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COLONIC FUNCTION INVESTIGATIONS IN CHILDREN: POSITION PAPER BY THE ESPGHAN MOTILITY WORKING GROUP.

*A. **Rybak**[1], *M. **Martinelli**[2], N. **Thapar**[3], M.P. **Van Wijk**[4], Y. **Vandenplas**[5], S. **Salvatore**[6], A. **Staiano**[2], §M.A. **Benninga**[4], §O. **Borrelli**[1,7]

***AR and MM contributed equally to this manuscript**

§MB and OB act equally as senior authors

[1]Neurogastroenterology & Motility Unit, Gastroenterology Department, Great Ormond Street Hospital for Children, London, UK;

[2]Department of Translational Medical Science, Section of Pediatrics, University Federico II, Naples, Italy;

[3]Department of Pediatric Gastroenterology, Hepatology and Liver Transplant, Queensland Children's Hospital, Brisbane, Australia;

[4]Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, The Netherlands;

[5]KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels Belgium;

[6]Department of Pediatrics, University of Insubria, Via F. Del Ponte 19, 21100 Varese, Italy;

[7]Stem cell and Regenerative Medicine, UCL Great Ormond Street Institute of Child Health, London, UK;

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ABSTRACT

Disorders of colonic motility, most often presenting as constipation, comprise one of the commonest causes of outpatient visits in paediatric gastroenterology. This review, discussed and created by the ESPGHAN Motility Working Group, is a practical guide, which highlights the recent advances in pediatric colonic motility testing including indications, technical principles of the tests, patient preparation, performance and basis of the results' analysis of the tests. Classical methods, such as colonic transit time (CTT) with radiopaque markers and colonic scintigraphy, as well as manometry and novel techniques, such as wireless motility capsule and electromagnetic capsule tracking systems are discussed.

KEY WORDS:

Colonic motility; colonic function; colonic scintigraphy; colonic manometry; colonic transit

WHAT IS KNOWN

- Chronic constipation is one of the most common cause of outpatient visits in paediatric gastroenterology.
- Pediatric disorders of colonic motility may include a huge variety of symptoms ranging from constipation to diarrhea to bloating, abdominal pain and fecal incontinence.
- High-resolution colonic manometry has become standard of care in severe large bowel dysmotility, with increasing availability worldwide.

WHAT IS NEW

- Various methods have been standardized to investigate colonic neuromuscular function with a number of technical advances.
- Presented review, endorsed by the ESPGHAN Motility Working Group, reviews the literature of all the available techniques for the study of colonic motility function in children thought to suffer from disorders of colonic motility, in order to offer a practical guide for physicians involved in their care.

INTRODUCTION

Colonic motility is an essential component of colonic physiology controlling crucial functions such as stool propulsion, storage, and expulsion (1). Pediatric disorders of colonic motility may include a huge variety of symptoms ranging from constipation to diarrhea to bloating, abdominal pain and fecal incontinence (2). Various methods have been standardized to investigate colonic neuromuscular function with the last decade witnessing a number of technical advances, including the development of miniaturized probes, novel pressure recording systems and devices (3,4). At the same time high-resolution manometry has become standard of care and is currently available in all the major pediatric motility centers. The widespread use of this technique has allowed better characterization of colonic motor patterns and anorectal function, helping enhancing the understanding of the pathophysiology of various colonic disorders (5,6,7,8). Despite the undoubted value of these newly developed techniques, classical methods such as colonic transit time (CTT) evaluation, either with radio-opaque markers (ROM) or colonic scintigraphy, have some advantages and still retain their usefulness in the initial clinical assessment of children with defecatory disorders (9,10).

The purpose of this article is to review the literature of all the available techniques for the study of colonic motility function in children thought to suffer from disorders of colonic motility, in order to offer a practical guide for physicians involved in their care. In particular, the paper will focus on ROM colonic transit studies, scintigraphy, manometry and novel techniques, such as wireless motility capsule and electromagnetic capsule tracking systems.

The diagnostic planning and management pathway were previously described in details and is not a part of this position paper (16).

METHODS

A non-systematic literature search was carried out using PubMed and MEDLINE. Databases were searched for relevant publications in English, up to January 2021. Due to the limited number of randomized controlled trials, the cohort studies and case-controls studies addressing the topic, as well as the studies performed in adult cohorts of patients we included. Various methods for each investigations and current practice were compared, with the emphasis on their strengths and limitations. Based on pediatric data (or adult data, depending on availability), we provided guidance on protocols how to perform and interpret individual colonic function tests in children.

