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Post-operative Colonic Manometry in Children with Hirschsprung Disease: A Systematic Review

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Abbreviations: FI: fecal incontinence; **HAEC**: Hirschsprung associated enterocolitis; **HAC**: high-amplitude contraction; **HAPC**: high-amplitude propagated contraction; **HD:** Hirschsprung disease; **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PROSPERO**: International Prospective Register of Systematic Reviews; **QoL**: quality of life; **TAEPT**: transanal endorectal pull-through; **WP**: water-perfused.

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ABSTRACT

Background: A significant proportion of children experience bowel dysfunction (including constipation and faecal incontinence) following surgical repair of Hirschsprung disease (HD). Persistent symptoms are thought to relate to underlying colonic and/or anorectal dysmotility. Manometry may be used to investigate the gastrointestinal motility patterns of this population.

Purpose: (1) Evaluate the colonic manometry equipment and protocols used in the assessment of the post-operative HD population. (2) Summarize the available evidence regarding colonic motility patterns in children with HD following surgical repair.

Data Sources: We performed a systematic review of the Cochrane Library, Embase, MEDLINE, and PubMed databases (1st January 1980 and 9th March 2020). Data were extracted independently by two authors.

Study Selection: This systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Studies reporting the post-operative assessment of children with HD using colonic manometry were considered for inclusion.

Results: Five studies satisfied selection criteria, providing a combined total of 496 children. Of these, 184 children with repaired HD underwent colonic manometry. Studies assessed heterogeneous populations, utilised variable manometry equipment and protocols, and reported limited baseline symptom characteristics, thus restricting comparability. All studies used low-resolution colonic manometry.

Conclusions: This systematic review highlighted the paucity of evidence informing the understanding of colonic dysmotility in the post-operative HD cohort. Current literature is limited by variable methodology, heterogeneous cohorts, and the lack of high-resolution manometry.

Keywords: manometry, Hirschsprung Disease, gastrointestinal motility, high-resolution colonic manometry, colon.

INTRODUCTION

Hirschsprung disease (HD) is characterized by a lack of ganglion cells in the distal bowel, with a variable extent proximally. Affecting one in 5000 live births, children typically require surgical intervention in the first months of life to remove the affected segment of bowel. Recent decades have seen advances in the surgical management of children with HD. However, a significant proportion of these children continue to experience post-operative bowel dysfunction (predominately constipation and/or faecal incontinence) throughout childhood and adolescence [1-7]. Although the impact of bowel dysfunction on the quality of life of these patients is increasingly well documented [4, 5, 7-10], the underlying pathophysiology of the dysfunction is not. Persistent symptoms may relate to colonic and/or anorectal dysmotility [11-14].

Manometry is a key investigatory tool in the assessment of gastrointestinal motility, recording intraluminal pressure changes to measure contractions of the bowel. Manometry is a well-established and diagnostic investigation in the esophagus and anorectum. However, the relative inaccessibility of the colon, the need for prolonged recording (typically 2 – 8hrs), and the lack of standardization in the analysis and interpretation of results, has hindered robust application of manometry to the colon. Little is known about the colonic motility patterns of children with HD following surgical intervention.

The aim of the systematic review was to summarize the reported methodology and outcomes of colonic manometry conducted in children following surgical repair of HD.

METHODS

This systematic review was conducted in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. A primary search was conducted in Embase, MEDLINE, PubMed, and the Cochrane Library in November 2019. A supplementary search was repeated in the same databases in March 2020, to identify further studies which satisfied inclusion criteria. The search was restricted to human studies published from 1st January 1980 to 9th March 2020. The search strategy is provided in further detail in Appendix 2. The methodology was published prospectively on PROSPERO (CRD42020155806).

Study Selection

After removal of duplicate articles, title and abstract were independently screened for eligibility by two authors (H.E.B. and J.S.). Cohort, case-control, cross-sectional, and longitudinal studies were included for review, as were clinical trials. Conference abstracts, meta-analyses, systematic reviews, and animal studies were excluded.

The following inclusion criteria were utilised for abstract screening: anorectal or colonic manometry in children following surgical correction of HD, children aged 0 – 18 years, and English language. Studies assessing mixed populations (HD and other conditions) were included, provided results from children with HD were reported separately in the final analysis. Studies reporting only pre-operative assessment with manometry were excluded.

Data Extraction

Two authors (H.E.B. and J.S) independently extracted data from eligible studies. Extracted data relating to study characteristics included: first author, study year and location, cohort size, patient age and sex, length of affected colon, operative repair type, and post-operative bowel function assessment (instruments and outcomes). Manometry characteristics included type of manometry, sensor spacing, preparation, sedation, manometry parameters, and reported motility outcomes.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of included non-randomized studies. The NOS applies eight criteria in three groups: selection, comparability, and exposure. The highest quality studies may receive a maximum total score of nine [16].

RESULTS

Search Results

Five studies reported utilizing colonic manometry and were suitable for analysis (Figure 1) [13, 17-20]. From the combined total of 496 patients, 184 (127 male, age range <1 – 17 years) children with repaired HD underwent colonic manometry. The median HD cohort size was 46 patients (range 2 – 59). Study characteristics are provided in Table 1.

