Received: 23 March 2024 | Accepted: 5 September 2024

DOI: 10.1002/jpn3.12376

JPGN

INVITED REVIEW

Endoscopy and Procedures

# Drugs in focus: Botulinum toxin in the therapy of gastrointestinal disorders in children

**Matjaž Homan[1] | Mike Thomson[2] | Patrick Bontems[3] | Marco Deganello Saccomani[4] | Jorge Amil Dias[5] | Simona Faraci[6] | Raoul Furlano[7] | Iva Hojsak[8] | Oren Ledder[9] | Mordechai Slae[10] | Priya Narula[2] | Andreia Florina Nita[11] | Lorenzo Norsa[12] | Salvatore Oliva[13] | Alexandra Papadopoulou[14] | Claudio Romano[15] | Anna Rybak[11] | Vasiliki Spyropoulou[16] | Renato Tambucci[6] | Christos Tzivinikos[17] | Michiel van Wijk[18] | Osvaldo Borrelli[11] | Endoscopy SIG and Motility SIG of ESPGHAN Organisation**

[1]Department of Gastroenterology, Hepatology, and Nutrition, University Children's Hospital, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[2]Department of Paediatric Gastroenterology, Sheffield Children's Hospital NHS FT and University of Sheffield, Sheffield, UK

[3]Paediatric Gastroenterology, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium

[4]Department of Paediatrics, Woman's and Child's University Hospital of Verona, Verona, Italy

[5]Department of Gastroenterology, Hospital Lusíadas, Porto, Portugal

[6]Gastroenterology and Nutrition Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[7]Department of Gastroenterology, University Children's Hospital Basel (UKBB), University of Basel, Basel, Switzerland

[8]Children's Hospital Zagreb, University of Zagreb Medical School, Zagreb, Croatia

[9]Juliet Keidan Institute of Pediatric Gastroenterology, Shaare Zedek Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel

[10]Pediatric Gastroenterology, Hepatology and Nutrition Unit, Hadassah University Hospital, Jerusalem, Israel

[11]Paediatric Gastroenterology Department, Great Ormond Street Hospital, London, UK

[12]Pediatric Department, Children's Hospital Vittore Buzzi, University of Milan, Milan, Italy

[13]Pediatric Gastroenterology and Liver Unit, Maternal and Child Health Department, Sapienza—University of Rome, Rome, Italy

[14]Division of Gastroenterology and Hepatology, First Department of Pediatrics, University of Athens, Children's Hospital Agia Sofia, Athens, Greece

[15]Claudio Romano Pediatric Gastroenterology and Cystic Fibrosis Unit, University of Messina, Messina, Italy

[16]Division of Gastroenterology, Hepatology and Nutrition, University Children's Hospital Zurich, Zurich, Switzerland

[17]Pediatric Gastroenterology Department, Al Jalila Children's Specialty Hospital, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates

[18]Emma Children's Hospital-Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

**Correspondence**

Matjaž Homan, Department of Gastroenterology, Hepatology, and Nutrition, University Children's Hospital, Faculty of Medicine, University of Ljubljana, 1000 Ljubljana, Slovenia.
Email: matjaz.homan@guest.arnes.si

**KEYWORDS**

constipation, oesophagus, weight loss

Disclaimer: Although this paper is produced by the Endoscopy SIG and Motility SIG of ESPGHAN it does not necessarily represent ESPGHAN policy and is not endorsed by ESPGHAN.

## 1 | INTRODUCTION

Botulinum toxin (BoNT) is a protein produced by the anaerobic bacterium *Clostridium botulinum* and its related species. There are several types of BoNT. BoNT Type A was first described for medical use in the 1970s by Dr. Alan Scott.[1] The drug was named 'Botox' after Dr. Scott sold the rights to the pharmaceutical company Allergan (Botox; Allergan Pharmaceuticals).[2] Since then, research about BoNT has increased significantly, and newer formulations with an increasingly broad range of indications have become available.

The main action of BoNT is related to the prevention of acetylcholine release from axon terminals at the neuromuscular junction. The toxin cleaves the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE). SNARE contributes to the formation of synaptic fusion between acetylcholine-containing vesicles and the plasma membrane of the axon terminal. Thus, BoNT inhibits the connection of vesicles with the axonal membrane, preventing the release of acetylcholine into the synaptic cleft.[3] This results in functional muscle paralysis that lasts for several months.[4] Although the effect on the neuromuscular junction is considered the most important, this is not the only mechanism of action. Animal models have shown that BoNT reduces and alters neuropathic pain by inhibiting the secretion of pain mediators but also reduces local inflammation around nerve endings and affects axonal transport.[5] These effects could explain the efficacy of BoNT treatment in various medical indications.

Currently, four BoNT formulations are approved: OnabotulinumtoxinA (Botox®), AbobotulinumtoxinA (Dysport®), IncobotulinumtoxinA (Xeomin®) and Rimabotulinumtoxin B (Myobloc®).[4] The therapeutic use of the formulations consists of injecting small amounts of type A or type B toxin directly into specific muscles to release muscle spasm attempting to relieve associated symptoms.[6] Since its initial use in the treatment of strabismus, the number of therapeutic indications for BoNT in other systems, including the gastrointestinal tract, has increased significantly.[7] In paediatric gastroenterology, in particular, BoNT is mainly used to treat intestinal motility disorders and is usually administered endoscopically as an injection into the target muscle under direct vision. Diseases for which it may be used include oesophageal achalasia, gastroparesis, Hirschsprung's disease (HD), achalasia of the internal anal sphincter (IAS) and refractory constipation.[6] Reported adverse events are rare and usually temporary, mainly related to the site of injection.[3] Described complications include transient chest pain, heartburn, skin rash and transient faecal incontinence.[8,9] Serious complications, such as pharyngocutaneous fistulae, mediastinitis and perforation of the oesophagus have also been reported but only in the treatment of hypertensive upper oesophageal sphincter.[10] Furthermore, several cases of iatrogenic botulism due to accidental overdose or use of contaminated (substandard) products have been described after bariatric procedures, for which there is no clear indication.[11]

**What is Known**

- Botulinum toxin (BoNT) causes muscle relaxation by inhibiting acetylcholine release from presynaptic motor neurons at the neuromuscular junction.