RADIOPAQUE MARKER COLONIC TRANSIT STUDY

ROM test is the most widely used method for estimating both total and segmental CTT, being readily available and providing an approximation of CTT with good correlation with scintigraphic techniques (11,12,13,14,15). The total and the segmental CTT are estimated by counting the number of ingested radio-opaque markers remaining in the abdomen on a simple abdominal X-ray performed at a specific pre-determined time.

Indications

Classically, the use of ROM tests allows the distinction between normal colonic transit, slow transit constipation and rectal outlet obstruction (9). Given the widespread implementation of the Rome Foundation clinical criteria for the diagnosis of functional constipation and the potential risks from repeated radiation exposure from X-rays, the latest ESPGHAN-NAPSGHAN guidelines on pediatric constipation defined specific instances for the use of CTT evaluation by ROM test (16). They recommend that these tests should not be routinely performed to diagnose functional constipation and only used for discriminating functional constipation from functional non-retentive fecal incontinence or, where the diagnosis is unclear, provide clarity and allow the selection of those children who may benefit from more invasive motility investigations (16). Figure 1 shows the indications for ROM test in the diagnostic algorithm of children with constipation.

Technical principles of the test

In the ROM test, one or more (often 3) capsules containing plastic markers, are ingested. The plastic markers contain barium salts to make them visible on X-rays. Since 1969, when ROM tests were first reported (17), different protocols have been suggested, ranging from single or multiple capsule ingestions followed by abdominal x-rays at various time points over subsequent days (9,18,19,20,21,22,23,24,25,26). The single capsule technique protocol requires the ingestion of a single ROM capsule (24 markers) on day 1, followed by either one abdominal film on day 4 or 5, or repeated abdominal images obtained every 24hr until the markers are no longer visible (27). Among the multiple capsule technique protocols, the most used methods are the Metcalf (9) and the Abrahamsson (23). The method of Metcalf is characterized by the ingestion of 20 ROM each day for 3 consecutive days followed by an X-ray taken on day 4, which can eventually be repeated on day 7 (9). The Abrahamsson method consists of the ingestion of 3 sets of distinctive pellets on 3 consecutive days followed by an x-ray on day 7 (23).

Patient preparation

The need of bowel cleansing before ROM test is a matter of discussion. In 1993, Bergin and Read, comparing CTT in 25 adults with constipation before and after bowel cleansing, showed that in the latter although the overall CTT was unchanged, the ROMs tended to shift more distally in the colon (28). More recently Quitadamo et al. enrolled 24 children and compared CTT with and without bowel cleansing (29). The authors demonstrated that colonic filling state appeared to significantly influence CTT. Indeed, the presence of a fecal mass may delay CTT, mimicking slow transit constipation (29). Thus, bowel disimpaction prior to ROM tests should be performed in order to provide a more accurate discrimination between normal and abnormal colonic transit.

During ROM test patients should remain off laxatives, unless the aim of the study is to check the effectiveness of current treatment regime or patient’s compliance.

Basics of the test analysis

Overall CTT is calculated by counting the total number of markers on the plain x-ray, whereas equations are used to calculate segmental transit (9). In details, for segmental transit time, bone landmarks (fifth lumbar vertebra and the pelvic outlet) and clear bowel outlines are used to locate markers (30). Successively, the number of retained markers for each different colonic segment (right colon, left colon and rectosigmoid region) is counted.

Finally, the use of specific formulas allows the precise estimate of colonic transit in each different segment. The most used equation is the modified Metcalf formula (19). The number of markers per segment is multiplied by 1.2, which represents the ratio between the period during which the examination is performed (72 hours) and the number of markers ingested (60), expressed in hours (19).

Normative data

Normative data for total and segmental CTT in children from six studies using multiple capsule technique protocols were summarized by Wagener et al (31). The CTT and segmental transit times in children were found to be similar to adult values. Normal mean transit time presented in a review by Southwell et al is defined as a CTT < 32 hours (upper 95th centile: 54 hours) (13). Differently, using the segmental transit times, children are considered as having slow transit constipation when there is a delay in transit, with the pellets spread throughout the colon. When the delay occurs and over 50% of the markers are held up in the rectosigmoid colon, children are labelled as having rectal outlet obstruction (13). Table 1 shows segmental transit times in healthy children reported in previous studies. Figure 2 shows examples of the CTT of children with slow transit constipation and rectal outlet obstruction.

Study by Dranove et al. on 34 children showed that CTT (authors used the oral-anal transit test) is a good tool to rule out slow transit constipation, but one should plan further investigations to assess for the location of segmental dysmotility, especially if surgical treatment is considered (32).

Limitations of the test:

Even though the ROM CTT is used to distinguish between normal colonic transit, slow transit constipation and rectal outlet obstruction, it does not provide information regarding the differentiation between dyssynergia or other causes of rectal outlet obstruction (e.g. aganglionosis, anismus, rectocele).