Children were assessed following endorectal pull-through (n = 46, 25%), transanal endorectal pull-through (n = 21, 11.5%), and laparoscopic modified Duhamel repair (n = 2, 1%). The remainder (n = 115, 62.5%) were reported as being post pull-through procedure, without further specification. Length of aganglionosis was described by one of five included studies. Kohno *et al*. [19] assessed children with short segment disease, confined to the rectum or rectosigmoid region. Clinical characteristics are summarized in Table 1.

Three of five eligible studies aimed to investigate the pathophysiology of bowel dysfunction following surgical correction of HD, and assessed the proximal colon to anorectum [13, 17, 18]. Martin *et al*. [20] evaluated the utility of colonic manometry to inform surgical management of functional obstruction. Kohno *et al*. [19] assessed clinical outcomes of a specific surgical technique, the transanal endorectal pull-through, and recorded motility events at three distal locations: (1) the anal canal; (2) 5cm proximal to the anal canal; and (3) 10cm proximal to the anal canal [19].

Quality assessment

The quality of all included publications was assessed using the Newcastle-Ottawa Scale for non-randomized studies. Kaul *et al*. [18] was classified as "good quality". The remainder were classified as "poor quality", demonstrating limitations in the "Selection" and "Comparability" assessments of this scale [13, 17, 19, 20]. Quality assessments are presented in Appendix 3.

Colonic manometry characteristics

Equipment

Two studies utilised catheters with six to eight recording sites, spaced at 10 - 15cm intervals [13, 17]. Martin *et al*. [20] also utilised eight recording sites; however, reported a shorter inter-sensor distance of 5 - 10cm. Kohno *et al*. [19] used a three channel Dentsleeve catheter; sensor spacing was not reported. Three studies reported use of water-perfused colonic manometry [17, 18, 20]. Although not specified, based upon the described catheter, the remaining two studies were also inferred to have used water-perfused catheters [13, 19]. Equipment characteristics are summarized in Table 3.

Preparation and sedation

Three studies used a colonic lavage solution containing polyethylene glycol for bowel preparation prior to colonoscopy for manometry placement [13, 17, 20]. The remainder did not describe the bowel preparation regimen that was utilised [18, 19].

Three of five eligible studies did not describe the sedation protocol used [17, 18, 20]. Jacobs *et al*. [13] reported a change in sedation regimen during the study, from narcotics and benzodiazepines to benzodiazepines and propofol. Kohno *et al*. [19] did not use sedation.

Catheter placement

All four studies that assessed the proximal colon reported colonoscopic guidewire placement with the manometry catheter subsequently positioned under fluoroscopy [13, 17, 18, 20]. Three studies referenced the methodology of preceding publications, all of which described taping the catheter to the patient externally [13, 17, 18]. Kohno *et al*. did not describe catheter placement, securement or reference a primary source with such details [19]. No studies reported securing the catheter tip to the colonic mucosa to minimize catheter migration. Placement techniques are summarized in Table 2.

Motility parameters

High-amplitude propagating contractions

Four of the five studies focused on the assessment of high-amplitude propagating contractions (HAPCs) [13, 17, 18, 20]. However, the definitions of HAPCs used in each study varied, as did the method of reporting. Only two studies quantified the number of HAPCs observed during fasting and post-prandial assessment [13, 18]. Study parameters and HAPC criteria are summarized in Table 3.

All four of the studies included assessment of HAPCs in both fasting and post-prandial states, and following stimulation with Bisacodyl. The indications and dosages for Bisacodyl varied between protocols. Participants in three studies received Bisacodyl only if no HAPCs were observed prior to or following a meal. Participants assessed by Martin *et al*. [20] received Bisacodyl, irrespective of colonic activity. Bisacodyl dosage ranged from 0.2 - 0.4mg/kg [13, 17, 20]; dosage was not reported by Kaul *et al*. [18].

Kohno *et al*. [19] assessed motility at three distal sites only. Measurements were taken at: (1) the anal canal; (2) 5cm proximal to the anal canal; and (3) 10cm proximal to the anal canal, during defecation. Due to the restricted colonic region assessed, only high-amplitude contractions (HACs) were reported. The HACs were defined as contractions lasting more than 10 seconds, with an amplitude or more than 100cm H_2O (73.5mmHg).

Assessment of meal response

Variable criteria were used to define the meal (post-prandial) response. Di Lorenzo *et al*. [17] recorded colonic motility for 60 minutes following administration of a "balanced meal", which was "individualized on the basis of age and patient preferences" but not further defined with respect to caloric or macronutrient content. A colonic motility index was calculated as the "area under pressure" for one 30 minute period pre-meal and for two 30 minute periods post-meal [17]. The "gastrocolonic response" was calculated on the basis of the colonic motility index, with ≥50% increase in the motility index considered indicative of a response [17]. This was in contrast to Martin *et al*. who assessed the "gastrocolic reflex", defined as the presence of one or more HAPCs arising in the mid-transverse colon and propagating to the rectosigmoid colon [20]. Jacobs *et al*. [13] considered a variable increase in motility following a non-standardized meal as indicative of the "gastrocolonic response". Meal response criteria are summarized in Table 3.

Assessment criteria: reported features of normal colonic motility and dysmotility

Three of five included studies defined normal colonic motility based on the characteristics of HAPCs and presence of a meal response [13, 17, 20]. Two studies classified normal HAPCs as those which terminated in the sigmoid colon, reaching the rectum only infrequently. In contrast, Martin *et al*. considered normal HAPCs to terminate in the rectum [20]. Appraisals of the meal response – used to inform assessment of normal motility – were conflicting. Study motility criteria are summarized in Table 4.