**What is New**

- In children with achalasia, BoNT can be considered only in patients in whom rapid weight gain is important to improve surgical outcomes.
- BoNT has been suggested for treating cricopharyngeal achalasia and delayed gastric emptying.
- Anal achalasia and constipation after Hirschsprung disease corrective surgery are very promising indications for BoNT use.
- In selected children with resistant type of functional constipation and chronic anal fissure, BoNT is a viable option for treating.

The purpose of this paper is to describe the indications (if any), techniques and limitations of using BoNT in paediatric gastroenterology.

## 2 | METHODS

Members of the Endoscopy SIG (Special interest group) and Motility SIG of ESPGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition) with clinical experience of this area were involved in a critical assessment of the available literature. The participating members of both SIG were divided into five working groups of coauthors based on expertise and knowledge of five topics: Introduction (basics about toxin), Use of BoNT in oesophagus, Use of BoNT in stomach, Use of BoNT in intestine, Summary and conclusions. A systematic literature review was performed using PubMed, MEDLINE, EMBASE, Cochrane library and Scopus databases until November 2023 using the following subject headings and keywords: 'Botox', 'botulin toxin', 'oesophagus', 'stomach', 'Hirschsprung disease', 'weight loss', 'achalasia' and 'constipation'. The review was limited to research on humans in journal articles published in English. A critical evaluation in each area was produced and collated by M. H. with subsequent repeated feedback and appraisal by the other authors.

# 3 | RESULTS

## 3.1 | BoNT in oesophageal disorders in children

### 3.1.1 | BoNT injections in the upper oesophageal sphincter

#### 3.1.1.1 | *Cricopharyngeal achalasia*

Paediatric cricopharyngeal achalasia is rare and, although the aetiology is poorly understood, the immaturity of the neuromuscular system is believed to play a role. Scholes et al. describe the use of BoNT in six patients (0.4–10 years) with cricopharyngeal achalasia who were injected with a mean dose of 5.6 U/kg (1.6–7.9 U/kg, median 6 U/kg). Median interval between doses was 13 months (range: 8–18 months) and injected under direct vision with laryngoscopy, into the cricopharyngeal muscle in two to four areas, avoiding the anterior cricopharyngeus because of proximity to the glottis. Of the six patients treated, two eventually required myotomy. In another series including five patients with cricopharyngeal achalasia referred to myotomy, BoNT was subsequently used in one patient for residual dysphagia with partial improvement. A third small case series reports on three infants aged 4.4 and 5 months, who received injections with 5.1, 2.2 and 1.4 U/kg and were followed for 34, 13 and 4 months, respectively. All needed at least one repeat injection and had complete resolution of symptoms at their last visit.[12] Case reports show varying results.[13–15]

Episodes of aspiration after the procedure were mentioned in 2/14 patients that were included in the aforementioned case series.[12,16]

Cricopharyngeal achalasia does occur in adults, but mostly because of progressive neurological disease or the complications of head and neck cancers. As the aetiology is clearly different, we do not present adult data on the efficacy of BoNT injections in adults.

#### 3.1.1.2 | *Retrograde cricopharyngeal dysfunction*

Retrograde cricopharyngeal dysfunction or the 'inability to belch syndrome' is recognised more often in recent years. The first paediatric case series with five female adolescents was recently published.[17] All patients received BoNT injections in the cricopharyngeal muscle and all had significant improvement after their treatment (median follow-up 6 months [0.1–9 months]). One patient required a second treatment with BoNT injections 8 months after the first injection.[17] These results are in line with previous case series in adults that showed excellent results.[18,19]

### 3.1.2 | Botox injections in the lower oesophageal sphincter (LOS)

Historically, BoNT was used as an alternative treatment to dilation in achalasia.[20] During upper endoscopy, 100 IU of BoNT is injected into the LOS, with each quadrant receiving one-quarter of the dose. A paediatric case series identified only short-lived symptomatic improvement in 19/23 cases. Six required subsequent surgery, and the mean duration of the BoNT effect was 4.2 ± 4.0 months (Figure 1).[21] Consequently, the authors of the study suggested that BoNT might be indicated only in children with achalasia who are poor candidates for dilation or surgery. In another cohort of seven patients (median age 9 years [2–15 years]), three showed sustained response of BoNT beyond 6 months of follow-up and again after a second injection when symptoms recurred.[9] In this study, pretreatment LOS pressure was inversely related to the duration of the effect of BoNT.

In a retrospective comparison of Heller's myotomy (HM) with pneumatic dilation (PD) with or without BoNT injections, it was concluded that BoNT is inferior to HM, but only three out of the 14 patients treated with PD received BoNT. None of them had sustained resolution of symptoms.[22] Finally Khoshoo et al. describe three patients, aged 8, 11 and 13 years, who showed resolution of symptoms for 5, 3 and 10 months after injection with 20 U of BoNT in each quadrant of the LOS.[23]

In adults, a meta-analysis included nine prospective case-control and cohort studies evaluating the efficacy of BoNT injections. A treatment response (Eckardt score ≤ 3) was seen in 79% of patients at 1 month, with response rate dropping to 70%, 53% and 41% at 3, 6 and 12 months, respectively.[24]

From adult data, we know that adverse events are rare and include chest pain, heartburn and oesophageal perforation with mediastinitis.[25]

### 3.1.3 | Botox injections in the oesophageal body

Other dysmotility conditions, like distal oesophageal spasm and hypercontractile (jackhammer) oesophagus are very rare in the paediatric population. BoNT has been used in these conditions in adults in small uncontrolled series, with variable results in both manometric and clinical outcomes.[26–31] A single paediatric

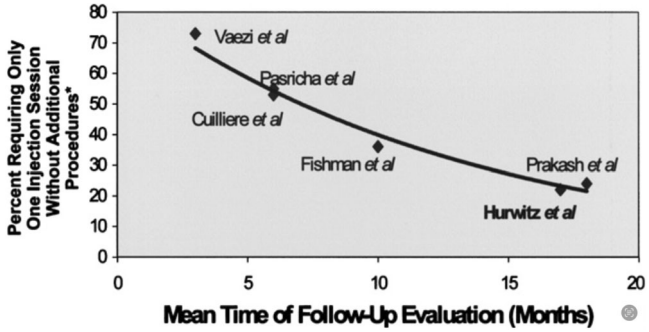


**FIGURE 1** Mean duration of botulinum toxin effect in achalasia. *Source*: From Hurwitz et al.[21] with permission.

case reported the use of BoNT in children with jackhammer oesophagus; however, the procedure was not effective and POEM (Peroral Endoscopy Myotomy) was later needed in all patients to improve symptoms.[32]

Relevant paediatric studies on BoNT effect on upper gastrointestinal symptoms are shown in Table 1.