The utility of the CTT is limited to children able to swallow the ROM capsules or separated markers (for example mixed with spoon of thick liquid or pureed food).

It is difficult to conclude the accuracy, specificity and sensitivity of the CTT. In many published articles, CTT was performed in patients mostly referred to tertiary centers with severe chronic idiopathic constipation and none of these studies employed a gold or reference standard. Investigations in patients with severe constipation, and especially in paediatrics, rarely include blinded assessment.

Other drawbacks of CTT include radiation exposure, lack of standardized protocol across centers, need for multiple visits in some protocols, which can in turn affect compliance.

COLONIC SCINTIGRAPHY

Nuclear medicine has had a place in pediatric medicine for decades and facilities are widely accessible across tertiary care hospitals, including children's hospitals. The use of radionuclide transit studies of the gastrointestinal tract, however, are still fairly new and a standardized protocol for transit assessment of the colon is still lacking. With the increased use of colonic scintigraphy it is hoped that more data will be soon be available.

In 2005, the American Motility Society (AMS) and the European Society of Neurogastroenterology and Motility (ESNM) task force committee on gastrointestinal transit studies reached consensus on measuring gastrointestinal transit, including of the colon (33). The consensus pointed out that the ROM colonic transit study is actually a measure of whole gut transit, given it includes the transit of markers via the esophagus, stomach, small bowel and colon. Scintigraphy, on the contrary, can be executed either to assess whole gut transit or can be focused on that of the colon (33). Scintigraphy, however, only assesses bulk transit and does not allow detailed assessment of motor patterns, which may be relevant when planning targeted treatment. Of note, it has been shown that there is a fair agreement between colonic manometry and colonic scintigraphy regarding the categorization of constipation (34), but abnormal scintigraphy suggestive of colonic inertia should be confirmed in other investigations (e.g. colonic manometry) before any medical or surgical treatment is planned.

Indications

Colonic scintigraphy is a safe and non-invasive study, used as a diagnostic tool in children with chronic, refractory constipation. It helps to predict the motor function of the colon and discriminates between whole colonic delayed transit, localized colonic dysmotility and functional rectal obstruction with the hold-up of the radionuclide in the recto-sigmoid colon (35). It is also advised in patients in whom surgery is considered for slow transit constipation, if colonic manometry is not available.

Technical principles of the test

There are two options available for nuclear medicine colonic transit assessment: a delayed-release capsule (3.7 MBq ^{111}In-DTPA charcoal particles) coated with a pH-sensitive polymer (methacrylate), which dissolves in the terminal ileum, or the same isotope, ^{111}In-DTPA, dissolved in 300ml of water (3.7-7.4 MBq) followed by an unlabelled solid meal (36). The radioisotope is not absorbed in the gut. While simultaneous evaluation of the gastric emptying with Tc-99m-colloid-labelled solid test meal is usually suggested in the assessment of small bowel transit, a dual isotope acquisition is not required for the colonic transit assessment.

The test is performed over 6 hours on day 1, with subsequent imaging at 24, 48 and 72 hours (35). Movement of the radioisotope is tracked with a gamma camera. Anterior and posterior gamma camera images are obtained at specified time points. Static imaging is continued until the colon is empty or up to 5 days. At the end of the first day, activity in the colon is usually seen. If tracer is still seen in the colon by the end of the study, the patient should have bowel wash out (35).

Patient preparation

The patient is prepared with a bowel wash out to ensure that there are no impacted feces in the colon. Medications that affect colonic transit are withdrawn at least 48 hours prior to the commencement of the study, unless the purpose of the study is to assess the effectiveness of medication. The patient is fasted the night before the test. The investigation protocol and an example of colonic scintigraphic images are reported in figure 3.

Basics of the test analysis

Images are captured and analyzed according to hand-drawn regions of interest (ROI) using dedicated nuclear medicine computer software: six ROI are marked in the Mayo method (ileocecal, ascending colon, transverse colon, descending colon, rectosigmoid, and expelled stool) (37) or seven ROI in the Temple method (ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon and rectosigmoid colon, expelled stool) (38). The quantification of colon transit is based on serial measurements of the geometric center of the radioisotope (i.e. labelled liquid meal) as it moves through the colon. The geometric center (GC) is defined as the weighted average of the radioactivity over regions of the bowel and is calculated as the proportion of counts in each region multiplied by weighting factor of a specific region (1 for ascending colon, 2 for transverse, 3 for descending and 4 for rectosigmoid colon) (37). A low GC value indicates that most of the radiolabelled material is in the proximal colon, whereas a high GC value suggests that most of radioactivity is either in the distal colon or in the excreted stools.