A range of definitions relating to dysmotility were provided by included studies. These broadly encompassed colonic hypomotility [13, 17, 18, 20]; colonic hyperactivity [18]; abnormalities of HAPC propagation distance [13, 17, 20]; and extracolonic factors, such as anal sphincter hypertension and functional constipation symptoms [13, 17]. Features of abnormal motility reported by the five included studies are summarized in Table 4.

Manometry outcomes

Pathophysiology of post-operative bowel dysfunction

Di Lorenzo *et al*. [17] used colonic and anorectal manometry to elucidate the pathophysiology of persistent post-operative bowel dysfunction. Forty-six symptomatic children, more than ten months after endorectal pull-through, underwent colonic manometry.

Four distinct motility patterns were identified:

1. HAPCs migrating through the neorectum to the anal sphincter, associated with faecal incontinence (n=18); treated with anticholinergics and loperamide.
2. Normal colonic manometry associated with fear of defecation and retentive posturing (n=9); treated with a regimen of behaviour modification and stool softeners.
3. Absence of HAPCs or persistent simultaneous contractions associated with constipation (n=13); treated with surgical resection of the abnormal colon.
4. Normal colonic manometry and hypertensive internal anal sphincter (n=4); treated with injection of Botox into the anal sphincter.

Kaul *et al*. [18] focused on children with multiple daily episodes of soiling. The authors conducted a retrospective review of anorectal and colonic manometry results of 59 children (6.5 ± 3.5 years, range 16 months - 15 years). They hypothesized that frequent faecal incontinence was associated with colonic hyperactivity and quantified HAPCs, reported as mean / minute. Children with functional constipation were used as the "control" population. Children were grouped according to the absence (n = 21) or presence (n = 38) of HAPCs during fasting or following a meal challenge. Of the 21 children without HAPCs, eight subsequently produced one or more HAPCs following administration of Bisacodyl. The remainder were considered to have colonic inertia (n = 13). The second group (n = 38) included children with

HAPCs. Colonic hyperactivity (defined as >2 SD above the mean number of HAPCs in controls (≥ 0.11 HAPCs/ min)) was identified in 15 children with repaired HD. Frequency of HAPCs are summarized in Table 4.

Jacobs *et al*. [13] explored the aetiology of colonic hyperactivity in post-operative HD patients. The frequency of HAPCs in children with HD (n = 56) was compared with that in children with normal anatomy (functional constipation, n = 237; or chronic abdominal pain, n = 48) and previous colon transection (n = 20). Colon transection had been performed for a variety of indications, including intestinal pseudo-obstruction, malrotation, refractory constipation, resection of necrotic bowel, and congenital anomalies (not further specified). Fasting children with repaired HD had 2.2 ± 3.4 HAPCs/hour fasting, which increased to 4.0 ± 5.4/hour following a meal.

Evaluation of the utility of colonic manometry

Martin *et al*. [20] assessed a smaller cohort with refractory colonic obstruction, including two children with previous HD repair (n = 2). Normal motility was defined as the presence of HAPCs propagating from the caecum to the rectum and a demonstrated gastrocolic reflex, signified by one or more HAPCs propagating from the mid-transverse to rectosigmoid colon following a meal [20]. Both patients were reported to have globally abnormal motility consistent with myopathic bowel injury, associated with marked colonic distension. Manometry was characterized by low amplitude pressure waves throughout the colon, weak gastrocolic reflex, no HAPCs in response to Bisacodyl, and infrequent, non-propagated, high-amplitude contractions. The method of colonic distension assessment was not described.

Both children underwent ileostomy formation. Return of normal colonic motility was reported on repeat assessment four to six months post-operatively. However, the characteristics of post-ileostomy manometry were not further described [20]. Reportedly successful ileostomy closure was subsequently performed in one child, with closure planned in the other. The authors concluded that colonic manometry was valuable in tailoring post-operative HD management [20].

Assessment of surgical technique

Kohno *et al*. [19] evaluated clinical and functional outcomes after transanal endorectal pull-through in children with short segment HD (n = 21). Lower colonic manometry (extending 10cm proximally from the anal canal) was performed in eight children, with assessment during defecation in six. High-amplitude contractions (HACs) were identified in 5/6 (83%) children. As HACs occurred in association with defecation, the authors hypothesized that they were comparable to HAPCs, which are considered indicative of normal colonic function [19]. The occurrence of HACs was proposed to contribute to the "satisfactory" clinical outcomes [19].

Assessment of post-operative outcomes

Post-operative outcome evaluation measures

A variety of methods were used to assess post-operative bowel function. These included presenting symptom [13, 18]; parent assessment of symptom severity [17]; stooling characteristics (frequency, size, and /or consistency) [19, 20]; bowel management strategies required [19, 20]; and admission for complications, such as Hirschsprung associated enterocolitis [19, 20]. Functional outcomes are summarized in Table 1. Two studies included more global consideration of emotional health or quality of life, which were assessed by parent report [17, 20] and/or clinician impression [20].