## 3.2 | Botox in gastric disorders in children

### 3.2.1 | BoNT therapy for gastroparesis and disorders of gut–brain interactions

Several studies conducted in adults with gastroparesis have shown that intrapyloric BoNT injection improves gastric emptying, whilst the symptom improvement was not superior to placebo.[44,45] In addition, the American College of Gastroenterology does not recommend intrapyloric injection of BoNT in patients with gastroparesis based on randomised controlled trials (RCTs), which is a strong recommendation with moderate-quality evidence.[46]

Experience in the paediatric population is limited. Rodriguez et al. showed that the use of intrapyloric BoNT in children with gastroparesis in whom vomiting was the main symptom, responded better to treatment than children in whom vomiting did not occur, however, the difference was not statistically significant. The overall response lasted 3.5 months.[35] A recent retrospective study from the Mayo Clinic analysed the response to intrapyloric BoNT in children ($n = 20$) with gastroparesis and concluded that intrapyloric BoNT injection in children is safe and can provide temporary relief for patients with refractory upper gastrointestinal symptoms with and without gastroparesis.[43] Along with reporting data from their department, Ezaizi et al. performed a meta-analysis, including six studies, 160 patients, which showed that 68% of patients responded to intrapyloric BoNT irrespective of the presence of

**TABLE 1** Studies on BoNT effect on upper gastrointestinal symptoms.

| References | Number of patients | Age | Indications |
|---|---|---|---|
| Scholes et al.[16] | 6 | 6 months to 10 years | Emesis, cough, FTT, regurgitation |
| Drendel et al.[33] | 4 | 2 months to 4 years | Choking, aspiration, dysphagia |
| Messner et al.[12] | 3 | 4–5 months | Nasal regurgitation, choking and gagging, FTT |
| Türer et al.[13] | 1 | 8 years | Recurrent aspiration |
| Marchica et al.[14] | 1 | Newborn | Drooling |
| Givens et al.[15] | 1 | 4 months | FG, stridor, poor swallowing |
| Dorfman et al.[17] | 5 | 15–20 years | Inability to burp and involuntary throat sounds |
| Oude Nijhuis et al.[18] | 8 | 18–37 years | Inability to belch |
| Arnaert et al.[19] | 50 | 17–65 years (mean 27.5) | Inability to belch |
| Hurwitz et al.[21] | 3 | 8–13 years | Achalasia |
| Ip et al.[34] | 7 | 7–15 years | Achalasia |
| Zagory et al.[22] | 23 | Mean age 11.6 years | Achalasia |
| Khoshoo et al.[23] | 3 | 8–13 years | Achalasia |
| Rodriguez et al.[35] | 45 | 9.98 | Gastroparesis |
| Hirsch et al.[36] | 85 | 2.9 | Upper GI symptoms with or without feeding disorders |
| Popescu et al.[37] | 12 EndoFLP | 10.7 | Children with poor gastric emptying |
| Osgood et al.[38] | 25 | 12.6 | Nausea, vomiting |
| Hirsch et al.[39] | 45, 23 EndoFLIP | 14.2 | Refractory nausea, vomiting or feeding difficulties |
| Included in meta-analysis | | | |
| Leal et al.[40] | 1 | 9 | Gastroparesis |
| Woodward et al.[41] | 1 | 9 | Gastroparesis |
| Mercier et al.[42] | 8 | 3.7 | Gastroparesis |
| Ezaizi et al.[43] | 20 | 9.7 | Vomiting and nausea |

Abbreviations: EndoFLIP, endoluminal functional lumen imaging probe; FG, faltering growth; FTT, failure to thrive; GI, gastrointestinal.

gastroparesis, while among patients diagnosed with gastroparesis the therapeutic response was 66%.[43] These results suggest that intrapyloric BoNT can be effective not only in children with gastroparesis but also in children with refractory functional upper gastrointestinal symptoms.

Hirsch et al. evaluated the effectiveness of intrapyloric BoNT for treatment of feeding disorders and associated gastrointestinal symptoms in 85 children younger than 5 years old (receiving 118 injections).[36] The authors found that 67% of patients had a partial or complete symptoms improvement; moreover, there was an improvement in feeding pattern (among those with enteral tubes), with more patients receiving oral feeds and less receiving postpyloric feeds post-BoNT injection.[36] No complications or side effects were reported. It is worth noting that gastric emptying study did not predict the response to intrapyloric BoNT and there was no difference between baseline and follow-up gastric emptying results, suggesting the effect of BoNT might involve modulating sensory perception rather than acting on the motor effect on pyloric muscle. Similar findings were reported by Osgood et al. supporting the idea that intrapyloric BoNT may have therapeutic benefit mainly in children with refractory nausea and vomiting.[38]

When using an endoluminal functional lumen imaging probe (EndoFLIP) to predict clinical response to intrapyloric BoNT, it appears that adult patients with gastroparesis and abnormal pyloric distensibility on EndoFLIP (measured before BoNT injection) showed sustained improvement in symptoms after 3 months following intrapyloric BoNT compared to patients with gastroparesis and normal EndoFLIP parameters.[47] In some studies, EndoFLIP measurements were performed in children after intrapyloric BoNT injections. Hirsch et al. found a trend towards lower pyloric distensibility in patients with delayed versus normal gastric emptying, but there were no differences in EndoFLIP measurements between the responders to intrapyloric BoNT and nonresponders.[39] Popescu et al. reported EndoFLIP measurements in 12 children before and 6–9 months after intrapyloric BoNT injection.[37] They found an improvement in symptoms as well as in diameter, distensibility, compliance and pressure at balloon volumes of 20, 30 and 40 mL, although diameter and distensibility remained outside the normal values for adults. However, no paediatric standard values have yet been defined for the pyloric EndoFLIP measurements.