There are three diagnostic subtypes according to the colonic scintigraphy patterns:

- Segmental colonic dysmotility (GC<4.1 at 48 and 72 hours; tracer hold-up in proximal colon);
- Slow transit constipation (GC <4.1 – slow progression of tracer at 48 and GC 4.1-6.2 at 72 hours, tracer spread throughout the colon, but majority in proximal colon);
- Functional rectal outlet obstruction (GC >4.1 at 48h – normal progression of tracer, <6.2 at 72h, tracer in descending-rectosigmoid colon- slow evacuation of tracer);

Normative data

There is little data for normal values in the pediatric population. In most pediatric studies, the normal values from studies on adults, described by Camilleri and Zinsmeister, were used (37): mean GC at 4 hours 1.2 (range 0.7–1.7); mean GC at 24 hours 2.7 (range 1.6–3.8); mean GC at 48 hours 3.9 (range 3–4.8). Tota et al. studied 15 normal children, but the results were displayed only as colonic transit time, rather than GC (39). Chitkara et al performed colonic scintigraphy in 41 of the 67 adolescents with refractory constipation who had undergone both ano-rectal manometry and balloon expulsion. The authors described colonic scintigraphy based on the Mayo method and reported values for functional constipation (GC at 24h: 1.73 +/- 0.29), functional fecal retention (GC at 24h: 2.04 +/- 0.38) and slow colonic transit (GC a 24h: ≤1.6) (40). Carmo et al., performed colonic scintigraphy in 28 children with refractory constipation. Utilizing visual analysis as a method to evaluate the progression of radioisotope through the colon, the authors described two types of colonic motor patterns: slow colonic transit, when the tracer remained mainly in the proximal and transverse colon at 48-hour scans, and distal retention, when the radioisotope had passed the transverse colon at 30 h after the study but persisted in the rectosigmoid region up to 48 h

(41). Finally, Cook at al performed colonic scintigraphy in 101 children with chronic constipation using ^{99m}TC and defining 6 intestinal regions of interest (10). The authors described 3 colonic motor patterns based on the visual analysis, namely; 1. Normal transit, when the tracer reaches the cecum by 6 hours, passed through the colon, and is largely excreted by 48 hours; 2. Slow transit, when the tracer reaches the cecum at 6 hours but most radioactivity remains in the proximal and transverse colon at 24, 30, and 48 hours; 3. Functional outlet obstruction, when the radioisotope reaches the rectosigmoid area by 24 to 30 hours but it is not evacuated at 48 hours. Moreover, the authors reported the GC for the 3 different patterns of colonic transit (Normal transit: GC at 6h: 2±0.5h, at 24h: 3.9±1.1, 48h: 5.2±0.9; Functional rectal obstruction: GC at 6h: 2±0.4, at 24h: 3.6±0.7; 48h: 5.1±0.3; Slow Transit: GC at 6h: 1.8±0.3, at 24h: 2.6±0.5, 48h: 3.7±0.9).

Limitations of the test:

Colonic scintigraphy has been shown, especially in the adult population to be a reliable, reproducible and validated study. The main drawbacks are the related to the expense, need for specialized equipment, available mainly tertiary centers and lack of standardization in pediatric cohorts of patients.

COLONIC MANOMETRY

Colonic manometry (CM) is advocated as a gold standard for assessing colonic neuromuscular function in children with intractable chronic constipation (16). It is a safe and well tolerated investigation and its availability is increasing across tertiary centers (42,43,44). By showing the extent and nature of the colonic motor abnormalities, CM has been suggested to be most useful in providing subsequent guidance for further therapy, including pharmacological and surgical management in children with intractable defecatory disorders (16,45,44,45). However, thus far, no specific predictor factors determining the clinical outcome post-surgical management have been identified.

Indications

Indications and technical characteristics of CM have been well established in the pediatric population (5). CM is used as a diagnostic tool in a variety of severe defecatory disorders (Table 2).

Technical principles of the test

A manometric system consists of a combination of pressure sensors and transducers able to detect colonic pressure activity and transduce it into electrical signals, and a recording device, which amplifies, records and stores the electrical signals generated. The pressure sensor/transducer components are available in two general system designs: water perfused and solid-state. Most commonly used catheters contain 8-36 ports or sensors at 1-5-cm intervals and a number of radiopaque markers at distinct distances along their length.

