda 2018¹⁹ is an abstract reporting a retrospective cohort study to investigate the effect of ACE on children with refractory constipation and overflow retentive stool incontinence (ORSI). 16 participants took part (no age or gender related information was provided). Findings from the study showed that children who underwent the ACE procedure

successfully stopped using their ACE more frequently and faster than children using rectal enemas.

Three survey studies explored perceived effects of ACE / MACE procedures³⁴⁻³⁶. Har 2013³⁴ aimed to explore if the MACE procedure had an impact on children's quality of life. Fifteen children with unremitting functional constipation and/or encopresis, mean age 9.8 years, were included in the study. The results showed an improvement in QOL at 6 months and 12 months post-MACE procedure (p=0.03). Church 2017³⁵ aimed to investigate the success of ACE in children, mean age 8.9 years, with encopresis (n=10). All patients experienced faecal incontinence before the procedure, whereas 62.5% of patients reported absence of incontinence post procedure. King 2005³⁶ interviewed children (n=1) and parents (n=41) of children who had undergone the ACE procedure for idiopathic constipation. The mean follow-up was 48-months post-surgery and mean age of the children was 13.1 years. The survey results showed improvements in quality of life (p<0.001), soiling frequency (p<0.001), abdominal pain frequency and severity (p<0.001) after receiving the ACE procedure. Most children (30/42, 71%) had symptoms during ACE at some stage of treatment. Symptoms included cramping (18/30), nausea (17/30), vomiting (7/30), sweating (14/30), dizziness (10/30), and pallor (10/30). Three or more symptoms were present in 40% of patients. Granulation tissue was the most common long-term complication but was able to be adequately controlled in 85% of the affected patients. 36% of parents reported that their children were embarrassed about the device.

In summary: There is very low certainty that the use of ACE/MACE may be effective for CFC. Although studies were consistent in their findings that ACE/MACE is effective, many of the outcomes of interest were not addressed by the studies. Complications (e.g. granulation, leakage, additional surgery required) arising from ACE/MACE use were common.

What is the effect of MACE compared to caecostomy button?

(related studies n = 1³⁷, Low ROB)

Cascio 2014³⁷ conducted a retrospective cohort study to explore outcomes of children, aged 3-18 years, who had either MACE (n=37) or caecostomy button (CB, n=12) performed.

Soiling stopped completely in 81% and 75% of patients who had received MACE and CB, respectively. MACE failed in 16% of patients, whereas CB failed in 8% of patients.

Complications requiring operative intervention after MACE occurred in 22% of patients.

There were no operative complications after CB. Complications that did not require operative

intervention occurred in 19% of patients after MACE and 92% of patients after CB. The authors suggest that CB is a safe and effective alternative to MACE.

In summary: There is some very low quality evidence that caecostomy button may have less complications than MACE, but this is insufficient to support generalisable conclusions.

What is the effect of ACE compared to sacral nerve stimulation?

(Related studies n=2; Retrospective cohort study³⁸: low ROB; Prospective cohort study³⁹: moderate ROB).

We identified two retrospective cohorts which investigate the effect of ACE compared to sacral nerve stimulation (SNS) in paediatric patients with CFC and faecal incontinence^{38,39}. The study reports are very similar and studies were conducted by the same research team. Wang 2019³⁹ is reported as an abstract only. It is unclear whether some of the same patients were included in both analyses, and both studies have similar findings; therefore, below we only report on the results from the Vriesman 2020³⁸ paper.

Vriesman 2020³⁸ conducted a retrospective cohort study to investigate the effect of ACE compared to sacral nerve stimulation (SNS) in paediatric patients with CFC and faecal incontinence. Twenty-three patients were treated with ACE and 19 patients were treated with SNS (median age 10 years). Faecal incontinence improved significantly better for the SNS group compared to the ACE group at 12 (p=0.03) and 24 (p=0.02) months. Defecation frequency and abdominal pain significantly improved for the ACE group but not the SNS group. Defecation frequency was significantly greater for the ACE group than the SNS group at all follow-up time points (all P<.05). Patients treated with ACE were more likely to be able to discontinue oral and/or rectal laxative use at all follow-up time points compared to patients treated with SNS (p<0.01). Complications were significantly more common in the ACE group (83%) compared with the SNS group (26%). The authors suggest that although both treatments are considered minimally invasive, they still require surgical procedures with risk of severe complications and should only be considered in patients with severe symptoms refractory to conventional treatment. The authors conclude that SNS may be more effective in children with incontinence, but more regular bowel movements, and ACE more effective at improving outcomes in those with a reduced number of bowel movements.