In summary, the practice of intrapyloric BoNT for gastroparesis in children has expanded, with results yet to be validated in larger studies. It looks like that intrapyloric BoNT can be also helpful for some disorders of gut–brain interactions. Additionally, EndoFLIP seems helpful in monitoring and predicting responses, but normative data is still awaited.

#### 3.2.2 | BoNT injection for weight loss

Animal studies have shown that intragastric BoNT injection can delay gastric emptying and achieve weight loss by controlling appetite and prolonging gastric emptying time to produce an early feeling of satiety.[48] A recent systematic review and meta-analysis of RCTs, which included six RCTs and 192 patients, showed that intragastric BoNT injection is effective for the treatment of obesity.[49] Intragastric BoNT injections (≥200 IU injections in several gastric areas), in combination with lifestyle measures, significantly reduced absolute weight compared to controls. In addition, there was a significant change in body mass index and a prolonged gastric emptying time.[49]

However, the heterogeneity of approach in terms of injection site (antrum vs. fundus vs. gastric body), dose, dietary treatment and follow-up prevents the possibility to draw any viable conclusion. The only case report in the paediatric population published recently, deals with the treatment of botulism following gastric injection of BoNT for the treatment of obesity.[50]

In summary, intragastric injection of BoNT for treating obesity cannot be currently suggested.

#### 3.2.3 | BoNT injection in infantile hypertrophic pyloric stenosis (HPS)

Until recently, the only effective treatment for HPS was Ramstedt pyloromyotomy, whether performed laparoscopically or through open surgery. Balloon dilation and/or endoknife division has been also reported in children with some efficacy.[51,52] BoNT has been used and an initial report showed a lack of response to BoNT injection in two infants with HPS.[53] Subsequently, 21 cases of late-onset HPS in children were reported, three of which showed an initial, transient response to BoNT injection, but all patients eventually required surgery.[54] More recently, Sarikaya et al. observed the effect of BoNT injection in an experimental HPS model.[55] They found that the BoNT group showed reduced thickness of the circular muscle and total muscle in the pylorus. The dose of BoNT used in the experimental HPS model was 20 U/kg, which was higher than the dose used by Heinen et al.[53]

In summary, there is currently no evidence to support the use of BoNT injections for the treatment of HPS.

### 3.3 | Botox in intestinal disorders in children

#### 3.3.1 | BoNT in HD

HD is a developmental disorder characterised by an abnormal cranio-caudal migration of neural crest cells

during intrauterine period.[46] HD treatment involves surgically removing the aganglionic colon, connecting the normally innervated bowel to the anus and preserving anal sphincter function. Despite proper surgery, up to 30% of patients may experience a nonrelaxing hypertonic IAS[56] (Figure 2), leading to obstructive symptoms and HD-associated enterocolitis in about one-third of cases.[57] To relieve obstruction, surgical anal myectomy is recommended, but it risks permanent sphincter damage.

Langer et al. described a successful outcome with BoNT injections in four children with HD and persistent constipation symptoms after surgery.[58] A systematic review of 14 relevant studies indicates that BoNT was effective in resolving obstructive symptoms in 66% of patients (event rate [ER] = 0.66, $p = 0.004$, $I^2 = 49.5$, $n = 278$ patients) for approximately 6 months, while conflicting results have been seen in the treatment of HD associated enterocolitis (ER = 0.58, $p = 0.65$, $I^2 = 71.0$, $n = 52$ patients).[59] According to the latest ERNICA (European Reference Network for rare Inherited and Congenital Anomalies) Guidelines, BoNT is recommended for treating HD-related outlet obstruction and/or recurrent enterocolitis.[60] If effective, the procedure can be repeated every 3–6 months depending on symptoms, without a limitation of the number of injections administered. The injection sites can be easily determined with the help of ultrasound or neurostimulation. Ultrasound-guided BoNT was described in five children with HD with good results.[61] Additionally, neurostimulation-guided BoNT was safely performed in 12 children, improving stool consistency in all patients.[62]

In summary, the use of BoNT can be suggested in preference to surgical treatment options for addressing outlet obstruction and/or recurrent enterocolitis in patients who have undergone surgery for HD.

### 3.3.2 | BoNT and IAS achalasia/hypertension in children

Ultrashort segment HD was initially defined as an abnormality confined to the IAS.[63] However, in these patients, rectal biopsies revealed the presence of ganglion cells in the submucosa. Consequently, a more accurate term for this condition is anal achalasia.[64]

In a recent retrospective study evaluating children with constipation undergoing anorectal manometry (ARM), the prevalence of anal achalasia was 2.9% (28 out of 983 children).[65] The diagnosis of anal achalasia is made when the recto-anal inhibitory reflex (RAIR) is not elicited upon the distension of a rectal balloon during ARM (Figure 2A,B). Myectomy or myotomy is the traditional approach to treating anal achalasia. Friedmacher et al. conducted a meta-analysis in paediatric studies comparing the efficacy of posterior IAS myectomy with intrasphincteric BoNT,[8] indicating that posterior IAS myectomy is more effective than BoNT, with the injection technique linked to higher rates of transient faecal incontinence, nonresponsiveness and subsequent surgical interventions. Halleran et al. examined 881 paediatric patients receiving anal sphincter BoNT for various defaecations disorders between 2014 and 2018.[66] They concluded that BoNT therapy is a safe and effective treatment for children with HD, severe functional constipation (FC) and anal achalasia. Several other paediatric studies confirmed these conclusions.[61,63,67] It is important to evaluate the relevance of anal achalasia in the clinical context and to consider BoNT only for children unresponsive to standard treatments for constipation. Presence or absence of a RAIR on ARM may not be predictive of response. BoNT is administrated under general anaesthesia in a lithotomy position (or lateral decubitus). A dose of 100 U of the lyophilised form of the toxin is diluted in 1 mL of saline and injected circumferentially, at the level of the