Post-operative outcomes

Di Lorenzo *et al*. [17] administered a structured questionnaire and phone interview to assess change in symptoms, global physical health, and emotional wellbeing, following the motility-guided intervention. Outcomes were based on parent report, using a 5 point Likert scale (poor - excellent), rated prior to manometry and at the time of the follow-up interview. Patients were reassessed an average of 34 months following motility-guided intervention. Parent-reported global health significantly improved in 76% of children (mean 3.9 +/- 1.1 versus 2.8 +/- 1.3, p = 0.01), being "excellent" or "very good" in 60%, compared with 23% pre-treatment. The majority demonstrated improvement in symptoms (bowel movement frequency normalized in 72%, abdominal pain decreased in 80%, abdominal distension reduced in 65%). Five children did not proceed with the recommended treatment. They reported persistent symptoms and unchanged global and emotional health scores [17].

Jacobs *et al*. [13] reported frequency of presenting symptoms. In the HD group, symptoms included constipation (50%), faecal incontinence (41%), and other (diarrhea and/or abdominal distension, 9%). Characteristics, including duration and severity, were not described [13]. In contrast, Kaul *et al*. [18] included only subjects presenting with multiple episodes of daily faecal incontinence. Further functional characteristics, including frequency of soiling or comorbid symptoms, were not reported [18].

DISCUSSION

A significant proportion of children with HD experience post-operative bowel dysfunction. To our knowledge, this is the first systematic review to summarize the literature relating to colonic manometry in children following surgical repair of HD. This review highlighted that despite advances in the investigation of gastrointestinal physiology, they are yet to be applied to this cohort. As a result, the persistent symptoms experienced by these children remain poorly understood.

Colonic manometry equipment and preparation

Four of five included studies utilised low-resolution, water-perfused manometry. Catheter sensor spacing ranged from five to 15cm [13, 17, 18, 20]. Describing their methodology, Kaul *et al*. [18] referenced a previously published protocol, which advocated inter-sensor spacing of 10 - 15cm [22]. However, subsequent advances in technology have seen the adequacy of this interval refuted. Namely, Dinning *et al*. [23] assessed the impact of sensor spacing on the identification and assessment of colonic motility patterns. The authors demonstrated that as sensor spacing increased, the ability to identify propagating contractions (with the exception of HAPCs) decreased. At 10cm catheter spacing, less than 5% of the propagating contractions seen at 1cm were still identified [23].

These findings were reflected in the 2018 Consensus Statement from the International Working Group for Disorders of Gastrointestinal Motility and Function [24]. This article advocates mandatory use of high-resolution colonic manometry (sensor spacing <2cm) to avoid gross misrepresentation of motility patterns [24]. No high-resolution colonic manometry studies in the post-operative HD population were identified for this review.

Motility parameters and assessment criteria

There was some consistency between manometry protocols used. Four studies included motility assessment during fasting, after a meal, and after stimulation with Bisacodyl [13, 17, 18, 20]. However, variable manometric parameters were used to assess motility. Reported standards for normal colonic motility subsequently differed.

High amplitude propagating contractions are associated with colonic mass movement and defecation [25]. In these studies, the criteria used to define HAPCs were inconsistent; however, as the motor pattern is one of the most recognizable of all colonic motor patterns, it is likely that all studies were identifying the same phenomenon. Of more concern is the criteria used to define "normal" propagation of HAPCs. Two studies classified normal HAPCs as those which terminated in the sigmoid colon, reaching the rectum only infrequently [13, 17]. In contrast, Martin *et al*. considered normal HAPCs to terminate in the rectum [20]. It must be recognized that even in healthy adults, HAPCs can terminate proximal to the sigmoid colon. "Normal" HAPCs in healthy children have never been defined.

These anatomical definitions are further complicated by the post-operative anatomy of the HD patient. As children with HD undergo surgical resection of a variable length of aganglionosis – frequently including resection of the rectum and sigmoid – reliance on the terms "rectum" and "sigmoid" to determine normal propagation lacks specificity. Standardizing the definition of location in this patient population is essential; reporting of manometry findings in this cohort should include assessment of both the distance of the sensor from the anus and its estimated post-operative anatomical location.

Normal colonic motility

Several studies reported normal colonic motility in a proportion of their population. In clinical practice, a normal manometry result may offer two benefits: the ability to provide information and reassurance to the patient, whilst avoiding unnecessary colonic interventions. Although limited symptom characteristics were provided, these patients presumably had significant bowel dysfunction, such that investigation with colonic manometry was clinically indicated. If an alternative explanation for the child's symptoms were identified in association with normal colonic motility – such as the subgroups with retentive posturing or a hypertensive anal sphincter reported by Di Lorenzo *et al*. [17] – these may be managed using targeted treatment strategies.

However, as with characteristics of "normal" HAPCs discussed above, normal colonic manometry is difficult to define. There are no accepted definitions of normal colonic motility, including in healthy adults. Definitions of normal motility, both unstimulated (fasted) or stimulated (meal response), vary amongst studies [25, 26]. In this review, the definition of a meal response differed between all studies [13, 17, 18, 20]. No colonic manometry studies have been performed in healthy children. Therefore, idiosyncratic definitions of "normal" have usually been determined by each laboratory. In 2016, a consensus document regarding colonic manometry in children proposed the study should be considered normal when a post-prandial increase in motility was observed, in association with HAPCs propagating to the rectosigmoid

[27]. The vagueness of "a post-prandial increase in motility" highlights the problem in defining normal motility. In 2019, a translational consensus statement highlighted the increasing complexity of motility insights from adult high-resolution colonic manometry, questioning the simplistic paediatric criteria [25].