The water infusion system includes a catheter composed of small capillary tubes (recording ports), a low compliance hydraulic capillary infusion pump and external transducers. Each recording port is perfused with air-free distilled water by a low compliance pneumo-hydraulic infusion pump at a constant flow rate (0.15 mL/min) and is connected to an external transducer. The constant flow perfusion rate prevents any increase in the compliance of the manometric system. The system yields a pressure rise to a distal occlusion of >500 mmHg. When a recording port is occluded by a muscular contraction, a pressure increase is transmitted to the external transducers, then amplified, digitized and stored on a PC computer for analysis using commercially available software (46).

In the solid-state system, the manometric catheter contains along its length pressure transducers, so that intraluminal changes in pressure changes directly stimulate the transducers to generate electrical output signals. The probe is usually plugged into a small box containing the electronics, which is connected to the recording device and to a PC. The solid-sate catheters can be also suitable for ambulatory recording, which allows the measurement of colonic motor activity during representative time periods for analysis. This could be important especially in light of recent data showing the impact of the anesthesia used for colonoscopy and catheter placement on CM parameters (47).

There are advantages and disadvantages in both systems. The solid-state catheters are more expensive and fragile. Some authors find them safer in comparison to the water-perfused systems, which carry a potential risk of water overload (48). Although it has been suggested that solid-state catheters are more sensitive compared to the water-perfused assembly in recording the main colonic motor activity, more data are required to confirm the superiority of one system over the other. It should be noted, however, that most of the published pediatric data is based on the water-perfused catheters.

In the last decades, colonic manometry has improved in a step-wise fashion from few pressure-recording channels along the length of the colon to the development of high-resolution manometry (HRM), which enables the recording of intraluminal pressure from up to 72 pressure sensors spaced less than 2 cm and, hence, allows a more detailed definition of the colonic neuromuscular activity (44). At the same time, advances in computer processing allow pressure data to be presented in real time as a compact, visually intuitive ‘‘spatiotemporal plot’’ of colonic pressure activity.

The manometry catheter measures the colonic contractions across all the ports, giving the information on the amplitude of the contractions, their frequency and direction of the propagation.

Investigation protocol

The CM protocol includes preparation of the patient, catheter insertion, manometry recording and removal of the catheter (Figure 4).

Patient preparation

Preparation for CM requires planning ahead. As the placement of the manometry catheter is generally done during colonoscopy, patients need to undergo bowel cleansing using either polyethylene glycol with electrolytes (Macrogol 3350, Sodium sulphate anhydrous, Sodium bicarbonate, Sodium chloride and Potassium chloride) or stimulant laxatives (magnesium citrate with sodium picosulphate, Senna) or both, according to the investigation center’s protocol for bowel preparation. In some centers, all medications that affect colon motility are stopped 24-72 hours prior to the study. As CM is performed in patients with significant, refractory constipation, one should consider extended bowel cleansing (2-5 days) to allow optimal manometry catheter placement.

It is important to inform the patient about the nature of CM, its length and possible symptoms during the investigation. Patients should be accommodated in a dedicated manometry room or a cubicle, with a dedicated nurse during the entire recording time. Patient and caregivers should be informed about the potential complications of catheter placement and the potential side effects of the stimulant medication given during CM (abdominal cramps, frequent bowel motions) and the need to stay in bed for the 3-6 hour duration of the study. Informed consent for the placement of the catheter and procedure should be obtained prior to the investigation. The support of a play or psychologist in the period of preparation should be considered.

Catheter placement and manometry recording.

Under anesthesia, the catheter is placed in the colon either during the colonoscopy or under fluoroscopy guidance. There are different colonoscopic techniques depending on the type of catheter. Often, biopsy or grasping forceps are passed through the biopsy channel in the colonoscope, grasping the manometry catheter via a suture loop tied to the catheter tip. The catheter is then advanced alongside the colonoscope to the optimal location. Once in a desirable place, possibly into the most possible proximal portion of the colon and ideally beyond the hepatic flexure, the forceps is opened, the catheter released and the suture loop is attached to the colonic mucosa with 1-2 hemostatic clips in order to avoid the dislodgement of the catheter during the recording (Figure 5). Alternatively, in patients with cecostomy, catheter can be inserted via stoma and pulled towards rectum using the colonoscope. In some centers, especially when a more rigid solid-state catheter is used, the catheter is left in the colon without securing it to the mucosa.

The final position of the catheter is usually confirmed by plain abdominal X-ray prior to commencing the study and again at the end of the study and the colonic position of each recording port should be defined according to the position of the catheter on the X-ray (Figure 5). The visualization of the final position of the catheter is helpful in identifying any catheter loops that could impact the manometry recording and influence the final analysis.