In summary: There is some very limited evidence that SNS may be superior to ACE for faecal incontinence, ACE superior to SNS at improving defecation frequency in those with reduced bowel movements, and that SNS may have less complications than ACE. This evidence is insufficient to support generalizable conclusions.

What is the effect of colonic resection?

(Related studies n = 2^{40,41}; Retrospective cohort study⁴⁰: moderate ROB; Prospective cohort study⁴¹: low ROB).

Tamura 2020⁴¹ evaluated the outcome of colonic resection in 22 children with idiopathic constipation (median age 13.7 years) for whom other treatments, including ACE or stoma, had been previously tried. Differences of outcomes between 3 different resection procedures (pan-proctocolectomy with ileal pouch anal anastomosis (IPAA), pan-colectomy with ileorectal anastomosis (IR), segmental resections (SR)) were also compared. Bowel function outcomes were categorised into 3 groups: i) Good: defecating through anus with no soiling, ii) Intermediate: defecating through anus with occasional soiling or requiring ACE, iii) Poor: permanent stoma. Ten patients (45%) achieved a good outcome, 4 patients (18%) achieved an intermediate outcome and 8 patients (36%) were left with a poor outcome. There was no significant relationship between type of surgery and outcome. Five acute postsurgical complications were recorded. There was no significant relationship between the procedures and the incidence of complications.

Bonilla 2013⁴⁰ reports retrospective data relating to paediatric patients (n=12) who failed to improve after ACE. This is a subgroup of 67 children who underwent ACE. All 12 patients (mean age 15 years) received colon resection (total or near total n=8, partial n=4). Post-operative complications included wound infection and fistula formulation. Nine of the 12 patients had good clinical outcomes at long-term (at least 3-year) follow-up although it is unclear how the outcome measures were collected.

In summary: There is very low quality evidence which suggests outcomes were mixed for the use of colonic resection to treat the symptoms of CFC. There is insufficient evidence to suggest the use of colonic resection is safe and effective for the treatment of CFC. The population of children to whom this evidence relates is limited to those with CFC for whom other treatments, including ACE, have failed.

What is the effect of colonic resection combined with malone appendicostomy?

(Related studies n=1⁴²; Retrospective cohort study: moderate ROB)

Gasior 2018⁴² reported outcomes of children (n=31, median age 12 years) who had undergone laparoscopic sigmoid resection combined with Malone appendicostomy, having failed to respond to medical management. Soiling was absent in 30 patients out of the 31 (97%) after surgery (median follow-up 10.3 months). Five postoperative complications were reported including colitis (n=2), Malone stricture (n=1) and anastomotic stricture (n=2) all of

which were rectified with further intervention. The authors suggested that colorectal surgery can effectively manage functional constipation in paediatric patients who have previously failed medical management.

In summary: There is very low quality evidence which suggests colonic resection combined with Malone appendicostomy may be safe and effective to treat the symptoms of CFC. There is only one small study, providing insufficient evidence to support generalisable conclusions.

What is the effect of surgical intervention (ileostomy, colostomy or (sub)total colectomy)?

(Related studies n=1⁴³; Prospective cohort study: Low ROB)

Kuizenga-Wessel 2017⁴³ assessed outcomes of surgical intervention (ileostomy, colostomy or (sub)total colectomy) in children with CFC (n=37). The median age at time of surgery was 68 months. Based on parental questionnaire responses, the study reported the incidence of defecation frequency, faecal incontinence abdominal pain, and school attendance. However, as these incidence rates were not compared to pre-surgery rates, it was not possible to determine whether there had been an improvement in any of these outcomes. The majority of parents (91%) were satisfied with the outcome of the surgical intervention. In total, 28 of 33 patients (85%) fulfilled the authors' criteria for success ("defined as no longer fulfilling the Rome III criteria for FC in patients after stoma closure or as having a functional ostomy in children with an ileostomy or colostomy, independent of pharmacological treatment"). The authors concluded that surgical interventions can lead to improvement of FC symptoms in children with intractable FC. The lack of data pre-surgical intervention limits understanding of effectiveness of the interventions.

In summary: There is insufficient evidence to support generalisable conclusions about the effectiveness of ileostomy, colostomy or (sub)total colectomy in the treatment of CFC.