With increasing uptake of high-resolution techniques, the current understanding of normal childhood motility may be replaced by a more nuanced assessment. Similarly, this is likely to be accompanied by increasingly detailed analysis of manometry data. Analysis is moving beyond simplistic measures, such as area under the pressure curve, motility index, and counts of HAPCs [13, 17, 18, 20], into measures that detail colonic motor patterns [28-30]. These developments may enable identification of symptom subtypes, with treatments ultimately targeted to a particular motility phenotype.

Increased post-operative HAPCs

Two studies quantified the number of HAPCs identified during colonic manometry [13, 18]. Kaul *et al*. [18] sought to identify whether a subgroup with frequent faecal incontinence (multiple episodes per day) demonstrated an increased mean number of HAPCs per minute (colonic hyperactivity). Colonic hyperactivity was observed in a subpopulation of children with frequent incontinence [18]. The authors contrasted their findings with those of Di Lorenzo *et al*. [17], who reported 65% of their cohort experienced faecal incontinence, associated with "normal" colonic motility in the majority [17]. However, as HAPCs were not quantified by Di Lorenzo *et al*. [17], the "colonic hyperactivity" defined by Kaul *et al*. [18] could not have been identified. In other words, children with colonic hyperactivity identified by Kaul *et al*. [18] may have been classified as demonstrating normal motility by Di Lorenzo *et al*. [17].

Jacobs *et al*. [13] explored the mechanism of increased HAPC number (HAPCs per hour), contrasting children with repaired HD, colon transection for other reasons, and normal anatomy. The HD group demonstrated a comparable number of HAPCs to children with prior colon transection. Both groups demonstrated a greater number of HAPCs than children without previous colon transection. Several mechanisms for post-operative hyperactivity have been proposed. These broadly relate to loss of inhibitory tone or an increase in excitatory inputs [13]. This finding suggests HAPCs were increased by colon transection, potentially due to the severance of an inhibitory nerve [13]. Further work is required to clarify this mechanism.

Post-operative outcome evaluation measures

The methods used to assess post-operative bowel function and quality of life were highly variable. No studies used validated measures of bowel function, symptom severity, or quality of life. Studies commonly reported only the percentage of participants with particular symptoms, without providing diagnostic criteria, characteristics, or indicators of severity. This limited characterization of bowel function impeded comparison of cohorts. Without understanding the symptom profile of each cohort, neither manometry-symptom correlates, nor the generalizability of results, may be determined.

A key indication for colonic manometry is to elucidate potential mechanisms underlying bowel dysfunction [25]. Few studies reported adequate cohort or symptom characteristics to correlate with manometry findings. Operative repair type was not specified for the majority (62.5%) of patients, whilst length of aganglionosis was provided by only one study [19]. No study reported clinical evaluation of dentate line or anal sphincter integrity; both are thought to be integral to the multifactorial faecal continence mechanism and may be disrupted during the pull-through procedure [31]. Di Lorenzo *et al*. [17] offered a detailed phenotypic classification system; however, the lack of baseline symptom data impedes comparison with other cohorts. Reporting of motility outcomes similarly lacked standardization, limiting comparability.

CONCLUSION

Our systematic review has highlighted the paucity of high-quality data informing current understanding of colonic motility in children with repaired HD. The available literature relied on variable equipment and outdated techniques. Whilst there were similarities between protocols used to conduct motility studies, studies assessed heterogeneous cohorts, reported limited comparable data, and employed variable definitions to identify motility events. Application of standardized reporting and procedure protocols would improve the consistency of research in this area.

To our knowledge, no studies have assessed the colonic motility of children with repaired HD using high-resolution manometry. Low-resolution manometry in the colon has been demonstrated to grossly misrepresent motility patterns [23]. In the esophagus, rapid uptake of high-resolution techniques has greatly enhanced understanding of esophageal function.

Given the prevalence of bowel dysfunction in children following repair of HD - and its documented impact of quality of life - improved understanding of the underlying pathophysiology is essential. This cohort would benefit from assessment with high-resolution manometry to better characterize the dysfunctional colonic motility patterns suggested by earlier studies.

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Contributors' Statement:

Dr Evans-Barns and Ms Swannjo searched the databases, coordinated data extraction, identified and analyzed articles that satisfied the inclusion criteria, and reviewed and revised the manuscript. Dr Evans-Barns drafted the initial manuscript.

Dr Trajanovska, Dr Safe, A/Prof. Dinning, A/Prof. Teague and Prof. Hutson critically reviewed and revised the manuscript for intellectual content.

A/Prof. King conceptualized and supervised the execution of the systematic review.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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TABLES

Table 1: Summary of post-operative colonic manometry studies in children with Hirschsprung disease