Manometry recording starts after the child has fully recovered from the anesthesia (i.e. patient regained stable vital postoperative protective reflexes and motor functions) and the position of the catheter has been confirmed on abdominal X-ray. The investigation lasts between 3 and 6 hours, and, when possible, should include the following:

- Fasting period recording (1 hr)
- Test meal (at least 400 kcal or 20 kcal/kg, given within 30 minutes)
- Postprandial recording (1 hr)
- Stimulation test (one or two doses of bisacodyl at 0.2mg/kg and 0.4mg/kg) with 1 hr recording after each dose; administration in 5 min via central channel or via rectal tube; if normal high amplitude propagating contraction (HAPCs) are seen after the first dose of stimulant, the second dose can be omitted) (49).

- Administration of other agents, e.g. neostigmine (7.5-30 mg), can be considered if there is no response to bisacodyl, however, this should be discussed on an individual basis.
- In some children, where the measuring ports only cover the proximal colon, partial withdrawal of the manometric catheter is required in order to assess the distal colon, and a further stimulation test might be necessary.

Once the investigation is finished, the catheter is pulled out from the colon and it is important to check the presence of the clips on the suture after the removal.

In some centers, due to the evidence of the effect of anesthesia on CM parameters on the day the catheter is placed with colonoscopy, the study is extended to the following day. Arbizu et al., in a study on 60 children in whom the colonic manometry was recorded on the day of the anesthesia and the following day, showed there was significant improvement in the colonic neuromuscular function in the recording performed the day after the anesthesia compared to the recording performed the day before, and in almost 50% of the patients the interpretation of the manometry changed from abnormal to normal (47).

Basics of the test analysis

The baseline information in the CM analysis should include: i. The indication for the investigation; ii. The type of catheter used; iii. The study duration; iv. The test meal, including the total caloric intake; v. the details of the stimulation test (number of bisacodyl doses), vi. The final position of the catheter (based on the abdominal X-ray); vii. Whether the catheter required repositioning during the procedure and its final position; viii. The number of clips seen after catheter removal.

There are several phases in the colonic manometry, each one with characteristic features to be assessed during the analysis. These include assessment during fasting periods with spontaneous motor activity, the post-prandial phase assessing the gastro-colonic reflex, and the stimulation phase with the use of pharmacological stimulation of the colonic contraction (e.g. with bisacodyl given intraluminally or rectally).

The analysis includes assessment of:

- The presence of spontaneous and stimulated high-amplitude propagating contractions (HAPCs), defined as contractions migrating for at least 10-30 cm with a peak amplitude >75 mmHg (number, length of propagation, amplitude, frequency),
- The presence of quiescent periods between HAPCs, defined as no neuromuscular activity between propagated contractions;
- The presence of low amplitude propagated contractions (LAPCs), defined as contractions migrating for at least 10-30 cm with a peak amplitude <50 mmHg;
- The presence of antegrade and retrograde segmental contractions (repetitive propagating pressure events with cyclic frequency of 2–6 cycles per minute; nonpropagating activity

- The pre-prandial and postprandial long single motor pattern;
- The presence of gastro-colonic response to food: pre- and postprandial motility index (MI), defined as the mean amplitude of all contractions, across all channels, calculated 30 min before and 30 min after test meal;
- The presence of colo-rectal reflex (relaxation of the anal sphincter with HAPC) (50,51,52).

Amongst features of normal colonic motility, HAPCs are the most easily recognizable and reliable motor patterns (Figure 6). They are initiated usually in the proximal colon and expected to stop at the recto-sigmoid junction. Based on their propagation, HAPCs are usually classified as: 1. Fully propagated, when the sequences reach the sigmoid colon; 2. Partially propagated, when HAPCs stop at the level of the splenic flexure or the descending colon (Left colonic dysmotility); 3. Absent HAPCs, when no sequences are observed in the entire colon (pan-colonic dysmotility/neuropathy). Based on the morphology of pressure waves within each sequence, HAPCs can be classified as normal and abnormal. Abnormal morphology is defined by the presence of contraction duration >30 seconds or the presence of two or more pressure peaks (44).

Normative data

There are no published data on normal values in CM in the pediatric population and the analysis is based on the recognition of the visual patterns (HAPCs, LAPCs, clusters of contractions, colo-anal reflex), therefore open to interobserver variability. Colonic motor patterns have been well described in healthy adult populations (53,54,55).

Limitations of the test:

Colonic manometry can be a difficult test for a child. It is an invasive test and the necessity of the general anesthesia and the long duration of the test after anesthetic recovery can be a limiting factor for some pediatric patients with complex medical conditions or behavioral issues. Age can be potential limiting factor depending on the size of the catheter and endoscope. In some centers, the investigation is abandoned in the presence of colonic inflammation. The availability of the test is limited to few specialized centers worldwide.