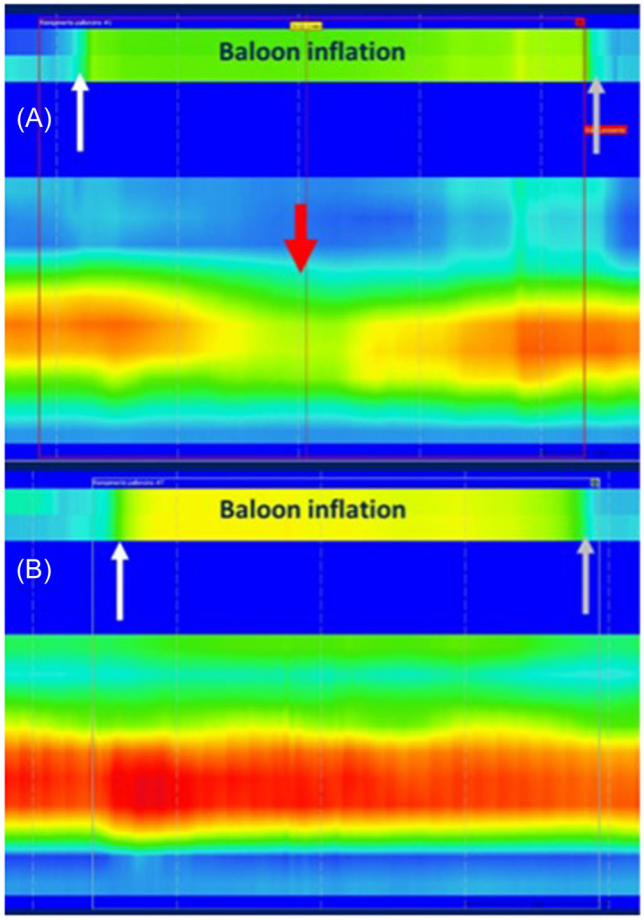


**FIGURE 2** (A) Present RAIR: anal relaxation (red arrow) responding to rectal balloon distension (grey arrows). (B) Absent RAIR: anal sphincter pressure does not decrease upon rectal balloon insufflation (grey arrows). RAIR is absent in both Hirschsprung disease and internal anal sphincter achalasia (with the courtesy of Renato Tambucci). RAIR, recto-anal inhibitory reflex.

dentate line, into the four quadrants of the anal sphincter with or without ultrasound/electric sphincter stimulation guidance (Figure 3).

In conclusion, BoNT presents a valuable approach for treating children with IAS achalasia. However, conclusive evidence of its efficacy and proper dosing requires large, prospective, randomised and double-blind studies.

### 3.3.3 | BoNT in constipation

FC is a common paediatric health problem worldwide. Pelvic outlet dysfunction with difficulty in defaecation is believed to be an important part of the constipation spectrum.[68] The first step in treating children with FC is a bowel management programme with osmotic agent. Additional possible forms of therapy are stimulant laxatives, behavioural therapy, biofeedback training, anal pain relief therapy, anal muscle complex relaxation (topical glycerine trinitrate) or intra-anal sphincteric BoNT injection. BoNT can improve pelvic disfunction by relaxing the anal sphincter, reducing the force required for stool expulsion.[69] In contrast with Radwan et al.'s study where BoNT injections did not result in additional defecatory functional improvement,[70] a retrospective study by Zar-Kessler et al. involving 164 children who underwent BoNT treatment for severe constipation persisting after conventional therapy demonstrated a positive response in 70% of cases.[71] Keshtgar et al. treated a small group of children with a similar condition and found a significant improvement.[72] Furthermore, Ahmadi et al. conducted an RCT in 88 patients with chronic constipation without assessing anal sphincter dynamics and found considerable decrease in symptoms in response to BoNT compared to conventionally treated controls.[73] BoNT is expected to remain effective for 3–6 months after treatment. Hence, the utilisation of BoNT could serve as a temporary intervention for children, as symptoms frequently improve with time in conjunction with patient maturation.

In summary, BoNT may be a viable option for managing FC in children who have not responded to comprehensive medical approaches.

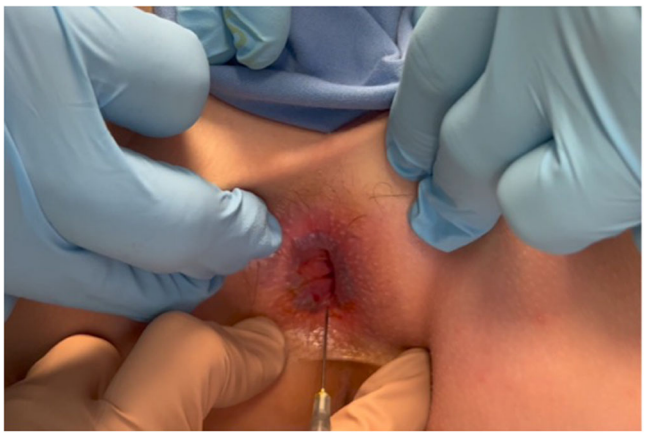

**FIGURE 3** Anal sphincter botulinum toxin procedure (with the courtesy of Renato Tambucci).

### 3.3.4 | Chronic anal fissure (CAF)

An anal fissure that is unresponsive to local and laxative therapy is then defined as a CAF. BoNT has been used in adult patients for the treatment of CAF with a success rate from 60% to 80%.[74] A recent systematic review including 29 trials and 1880 adult patients showed that surgery is superior to BoNT injection.[75] However, BoNT has fewer side effects. It has also been shown that injecting BoNT at the outer part of the fissure, regardless of the dosage, produces better results than injection on each side of the fissure.[75] According to a study conducted by the American Society of Colon and Rectal Surgeons, a dose of BoNT above 50 U seemed to provide a higher success and healing rate.[76] Based on existing knowledge, most studies recommend injecting BoNT into the IAS in quadrants around the anal canal, due to the important role of hypertonia and spasm of the internal sphincter in fissure pathogenesis.

Paediatric data are scarce. Husberg et al. included 13 patients (1–10 years of age).[77] Authors used the dose 1.25 U × 2 for children under 2 years and 2.5 U × 2 in children above 2 years. The injections were given in the external sphincter on both sides of the fissure using electromyography stimulation for guidance. After 1 week, 11 children showed improvement but six of them experienced recurrence of CAF.

In conclusion, while studies in children are limited, due to substantial evidence in the adult population, BoNT may be suggested for selected children with a CAF.