First author	Location Year	Cohort size (male)	HD population summary	Age at study (HD cohort)	Length of aganglionosis	Operative repair type	Post-operative outcome assessment method(s)	Reported post-operative bowel function
Di Lorenzo [17]	USA, 2000	46 (35 M)	**Symptomatic** HD patients >10 months after surgical correction. **Excluded**: total colonic aganglionosis, colostomy, ileostomy, enterocolitis.	5.5 ± 3.3 years (range 16 months - 14 years)	-	**Endorectal pull-through**: 46 (100%) Pull-through type not further specified.	Symptom prevalence Emotional and global health scored 1 - 5 (poor to excellent) Abdominal pain rated 1 - 6 (1 = very severe; 6 = no pain)	One of more of: FI = 30 (65%) Constipation = 28 (60%) Abdominal pain = 16 (35%) Emesis = 8 (17%) Diarrhea = 7 (15%) Urinary symptoms = 2 (4%)
Jacobs [13]	USA, 2015	**HD:** 56 (26 M) **Total cohort**: 500 (275 M)	Patients with repaired HD referred for colonic manometry **with demonstrated HAPCs** on the reviewed manometry study. **Excluded**: no HAPCs	7.4 ± 5 years (range <1 - 17 years)	-	**Pull-through** procedure: 56 (100% of HD sub-cohort). Pull-through type not further specified.	Symptom prevalence	One or more of: FI: 28 (50%) Constipation: 28 (50%) Diarrhea: 1 (2%) Constipation + FI: 2 (4%) Abdominal pain: 0 (0%) Other: 2 (4%)
Kaul [18]	USA, 2011	59 (48 M)	Patients with repaired HD presenting with **multiple episodes of fecal soiling daily**.	6.5 ± 3.5 years (range 16 months - 15 years)	-	**Pull-through** procedure: 59 (100%) Pull-through type not further specified.	-	Multiple daily episodes of fecal soiling
Kohno [19]	Japan, 2007	21 (18 M)	Children with short segment HD post **TAEPT**	34 months (range 26 - 52 months)	Short segment: limited to rectum or	**Transanal endorectal pull-through**: 21 (100%)	Clinical outcome evaluated based on: - requirement for enemas - number of defecations per day	Defecation frequency decreased from: - 4-5 stools per day to - 2-3 stools per day at 1 year post-op

					rectosigmoid		- severity of perianal erosion - incidence of HAEC requiring admission	Enemas: used by 4/21 (19%). Used for less than 12 months in 3/4 (75%) Perianal erosion: 3/21 (14%) HAEC: 2/21 (10%)
Martin [20]	USA, 2004	**HD**: 2 (-) **Total cohort**: 9 (-)	**Refractory colonic dysfunction** despite maximal medical therapy following repair of HD.	4.8 years (5 weeks - 17 years)	-	**Laparoscopic modified Duhamel**: 2 (100%)	Recorded data points were: - bowel movement: number, size, consistency - change in bowel medications - percentile for height and weight QoL: patient / parent report and clinician impression.	Refractory functional colonic obstruction

FI: fecal incontinence; **HAEC:** Hirschsprung associated enterocolitis; **HD:** Hirschsprung disease; **QoL:** quality of life; **TAEPT:** transanal endorectal pull

Table 2: Colonic manometry equipment and protocols reported by included studies

First author	Year	Catheter Type	Sensor spacing (cm)	Sensors (no.)	Preparation	Sedation / Anaesthetic	Catheter placement	Catheter securement
Di Lorenzo [17]	2000	WP	10-15	6 - 8	Polyethylene glycol colonic lavage.	-	Colonoscopic guidewire placement, fluoroscopic confirmation of catheter placement	Not described. Authors reference methodology of earlier paper, which reports catheters were taped to the patient's thigh [21].
Jacobs [13]	2015	WP	10-15	8	Polyethylene glycol colonic lavage	Sedation protocol changed during study. (1) Narcotics + benzodiazepines, to (2) propofol and benzodiazepines	Colonoscopic guidewire placement, fluoroscopic confirmation of catheter placement	Not described. Methods reported to comply with published standards, which advocate "careful catheter taping" [22].
Kaul [18]	2011	WP	-	-	-	-	Colonoscopic guidewire placement, fluoroscopic confirmation of catheter placement	Not described. Methods reported to comply with published standards, which advocate "careful catheter taping" [22].
Kohno [19]	2007	WP	-	-	-	No sedation	-	-
Martin [20]	2004	WP	5-10	8	Polyethylene glycol colonic lavage	-	Colonoscopic guidewire placement, fluoroscopic confirmation of catheter placement	-

HAC: high-amplitude contraction; **HAPC:** high-amplitude propagated contraction; **HD:** Hirschsprung disease; **WP:** water-perfused; (-): not reported

Table 3: Colonic manometry parameters: definitions and criteria reported by included studies.

First author	Parameters assessed	HAPC criteria	Assessment of meal response	Pharmacologic stimulation	Definitions of other included parameters
Di Lorenzo [17]	HAPCs; colonic motility index; gastrocolonic response. Motility recorded: -**Fasting**: 120 min -Balanced **meal**[1]: 60 min -Post-**Bisacodyl**[2]: 60 min	Contractions: - with an amplitude of at least **80mmHg** - lasting at least 10s - propagating at least 30cm	**Gastrocolonic response:** ≥50% increase in motility index in the hour after a meal.	Bisacodyl 0.2mg/kg	**Colonic motility index**: calculated by measuring the area under the pressure for one 30-min period before and two 30-min periods after completion of the meal.
Jacobs [13]	Number of HAPCs during fasting and post-meal. Motility recorded: -**Fasting**: 60 min -Non-standardized **meal**[3]: 60 min -Post-**Bisacodyl**[4]: 60 min	Contractions: - with amplitude of at least **60mmHg** -propagating at least 30cm	**Gastrocolonic response**: variable increase in motility that accompanies a meal	Bisacodyl 0.2-0.4mg/kg	
Kaul [18]	Mean HAPCs/min Motility recorded during fasted and postprandial states. Bisacodyl administered if no spontaneous HAPCs.	Contractions: - with an amplitude of at least **80mmHg** - lasting at least 10s - propagating at least 30cm	Assessment of meal response not reported. However, authors note that the motility index was not assessed.	Bisacodyl	**Mean HAPCs/min:** total HAPCs counted (in fasting and postprandial states) and divided by the recording duration of each phase (in minutes).
Kohno [19]	Amplitude of HAC during defecation; qualitative analysis of contraction patterns[5]; anorectal reflex Colonic manometry at three locations: (1) the **anal canal;** (2) **5 cm proximal** to the anal	Contractions: - with amplitude of more than 100cmH20 (**73.5mmHg**) - lasting at least 10s	-	-	**Amplitude of HAC** during defecation (cmH2O). **Anorectal reflex**: relaxation of anal sphincter following rectal balloon distension; not further defined.