WIRELESS CAPSULE

The WMC is a novel, non-radioactive and minimally invasive tool for the assessment of colonic motor function, approved by the FDA in July 2006 for use in adult patients (56,57,58,59). Most of the investigations have been reported in adults, with only 1 pediatric study demonstrating its feasibility and safety in children ≥8 years old presenting with upper gastrointestinal symptoms (3).

Indications and test description

The WMC, named SmartPill (SmartPill Corporation, Buffalo, NY), has similar dimensions to a video-capsule (26 mm by 13 mm) and contains a battery for 5 days' use, a data transmitter, and sensors to measure temperature (range of 25–49°C), pH (range of 0.05–9.0 pH units), and pressure (range of 0–350 mmHg) (50). The pH allows the identification of the location within the bowel, while the temperature is used to understand when the capsule is expelled. The pressure sensor is able to measure visceral pressure and contractility (50). The test is usually performed after an overnight fast and the capsule, once activated, is ingested just before a standardized meal. During the following 3-5 days patients are asked to proceed with their usual routine behaviors, except for strenuous physical activities, which can affect pressure measurements (58). The WMC continuously transmits data about pH, temperature, and pressure to a data receiver and, by analyzing all the measurements, it is possible to estimate gastric emptying, small bowel transit time, CTT, and whole gut transit time (WGTT). In addition, the WMC is able to generate a colonic pressure profile, without the need for invasive procedures or radiation exposure (60).

Evidence from adult data

In 2009 Rao et al. performed a multicenter study simultaneously administering the WMC and ROM in 78 adults with constipation versus a control group of healthy patients (58). No adverse events occurred in any patient ingesting the capsule. The group of constipated patients showed significantly slower transit times on Day 2 and Day 5 x-rays and the WMC measures of transit significantly correlated with those of the ROM on both days (Day 2/Day 5) (r= 0.74/r=0.69 for constipated subjects, r=0.70/r=0.40 in controls). Overall, the diagnostic accuracy of the WMC CTT to predict constipation from ROC analysis was 0.73, with a specificity of 0.95 and a normal CTT using the WMC was estimated from 24 to 59 h (58). In 2010 Camilleri et al. conducted a prospective, multicentre trial comparing ROM versus WMC in 158 adults with chronic constipation (59). The authors demonstrated good agreement between the two methods, up to 80% in the evidence of delayed transit and up to 91% when there was no evidence of impaired transit (59). In 2015, Wang et al. reported the results of a large, prospective study performed between Sweden and US on 215 healthy volunteers with the aim of evaluating the effect of testing protocol, gender, age and study country on gastric, small bowel, colonic and WGTT (61). The authors clearly demonstrated that if the WMC is not expelled within 72 h, transit through the whole gut is pathologically delayed. The authors also showed that regional gastrointestinal transit times differ depending on test protocol, gender, age and country of the study. With regards to pressure measurements, only one study by Hasler et al. reported significant differences in the contractility patterns of constipated patients versus healthy controls (60). However, the usefulness of WMC in evaluating colonic contractility is strongly limited by its single pressure sensor, which does not allow the characterization of propagating contractions (50).

Therefore, adult studies provide evidence that the WMC gives an accurate estimate of CTT and has good agreement with ROM studies. Its usefulness in measuring colonic pressure profile has to be further evaluated and also compared with manometric assessments. Considering its safety and low invasiveness, clinical trials in children are urgently needed in order to validate its use within clinical pediatric gastrointestinal scenarios.

ELECTROMAGNETIC CAPSULE TRACKING SYSTEM (MM)

An alternative approach for the study of colonic function is represented by the use of electromagnetic tracking systems (62). The first electromagnetic capsule system has been reported by Hiroz et al in 2009 and consisted of the stationary MTS 1, which was based on a permanent magnet and required the subject to be placed in a nonmagnetic bed during the entire examination (62). The system has been progressively improved until 2014, when the results of Motilis 3D-Transit (Motilis Medica SA, Lausanne, Switzerland) were reported (63). The 3D-Transit is able to simultaneously track the position and the orientation of up to 3 electromagnetic capsules from ingestion to expulsion (63).