## 4 | CONCLUSION

BoNT blocks the release of acetylcholine at the neuromuscular junction and leads to muscle paralysis that lasts for several months. BoNT also reduces inflammation around synapses. It is increasingly used for various medical conditions, including intestinal motility disorders. However, the effect is only temporary and there is still scarcity of solid evidence regarding efficacy. BoNT is used to relax the upper and LOS, especially in cases of achalasia. Its use in such instances should be limited to initial treatment only in selected cases while waiting for definitive treatments. Intrapyloric BoNT injection is increasingly used for the treatment of gastroparesis but evidence supporting its use in children is still scarce. Therefore, BoNT for

delayed gastric emptying treatment should be used with caution and not as standard practice. Similarly, routine intragastric injection for both weight loss promotion and intrapyloric injection for HPS is not supported by the current published data. There is more evidence supporting BoNT use for post-HD surgery, anal achalasia and FC, when the latter is not responsive to maximal medical therapy. As the effect of BoNT is not permanent, repeating the procedure can be suggested after a few months, if the symptoms recur.

## ACKNOWLEDGEMENTS

The authors have no funding to report. The open access was funded by University of Ljubljana.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## ORCID

*Matjaž Homan* https://orcid.org/0000-0001-5764-5430

## REFERENCES

1. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *J Pediatr Ophthalmol Strabismus*. 1980;17(1):21-25.
2. Lew MF. Review of the FDA-approved uses of botulinum toxins, including data suggesting efficacy in pain reduction. *Clin J Pain*. 2002;18(6 suppl):S142-S146.
3. Thomas A, de Souza Ribeiro B, Malespin M, de Melo Jr. SW. Botulinum toxin as a treatment for refractory gastroparesis: a literature review. *Curr Treat Options Gastroenterol*. 2018;16(4):479-488.
4. Pasricha TS, Pasricha PJ. Botulinum toxin injection for treatment of gastroparesis. *Gastrointest Endosc Clin N Am*. 2019;29(1):97-106.
5. Park J, Park H. Botulinum toxin for the treatment of neuropathic pain. *Toxins*. 2017;9(9):260.
6. Arbizu RA, Rodriguez L. Use of Clostridium botulinum toxin in gastrointestinal motility disorders in children. *World J Gastrointest Endosc*. 2015;7(5):433-437.
7. Choudhury S, Baker MR, Chatterjee S, Kumar H. Botulinum toxin: an update on pharmacology and newer products in development. *Toxins*. 2021;13(1):58.
8. Friedmacher F, Puri P. Comparison of posterior internal anal sphincter myectomy and intrasphincteric botulinum toxin injection for treatment of internal anal sphincter achalasia: a meta-analysis. *Pediatr Surg Int*. 2012;28(8):765-771.
9. Ip KS, Cameron DJ, Catto-Smith AG, Hardikar W. Botulinum toxin for achalasia in children. *J Gastroenterol Hepatol*. 2000;15(10):1100-1104.
10. Wei P. Botulinum toxin injection for the treatment of upper esophageal sphincter dysfunction. *Toxins*. 2022;14(5):321.
11. Jain N, Lansiaux E, Yucel U, Huenermund S, Goeschl S, Schlagenhauf P. Outbreaks of iatrogenic botulism in Europe: combating off-label medical use of botulinum neurotoxin (BoNT) in bariatric procedures. *New Microbes New Infect*. 2023;53:101152.
12. Messner A, Ho AS, Malhotra PS, Koltai PJ, Barnes MA. The use of botulinum toxin for pediatric cricopharyngeal achalasia. *Int J Pediatr Otorhinolaryngol*. 2011;75(6):830-834.
13. Türer ÖB, Demir N, Ciecieraga T, Günaydın RÖ, Soyer T. Assessment of pediatric cricopharyngeal achalasia with high resolution manometry. *Turk J Pediatr*. 2019;61(5):804-809.
14. Marchica C, Zawawi F, Daniel SJ. Management of cricopharyngeal achalasia in an 8-month child using endoscopic cricopharyngeal myotomy. *Int J Pediatr Otorhinolaryngol*. 2017;101:137-140.
15. Givens V, Brent K, Dunham M, Kanotra SP. Cricopharyngeal achalasia associated with laryngomalacia as a cause of failure to thrive. *J Laryngol Otol*. 2018;132(9):852-855.
16. Scholes MA, McEvoy T, Mousa H, Wiet GJ. Cricopharyngeal achalasia in children: botulinum toxin injection as a tool for diagnosis and treatment. *Laryngoscope*. 2014;124(6):1475-1480.
17. Dorfman L, El-Chammas K, Mansi S, Graham K, Kaul A. Pediatric retrograde cricopharyngeal dysfunction diagnosed by high-resolution impedance manometry. *J Pediatr Gastroenterol Nutr*. 2024;78(5):1098-1107.
18. Oude Nijhuis RAB, Snelleman JA, Oors JM, et al. The inability to belch syndrome: a study using concurrent high-resolution manometry and impedance monitoring. *Neurogastroenterol Motil*. 2022;34(5):e14250.
19. Arnaert S, Arts J, Raymenants K, Baert F, Delsupehe K. Retrograde cricopharyngeus dysfunction, a new motility disorder: single center case series and treatment results. *J Neurogastroenterol Motil*. 2024;30(2):177-183.
20. Stavropoulos SN, Friedel D, Modayil R, Parkman HP. Diagnosis and management of esophageal achalasia. *BMJ*. 2016;354:i2785.
21. Hurwitz M, Bahar RJ, Ament ME, et al. Evaluation of the use of botulinum toxin in children with achalasia. *J Pediatr Gastroenterol Nutr*. 2000;30(5):509-514.
22. Zagory JA, Golden JM, Demeter NE, Nguyen Y, Ford HR, Nguyen NX. Heller myotomy is superior to balloon dilatation or botulinum injection in children with achalasia: a two-center review. *J Laparoendosc Adv Surg Tech*. 2016;26(6):483-487.
23. Khoshoo V, LaGarde DC, Udall Jr. JN. Intrasphincteric injection of botulinum toxin for treating achalasia in children. *J Pediatr Gastroenterol Nutr*. 1997;24(4):439-441.
24. Campos GM, Vittinghoff E, Rabl C, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg*. 2009;249(1):45-57.
25. van Hoeij FB, Tack JF, Pandolfino JE, et al. Complications of botulinum toxin injections for treatment of esophageal motility disordersdagger. *Dis Esophagus*. 2017;30(3):1-5.
26. Mion F, Marjoux S, Subtil F, et al. Botulinum toxin for the treatment of hypercontractile esophagus: results of a double-blind randomized sham-controlled study. *Neurogastroenterol Motil*. 2019;31(5):e13587.
27. Philonenko S, Roman S, Zerbib F, et al. Jackhammer esophagus: clinical presentation, manometric diagnosis, and therapeutic results—results from a multicenter French cohort. *Neurogastroenterol Motil*. 2020;32(11):e13918.
28. Roman S, Kahrilas PJ. Management of spastic disorders of the esophagus. *Gastroenterol Clin North Am*. 2013;42(1):27-43.
29. Storr M, Allescher HD, Rosch T, Born P, Weigert N, Classen M. Treatment of symptomatic diffuse esophageal spasm by endoscopic injection of botulinum toxin: a prospective study with long term follow-up. *Gastrointest Endosc*. 2001;54(6):18A.
30. Vanuytsel T, Bisschops R, Farré R, et al. Botulinum toxin reduces dysphagia in patients with nonachalasia primary esophageal motility disorders. *Clin Gastroenterol Hepatol*. 2013;11(9):1115-1121.e2.
31. Marjoux S, Brochard C, Roman S, et al. Botulinum toxin injection for hypercontractile or spastic esophageal motility disorders: may high-resolution manometry help to select cases? *Dis Esophagus*. 2015;28(8):735-741.