[1] "Balanced meal individualized on the basis of age and patient preferences"; not further defined with respect to caloric or macronutrient content [17].
[2] Administered 60 min post-meal if no spontaneous or meal-induced HAPCs were observed [17].
[3] Meals administered were not standardized: children ate to their post-colonoscopy appetite; some refused to eat.
[4] Administered 60 min post-meal if no spontaneous or meal-induced HAPCs were observed [13].
[5] "Patterns of colon contractions during defecation were identified by a qualitative analysis" [19]. Not further specified.

	canal; (3) **10 cm proximal** to the anal canal, during **defecation**	*High amplitude contraction (HAC)			
Martin [20]	HAPCs; gastrocolic reflex Motility recorded: -**Fasting**: 60 min -**Meal** (standard, high-calorie for age (40% fat)): 60 min -Post-**Bisacodyl**: (-)	Contractions **>60mmHg** Velocity, propagation to rectosigmoid, cessation in less than 30cm, presence of retrograde HAPC also noted.	**Gastrocolic reflex:** represented by a HAPC arising in the mid-transverse colon and propagating to the rectosigmoid colon.	Bisacodyl 0.2mg/kg	Post-meal and post-Bisacodyl recordings evaluated for **segments that persistently failed to propagate** contractions. **Fasting patterns**: baseline rhythmicity, isolated segmental contractions, segmental burst activity[6]

HAC: high-amplitude contraction; **HAPC:** high-amplitude propagated contraction; **HD:** Hirschsprung disease; **WP:** water perfused; **(-):** not reported

[6] Fasting pattern evaluation criteria not further defined.

Table 4: Motility criteria and key findings of included studies.

First author	Criteria: normal motility classification	Criteria: abnormal motility classifications	Key findings
Di Lorenzo [17]	Propagation of HAPCs originating in the proximal colon and migrating to the sigmoid colon, rarely reaching the rectum. Gastrocolonic response present.	See: Key Findings.	Four motility groups proposed: (1) **HAPCs migrating through the neorectum** to the anal sphincter, associated with FI (n=18); **(2) Normal colonic manometry** associated with fear of defecation and retentive posturing (n=9) (3) **Absence of HAPCs** or **persistent simultaneous contractions** associated with constipation (n=13) **(4) Normal colonic manometry** and hypertensive internal anal sphincter (n=4)
Jacobs [13]	**Normal colonic motility:** HAPCs (>60mmHg that propagated >30cm) and a gastrocolonic response. In healthy subjects, HAPCs usually terminate in the sigmoid. Contractions were classified as HAPCs if they propagated >30cm, irrespective of whether they reached the neorectum. **Control groups**: children with functional constipation and chronic abdominal pain	**Absence of HAPCs**: colonic neuromuscular disease proximal to the aganglionic segment. Associated with constipation. Children who failed to produce HAPCs were excluded. **Persistent constipation associated with *normal* colonic motility (comparable to children with functional constipation):** secondary to failure to relax the internal anal sphincter (involuntary) or functional constipation. **HAPCs through neorectum to anal verge**: associated with FI.	**HD Subjects** - *Fasting*: 2.2 +/- 3.4 HAPCs/hour - *Post prandial*: 4.0 +/- 5.4 HAPCs/ hour **HD subjects with FI:** - *Fasting*: 3.8 +/- 4.1 HAPCs/hour - *Post prandial*: 6.4 +/- 6.6 HAPCs/hours **HD subjects with Constipation** - *Fasting*: 1.2 +/- 2.8 HAPCs/hours - *Post prandial*: 0.8 +/- 2.2 HAPCs/hour
Kaul [18]	*See abnormal motility classifications: HD2 "Normal".* **Normal values** for mean HAPCs/min not provided for children. Adults: 6-12 /day (up to 0.008 HAPCs/min). **Control group**: 25 children with chronic constipation found to have *normal* colonic manometry and subsequently diagnosed with functional constipation. *Normal* not further defined in this context.	**HD1:** absence of HAPCs in fasting and postprandial states **- Colonic inertia:** adynamic colon with no HAPCs in the fasting and postprandial states or in response to administration of Bisacodyl. **- Bisacodyl response:** HAPC following Bisacodyl administration. **HD2:** ≥1 HAPC (spontaneous or meal-induced) **- Normal:** as above, without meeting criteria for hyperactivity **- Hyperactive:** 2 SD above the mean frequency of HAPCs in the control group (≥0.11HAPCs/ min)	**Group HD1:** no HAPCs (21 subjects, 35%) - *Colonic inertia*: 13 (22%) - *Responded to bisacodyl:* 8 (13.5%) **Group HD2:** HAPCs (38 subjects, 65%) - *Fasting*: 0.07 HAPCs/min (0 – 0.33) - *Post prandial*: 0.13 HAPCs/min (0 – 0.45) **Colonic hyperactivity:** 40% of the HD2 group