References

1. Zar-Kessler C, Kuo B, Belkind-Gerson J. Botulinum toxin injection for childhood constipation is safe and can be effective regardless of anal sphincter dynamics. *J Pediatr Surg* 2018;**53**:693-7. <http://dx.doi.org/10.1016/j.jpedsurg.2017.12.007>
2. Basson S, Charlesworth P, Healy C, Phelps S, Cleeve S. Botulinum toxin use in paediatric colorectal surgery. *Pediatr Surg Int* 2014;**30**:833-8. <http://dx.doi.org/10.1007/s00383-014-3536-4>

3. Hallagan AP, H.; Ryan, K.; Halleran, D.; Levitt, M.; Wood, R.; Bali, N.; Vaz, K.; Yacob, D.; Di Lorenzo, C.; Lu, P. NASPGHAN Annual Meeting Abstracts. *Journal of Pediatric Gastroenterology & Nutrition* 2019;**69**:S1-S473.
<http://dx.doi.org/10.1097/mpg.0000000000002518>
4. Ahmadi J, Azary S, Ashjaei B, Paragomi P, Khalifeh-Soltani A. Intraspincteric botulinum toxin injection in treatment of chronic idiopathic constipation in children. *Iran J Pediatr* 2013;**23**:574-8.
5. Hameed AMN, L. T.; Al-Ghafoor, B. H. A. Evaluation the efficacy and outcome of intersphincteric injection of botulinum toxin in the treatment of children with chronic idiopathic constipation in iraqi hospital. *International Journal of Pharmaceutical Sciences Review and Research* 2018;**52**:142-9.
6. Lu PL, Asti L, Lodwick DL, Nacion KM, Deans KJ, Minneci PC, *et al.* Sacral nerve stimulation allows for decreased antegrade continence enema use in children with severe constipation. *J Pediatr Surg* 2017;**52**:558-62.
<http://dx.doi.org/10.1016/j.jpedsurg.2016.11.003>
7. Lu PLK, I. J.; Orsagh-Yentis, D. K.; Leonhart, K.; Ambeba, E. J.; Deans, K. J.; Minneci, P. C.; Diefenbach, K. A.; Alpert, S. A.; Benninga, M. A.; Yacob, D.; Di Lorenzo, C. World Congress of Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2016;**63 Suppl 2**:S1-S415.
<http://dx.doi.org/10.1097/01.mpg.0000503536.79797.66>
8. van der Wilt AA, van Wunnik BP, Sturkenboom R, Han-Geurts IJ, Melenhorst J, Benninga MA, *et al.* Sacral neuromodulation in children and adolescents with chronic constipation refractory to conservative treatment. *Int J Colorectal Dis* 2016;**31**:1459-66.
<http://dx.doi.org/10.1007/s00384-016-2604-8>
9. van der Wilt AA, Groenewoud HHM, Benninga MA, Dirksen CD, Baeten C, Bouvy ND, *et al.* Cost-effectiveness of sacral neuromodulation for chronic refractory constipation in children and adolescents: a Markov model analysis. *Colorectal Dis* 2017;**19**:1013-23.
<http://dx.doi.org/10.1111/codi.13869>
10. Van Der Wilt AAB, S. O.; Han, I. J.; Melenhorst, J.; Benninga, M. A.; Baeten, C. G. M. I. Sacral neuromodulation in adolescents with constipation refractory to conservative treatment *Colorectal Disease* 2014;**16**:21-36. <http://dx.doi.org/10.1111/codi.12708>
11. Janssen PTJ, Meyer YM, Van Kuijk SMJ, Benninga MA, Stassen LPS, Bouvy ND, *et al.* Long-term outcome of intractable constipation treated by sacral neuromodulation: a comparison between children and adults. *Colorectal Dis* 2018;**20**:134-43.
<http://dx.doi.org/10.1111/codi.13837>
12. Sulkowski JP, Nacion KM, Deans KJ, Minneci PC, Levitt MA, Mousa HM, *et al.* Sacral nerve stimulation: a promising therapy for fecal and urinary incontinence and constipation in children. *J Pediatr Surg* 2015;**50**:1644-7.
<http://dx.doi.org/10.1016/j.jpedsurg.2015.03.043>
13. van Wunnik BP, Peeters B, Govaert B, Nieman FH, Benninga MA, Baeten CG. Sacral neuromodulation therapy: a promising treatment for adolescents with refractory functional constipation. *Dis Colon Rectum* 2012;**55**:278-85.
<http://dx.doi.org/10.1097/DCR.0b013e3182405c61>
14. Benninga MA. Fifth European Paediatric Motility Meeting. Introduction. *J Pediatr Gastroenterol Nutr* 2011;**53 Suppl 2**:S1. <http://dx.doi.org/10.1097/MPG.0b013e31823cad6>
15. Redkar RG, Mishra PK, Thampi C, Mishra S. Role of rectal myomectomy in refractory chronic constipation. *Afr J Paediatr Surg* 2012;**9**:202-5.
<http://dx.doi.org/10.4103/0189-6725.104720>