32. Ramos R, Guidi MA, Kakisu M, Rocca A, Sakai P. Peroral endoscopic myotomy in pediatric jackhammer esophagus. *Rev Esp Enferm Dig*. 2018;110(7):464-465.
33. Drendel M, Carmel E, Kerimis P, Wolf M, Finkelstein Y. Cricopharyngeal achalasia in children: surgical and medical treatment. *Isr Med Assoc J*. 2013;15(8):430-433.
34. Ip KS, Cameron DJ, Catto-Smith AG, Hardikar W. Botulinum toxin for achalasia in children. *J Gastroenterol Hepatol*. 2000;15(10):1100-1104. doi:10.1046/j.1440-1746.2000.02341.x
35. Rodriguez L, Rosen R, Manfredi M, Nurko S. Endoscopic intrapyloric injection of botulinum toxin A in the treatment of children with gastroparesis: a retrospective, open-label study. *Gastrointest Endosc*. 2012;75(2):302-309.
36. Hirsch S, Nurko S, Mitchell P, Rosen R. Botulinum toxin as a treatment for feeding difficulties in young children. *J Pediatr*. 2020;226:228-235.
37. Popescu M, White E, Mutalib M. EndoFLIP assessment of pyloric sphincter in children: a single-center experience. *Transl Gastroenterol Hepatol*. 2023;8:17.
38. Osgood PT, Essner BS, Fountain L, Sullivan EC, Meegan C, Fortunato JE. Intrapyloric botulinum toxin injection for refractory nausea and vomiting in pediatric patients. *J Pediatr Gastroenterol Nutr*. 2023;77(6):726-733.
39. Hirsch S, Nurko S, Liu E, Rosen R. A prospective study of intrapyloric botulinum toxin and EndoFLIP in children with nausea and vomiting. *Neurogastroenterol Motil*. 2022;34(11):e14428.
40. Leal MC, Oliver MR, Francis P, Catto-Smith AG. Education and imaging. Gastrointestinal: botulinum toxin effective in refractory gastroparesis in paediatric practice. *J Gastroenterol Hepatol*. 2015;30(2):232.
41. Woodward MN, Spicer RD. Intrapyloric botulinum toxin injection improves gastric emptying. *J Pediatr Gastroenterol Nutr*. 2003;37(2):201-202.
42. Mercier C, Ley D, Aumar M, et al. Comparison of symptom control in pediatric gastroparesis using endoscopic pyloric botulinum toxin injection and dilatation. *J Pediatr Gastroenterol Nutr*. 2021;73(3):314-318.
43. Ezaizi Y, Hasan B, Manini ML, Absah I. Intrapyloric botulinum toxin A injection for gastroparesis and functional upper gastrointestinal symptoms in children: Mayo Clinic experience, review of the literature, and meta-analysis. *Pediatr Drugs*. 2022;24(5):539-545.
44. Friedenberg FK, Palit A, Parkman HP, Hanlon A, Nelson DB. Botulinum toxin A for the treatment of delayed gastric emptying. *Am J Gastroenterol*. 2008;103(2):416-423.
45. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther*. 2007;26(9):1251-1258.
46. Camilleri M, Kuo B, Nguyen L, et al. ACG clinical guideline: gastroparesis. *Am J Gastroenterol*. 2022;117(8):1197-1220.
47. Desprez C, Melchior C, Wuestenberghs F, et al. Pyloric distensibility measurement predicts symptomatic response to intrapyloric botulinum toxin injection. *Gastrointest Endosc*. 2019;90(5):754-760.e1.
48. Park JS, Zheng HM, Kim JM, Kim CS, Jeong S, Lee DH. The effect of intragastric administration of botulinum toxin type A on reducing adiposity in a rat model of obesity using micro-CT and histological examinations. *Gut Liver*. 2017;11(6):798-806.
49. Yen YA, Wang CC, Sung WW, et al. Intragastric injection of botulinum toxin A for weight loss: a systematic review and meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol*. 2022;37(6):983-992.
50. Yücer MF, Kaçar A, Dağ H, İrdem A. Successful treatment of a 15 years-old obese adolescent patient with botulinum anti-toxin after gastric Botox and systemic botulism findings: a case report. *Iberoam J Med*. 2023;5:176-180.
51. Yokoyama S, Uyama S, Iwagami H, Yamashita Y. Successful combination of endoscopic pyloromyotomy and balloon dilatation for hypertrophic pyloric stenosis in an older child: a novel procedure. *Surg Case Rep*. 2016;2(1):145.
52. Pirkle JRA, Deutsch D. Successful treatment of recurrent pyloric stenosis using balloon dilation. *JPGN Rep*. 2023;4(4):e364.
53. Heinen F, Mall V, Rückauer KD, et al. Lack of response to botulinum toxin A in patients with hypertrophic pyloric stenosis. *Eur J Pediatr*. 1999;158(5):436.
54. Wolf LL, Nijagal A, Flores A, Buchmiller TL. Late-onset hypertrophic pyloric stenosis with gastric outlet obstruction: case report and review of the literature. *Pediatr Surg Int*. 2016;32(10):1013-1016.
55. Sarıkaya M, Çiftci I, Ünlükal N, Sekmenli T, Gündüz M. The effect of botulinum toxin in experimental hypertrophic pyloric stenosis. *J Laparoendosc Adv Surg Tech A*. 2021;31(12):1460-1465.
56. Svetanoff WJ, Lim-Beutal IIP, Wood RJ, Levitt MA, Rentea RM. The utilization of botulinum toxin for Hirschsprung disease. *Semin Pediatr Surg*. 2022;31(2):151161.
57. Gosain A, Frykman PK, Cowles RA, et al. Guidelines for the diagnosis and management of Hirschsprung-associated enterocolitis. *Pediatr Surg Int*. 2017;33(5):517-521.
58. Langer JC, Birnbaum E. Preliminary experience with intrasphincteric botulinum toxin for persistent constipation after pull-through for Hirschsprung's disease. *J Pediatr Surg*. 1997;32(7):1059-1062; discussion 1061-1062.
59. Roorda D, Abeln ZA, Oosterlaan J, Heurn LW, Derikx JP. Botulinum toxin injections after surgery for Hirschsprung disease: systematic review and meta-analysis. *World J Gastroenterol*. 2019;25(25):3268-3280.
60. Kyrklund K, Sloots CEJ, de Blaauw I, et al. ERNICA guidelines for the management of rectosigmoid Hirschsprung's disease. *Orphanet J Rare Dis*. 2020;15(1):164.
61. Church JT, Gadepalli SK, Talishinsky T, Teitelbaum DH, Jarboe MD. Ultrasound-guided intrasphincteric botulinum toxin injection relieves obstructive defecation due to Hirschsprung's disease and internal anal sphincter achalasia. *J Pediatr Surg*. 2017;52(1):74-78.
62. Louis-Borrione C, Faure A, Garnier S, et al. Neurostimulation-guided anal intrasphincteric botulinum toxin injection in children with Hirschsprung disease. *J Pediatr Gastroenterol Nutr*. 2019;68(4):527-532.
63. Ciamarra P, Nurko S, Barksdale E, Fishman S, Di Lorenzo C. Internal anal sphincter achalasia in children: clinical characteristics and treatment with Clostridium botulinum toxin. *J Pediatr Gastroenterol Nutr*. 2003;37(3):315-319.
64. Kobayashi H, Hirakawa H, Puri P. Abnormal internal anal sphincter innervation in patients with Hirschsprung's disease and allied disorders. *J Pediatr Surg*. 1996;31(6):794-799.
65. Baaleman DF, Malamisura M, Benninga MA, et al. The not-so-rare absent RAIR: internal anal sphincter achalasia in a review of 1072 children with constipation undergoing high-resolution anorectal manometry. *Neurogastroenterol Motil*. 2021;33(4):e14028.
66. Halleran DR, Lu PL, Ahmad H, et al. Anal sphincter botulinum toxin injection in children with functional anorectal and colonic disorders: a large institutional study and review of the literature focusing on complications. *J Pediatr Surg*. 2019;54(11):2305-2310.
67. Chumpitazi BP, Fishman SJ, Nurko S. Long-term clinical outcome after botulinum toxin injection in children with nonrelaxing internal anal sphincter. *Am J Gastroenterol*. 2009;104(4):976-983.
68. Rajindrajith S, Devanarayana NM, Crispus Perera BJ, Benninga MA. Childhood constipation as an emerging public health problem. *World J Gastroenterol*. 2016;22(30):6864-6875.
69. Irani K, Rodriguez L, Doody DP, Goldstein AM. Botulinum toxin for the treatment of chronic constipation in children with internal