Kohno [19]	Not defined. *Summary of discussion*: HACs used as a pseudo marker for HAPCs; HAPCs suggestive of normal colonic function.	-	HAC during defecation: 5/6 children Moderate amplitude contraction: 1/6
Martin [20]	Propagation of HAPCs from cecum to rectum, with an intact gastrocolic reflex	**Colonic dysmotility with colonic distension**[7]: low amplitude phasic contraction, intact gastrocolic reflex, presence of HAPCs that did not propagate through the dilated segment. **Persistent segmental dysmotility despite decompression**: irregular phasic contractions, absent or retrograde HAPCs, in a limited segment. **Global colonic myopathy/total colonic dysmotility:** low-amplitude phasic contractions, no HAPCs, weak gastrocolic reflex.	Global dysmotility: 2/2 (100%)

FI: fecal incontinence; **HAC**: high-amplitude contraction; **HAPC:** high-amplitude propagated contraction; **HD:** Hirschsprung disease; **SD**: standard deviation; **WP:** water perfused.

[7] Method of colonic distension assessment not described.

FIGURE AND TABLES CAPTION LIST

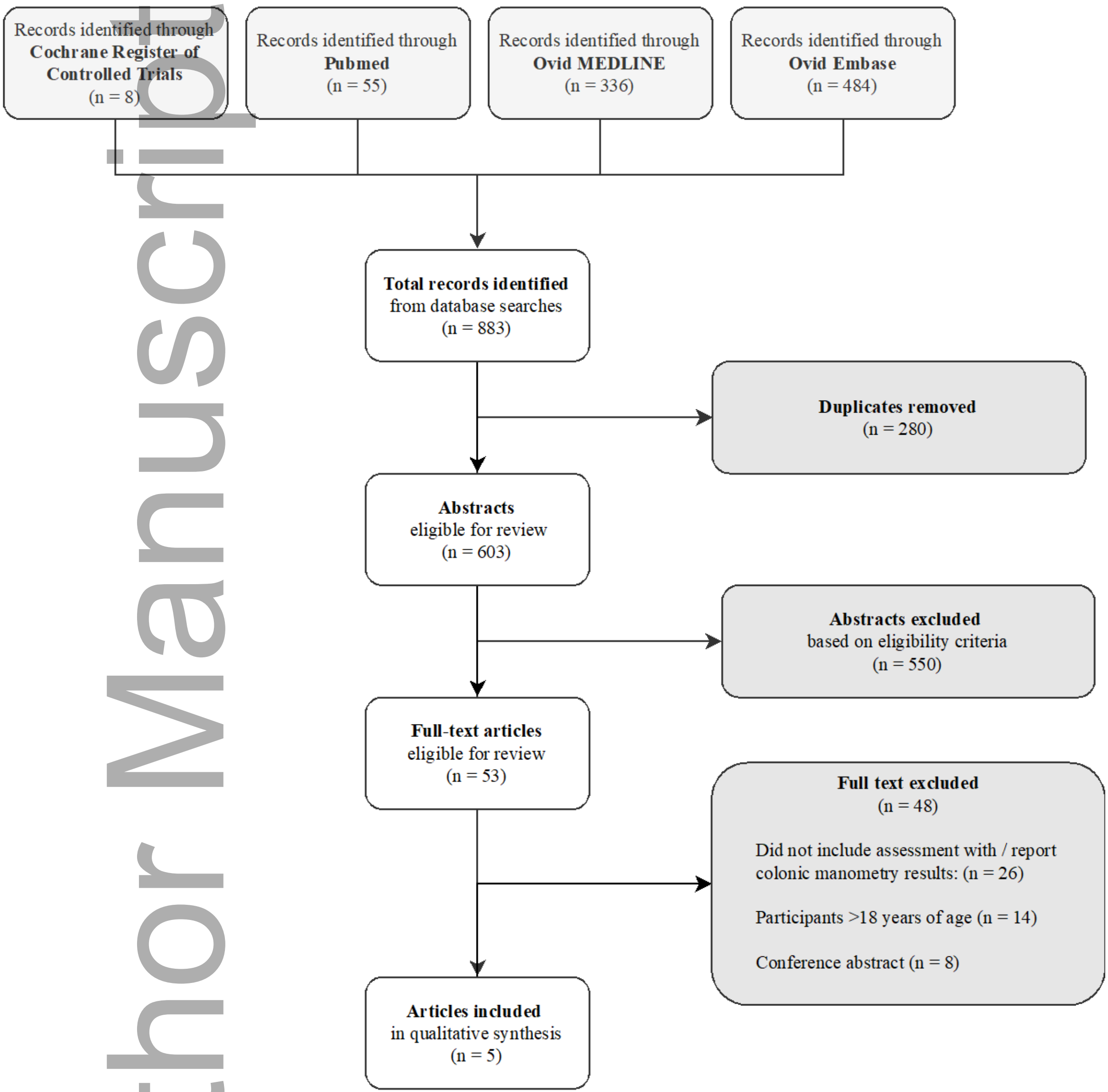

Figure 1: PRISMA flow diagram demonstrating the study selection process.