16. Redkar RG, Raj V, Bangar A, Hathiramani V, Chigicherla S, Tewari S. Role of ano rectal myomectomy in children with chronic refractory constipation. *Afr J Paediatr Surg* 2018;**15**:31-5. http://dx.doi.org/10.4103/ajps.AJPS_99_17
17. Peyvasteh M, Askarpour S, Talaiezadeh AH, Imani MR, Javaherizadeh H. Results of Posterior Myectomy for the Treatment of Children with Chronic Constipation. *Arq Gastroenterol* 2015;**52**:299-302. <http://dx.doi.org/10.1590/S0004-28032015000400009>
18. Mousavi SA, Karami H, Rajabpoor AA. Intractable chronic constipation in children: outcome after anorectal myectomy. *Afr J Paediatr Surg* 2014;**11**:147-9. <http://dx.doi.org/10.4103/0189-6725.132810>
19. Bellomo-Brandao MAA, V. P. A.; Bustorff-Silva, J. M.; Lomazi, E. A. Long-term outcomes in children with refractory constipation treated by conservative therapy or by antegrade continence enema procedure (ACE). *Journal of Pediatric Gastroenterology and Nutrition* 2018;**66**:448.
20. Chong C, Featherstone N, Sharif S, Cherian A, Cuckow P, Mushtaq I, *et al.* 5 years after an ACE: what happens then? *Pediatr Surg Int* 2016;**32**:397-401. <http://dx.doi.org/10.1007/s00383-016-3857-6>
21. Dolejs SC, Smith JK, Jr., Sheplock J, Croffie JM, Rescorla FJ. Contemporary short- and long-term outcomes in patients with unremitting constipation and fecal incontinence treated with an antegrade continence enema. *J Pediatr Surg* 2017;**52**:79-83. <http://dx.doi.org/10.1016/j.jpedsurg.2016.10.022>
22. Gomez-Suarez RA, Gomez-Mendez M, Petty JK, Fortunato JE. Associated Factors for Antegrade Continence Enemas for Refractory Constipation and Fecal Incontinence. *J Pediatr Gastroenterol Nutr* 2016;**63**:e63-8. <http://dx.doi.org/10.1097/MPG.0000000000001280>
23. Khoo AK, Askouni E, Basson S, Ng J, Cleeve S. How long will I have my ACE? The natural history of the antegrade continence enema stoma in idiopathic constipation. *Pediatr Surg Int* 2017;**33**:1159-66. <http://dx.doi.org/10.1007/s00383-017-4128-x>
24. Peeraully MR, Lopes J, Wright A, Davies BW, Stewart RJ, Singh SS, *et al.* Experience of the MACE procedure at a regional pediatric surgical unit: a 15-year retrospective review. *Eur J Pediatr Surg* 2014;**24**:113-6. <http://dx.doi.org/10.1055/s-0033-1357502>
25. Rodriguez L, Nurko S, Flores A. Factors associated with successful decrease and discontinuation of antegrade continence enemas (ACE) in children with defecation disorders: a study evaluating the effect of ACE on colon motility. *Neurogastroenterol Motil* 2013;**25**:140-e81. <http://dx.doi.org/10.1111/nmo.12018>
26. Siddiqui AA, Fishman SJ, Bauer SB, Nurko S. Long-term follow-up of patients after antegrade continence enema procedure. *J Pediatr Gastroenterol Nutr* 2011;**52**:574-80. <http://dx.doi.org/10.1097/MPG.0b013e3181ff6042>
27. Youssef NN, Barksdale Jr E, Griffiths JM, Flores AF, Di Lorenzo C. Management of intractable constipation with antegrade enemas in neurologically intact children. *J Pediatr Gastroenterol Nutr* 2002;**34**:402-5. <http://dx.doi.org/10.1097/00005176-200204000-00016>
28. Basson S, Zani A, McDowell S, Athanasakos E, Cleeve S, Phelps S, *et al.* Antegrade continence enema (ACE): predictors of outcome in 111 patients. *Pediatr Surg Int* 2014;**30**:1135-41. <http://dx.doi.org/10.1007/s00383-014-3602-y>
29. Husberg BO-J, M.; Michanec, M.; Frenckner, B.; Svensson, J. Lunchtime Posters. *Colorectal Disease* 2011;**13**:16-27. <http://dx.doi.org/10.1111/j.1463-1318.2011.02706.x>
30. Hoekstra LT, Kuijper CF, Bakx R, Heij HA, Aronson DC, Benninga MA. The Malone antegrade continence enema procedure: the Amsterdam experience. *J Pediatr Surg* 2011;**46**:1603-8. <http://dx.doi.org/10.1016/j.jpedsurg.2011.04.050>