anal sphincter dysfunction. *Pediatr Surg Int*. 2008;24(7):779-783.
70. Radwan AB, Gadallah MA, Shahawy MR, Albagdady AA, Talaat AA. Can botulinum toxin help in managing children with functional constipation and obstructed defecation? *J Pediatr Surg*. 2021;56(4):750-753.
71. 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(4):693-697.
72. Keshtgar AS, Ward HC, Clayden GS. Diagnosis and management of children with intractable constipation. *Semin Pediatr Surg*. 2004;13(4):300-309.
73. Ahmadi J, Azary S, Ashjaei B, Paragomi P, Khalifeh-Soltani A. Intrasphincteric botulinum toxin injection in treatment of chronic idiopathic constipation in children. *Iran J Ped*. 2013;23(5):574-578.
74. Perry WB, Dykes SL, Buie WD, Rafferty JF. Practice parameters for the management of anal fissures (3rd revision). *Dis Colon Rectum*. 2010;53(8):1110-1115.
75. Vitoopinyoparb K, Insin P, Thadanipon K, et al. Comparison of doses and injection sites of botulinum toxin for chronic anal fissure: a systematic review and network meta-analysis of randomized controlled trials. *Int J Surg*. 2022;104:106798.
76. Borsuk DJ, Studniarek A, Park JJ, Marecik SJ, Mellgren A, Kochar K. Use of botulinum toxin injections for the treatment of chronic anal fissure: results from an American Society of Colon and Rectal Surgeons Survey. *Am Surg*. 2023;89(3):346-354.
77. Husberg B, Malmborg P, Strigård K. Treatment with botulinum toxin in children with chronic anal fissure. *Eur J Pediatr Surg*. 2009;19(5):290-292.

**How to cite this article:** Homan M, Thomson M, Bontems P, et al. Drugs in focus: botulinum toxin in the therapy of gastrointestinal disorders in children. *J Pediatr Gastroenterol Nutr*. 2024;79:1096-1105. doi:10.1002/jpn3.12376