31. Mugie SM, Machado RS, Mousa HM, Punati JB, Hogan M, Benninga MA, *et al.* Ten-year experience using antegrade enemas in children. *J Pediatr* 2012;**161**:700-4.
<http://dx.doi.org/10.1016/j.jpeds.2012.04.042>
32. Mousa HM, van den Berg MM, Caniano DA, Hogan M, Di Lorenzo C, Hayes J. Cecostomy in children with defecation disorders. *Dig Dis Sci* 2006;**51**:154-60.
<http://dx.doi.org/10.1007/s10620-006-3101-7>
33. Randall J, Coyne P, Jaffray B. Follow up of children undergoing antegrade continent enema: experience of over two hundred cases. *J Pediatr Surg* 2014;**49**:1405-8.
<http://dx.doi.org/10.1016/j.jpedsurg.2014.02.090>
34. Har AF, Rescorla FJ, Croffie JM. Quality of life in pediatric patients with unremitting constipation pre and post Malone Antegrade Continence Enema (MACE) procedure. *J Pediatr Surg* 2013;**48**:1733-7. <http://dx.doi.org/10.1016/j.jpedsurg.2013.01.045>
35. Church JT, Simha S, Wild LC, Teitelbaum DH, Ehrlich PF. Antegrade continence enemas improve quality of life in patients with medically-refractory encopresis. *J Pediatr Surg* 2017;**52**:778-82. <http://dx.doi.org/10.1016/j.jpedsurg.2017.01.042>
36. King SK, Sutcliffe JR, Southwell BR, Chait PG, Hutson JM. The antegrade continence enema successfully treats idiopathic slow-transit constipation. *J Pediatr Surg* 2005;**40**:1935-40. <http://dx.doi.org/10.1016/j.jpedsurg.2005.08.011>
37. Cascio S, Flett ME, De la Hunt M, Barrett AM, Jaffray B. MACE or caecostomy button for idiopathic constipation in children: a comparison of complications and outcomes. *Pediatr Surg Int* 2004;**20**:484-7. <http://dx.doi.org/10.1007/s00383-004-1220-9>
38. Vriesman MH, Wang L, Park C, Diefenbach KA, Levitt MA, Wood RJ, *et al.* Comparison of antegrade continence enema treatment and sacral nerve stimulation for children with severe functional constipation and fecal incontinence. *Neurogastroenterol Motil* 2020;**32**:e13809. <http://dx.doi.org/10.1111/nmo.13809>
39. Wang LV, M. H.; Halleran, D. R.; Diefenbach, K. A.; Levitt, M. A.; Wood, R. J.; Alpert, S. A.; Benninga, M. A.; Bali, N.; Vaz, K.; Yacob, D.; Lorenzo, C. D.; Lu, P. L. PROSPECTIVE COMPARISON OF SACRAL NERVE STIMULATION VERSUS ANTEGRADE CONTINENCE ENEMAS FOR CHILDREN WITH SEVERE FUNCTIONAL CONSTIPATION. *Gastroenterology* 2019;**156**:S-201.
<http://dx.doi.org/http://dx.doi.org/10.1016/S0016-5085%2819%2937294-4>
40. Bonilla SF, Flores A, Jackson CC, Chwals WJ, Orkin BA. Management of pediatric patients with refractory constipation who fail cecostomy. *J Pediatr Surg* 2013;**48**:1931-5.
<http://dx.doi.org/10.1016/j.jpedsurg.2012.12.034>
41. Tamura R, Jaffray B. Outcomes of colonic resection for chronic idiopathic constipation in childhood. *J Pediatr Surg* 2020;**55**:269-72.
<http://dx.doi.org/10.1016/j.jpedsurg.2019.10.047>
42. Gasior A, Reck C, Vilanova-Sanchez A, Diefenbach KA, Yacob D, Lu P, *et al.* Surgical management of functional constipation: An intermediate report of a new approach using a laparoscopic sigmoid resection combined with malone appendicostomy. *J Pediatr Surg* 2018;**53**:1160-2. <http://dx.doi.org/10.1016/j.jpedsurg.2018.02.074>
43. Kuizenga-Wessel S, Koppen IJN, Zwager LW, Di Lorenzo C, de Jong JR, Benninga MA. Surgical management of children with intractable functional constipation; experience of a single tertiary children's hospital. *Neurogastroenterol Motil* 2017;**29**:e13005.
<http://dx.doi.org/10.1111/nmo.13005>