Indications and test description

The Motilis 3D-Transit system consists of ingestible electromagnetic capsules (dimensions: 21.5 mm x 8.3 mm), which when activated emit an electromagnetic tracking signal that is detected by an external detector positioned over the abdomen (63,64,65,66). The system allows signal monitoring for between 60 and 120 hours. Once a recording is complete, the data are downloaded to a computer and converted into 3D-spacetime coordinates using dedicated software (version 0.4, Motilis Medica, SA, Lausanne, Switzerland), which enables visualization of the 3D-position and the changes in 3D- orientation of capsules within the GI tract (63). In the original protocol, following an overnight fast, the subjects swallow the first capsule after a standardized breakfast, the second capsule after the evening meal and the third capsule following the breakfast on day 2 (63). Therefore, the Motilis 3D-Transit system allows the ambulatory evaluation of WGTT and segmental transit times with clear advantages in comparison with the other tests, such as the avoidance of radiation, the precise assessment of progression and the simultaneous tracking of more than one capsule (inter-segmental interactions). Of note, when compared with the WMC, the 3D-Transit system offers a better estimate of segmental transit time, since the WMC only relies on pH differences between the different segments of the gastrointestinal tract (63,64,65,66). Additionally, as recently reported, the 3D-Transit system is able to provide detailed information about colonic motility patterns (67).

Evidence from adult data

The first report of the 3D-Transit system comes from Haase and colleagues (62). In 2014 the authors enrolled 20 healthy subjects, who underwent both 3D-transit and ROM markers in order to compare WGTT and segmental transit time assessed with each method. No adverse event was registered. WGTT assessed by 3D-Transit capsules moderately correlated with standard ROM (Spearman's rho = 0.7). In addition, the authors reported an inter-observer agreement of 100% (62). These data were confirmed by 2 successive studies conducted by Mark and colleagues (64) and Kalsi et al (65). More recently, Nandhra et al. derived the normative values of WGTT and segmental transit time from a large cohort of 111 healthy volunteers (66). Among the huge amount of data coming from this study, the authors confirmed that CTT and WGTT were observed to cluster at intervals separated by approximately 24 hours, providing further evidence of the non-continuous nature of these measurements. The main factors influencing WGTT and CTT were age, gender and BMI (66). In 2019, Mark and colleagues described the usefulness of 3D-Transit system in the evaluation of colonic motility patterns, summarizing the results of 3 different trials (67). In details, the authors were able to identify the classical 5 colonic motility patterns (long fast antegrade, fast antegrade, slow antegrade, fast retrograde and slow retrograde).

Thus, adult studies identify the 3D-Transit system as a very promising tool to investigate colonic transit time and motility. No pediatric study has yet been performed, although possible drawbacks may include the difficulty of ingesting 3 different capsules.

CINE (MOTILITY) MRI

Data regarding the use of MRI to assess the gastrointestinal motility is increasing in the last few years, but is mostly adult (68,69). It is a non-invasive tool with the application of a high resolution spatio-temporal technique to facilitate dynamic MRI (cine MRI) and allow visualization of the bowel lumen diameter (69).

In the literature, cine MRI is described in the assessment of the stomach accommodation and emptying (70), the motility of the terminal ileum in adult and pediatric patients with Crohn's disease (71,72), and the small bowel in patients with chronic intestinal pseudo-obstruction syndrome (73) . Recently, a preliminary study on the validation of the cine MRI was published, describing the spatio-temporal mapping technique capable of capturing contractile activity in the gastrointestinal tract, mainly stomach and ascending colon (69). Vriesman et al. published the first pediatric study with simultaneous assessment of the colon motility using colonic manometry and cine MRI, proving potential feasibility of the technique (74).

The benefits of the cine MRI may address at least some of the limitations of manometry. The advantage of cine MRI is that it is non-invasive, omits the need for general anesthesia or sedation, which in younger patients can become a limitation and affect gut motility, and is increasingly available especially given the growing number of post-processing software available for the automated quantitation of the colonic motility. However, this investigation remains a research-based modality and further studies are needed to establish objective and systematic measurement of the colonic motility.

SUMMARY

During the past decades substantial efforts have been made to improve the assessment of colonic neuromuscular function by evolving old technologies and implementing new ones. In the present review we have described different methodologies for assessing colonic function, and although all of them are able to enlighten our understanding of the underlying mechanism of refractory defecatory disorders, one common trait is represented by the lack of pediatric normative data. Moreover, for all the aforementioned tests currently used in clinical practice, there is still significant variability in terms of equipment and protocols among centers, which in some cases might lead to conflicting results. Hence, it is also important to unify the protocols for the investigations to generate reproducible data.

One needs to appreciate that the measurement of colonic transit does not provide a direct measurement of colonic neuromuscular function, hence, a single study to assess colonic motor function might not be sufficient and often clinicians need to reach out for various methods, depending on the severity of the problem and interpret them in the clinical context. With new techniques on the horizon, like the motility MRI, careful planning of multicentre research projects in pediatric cohorts with chronic constipation should be considered.

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Figure 1. Radiopaque marker colonic transit study test – protocol for either 1 or 3 sets of ROM (see text) and interpretation in the diagnostic algorithm of constipated children.

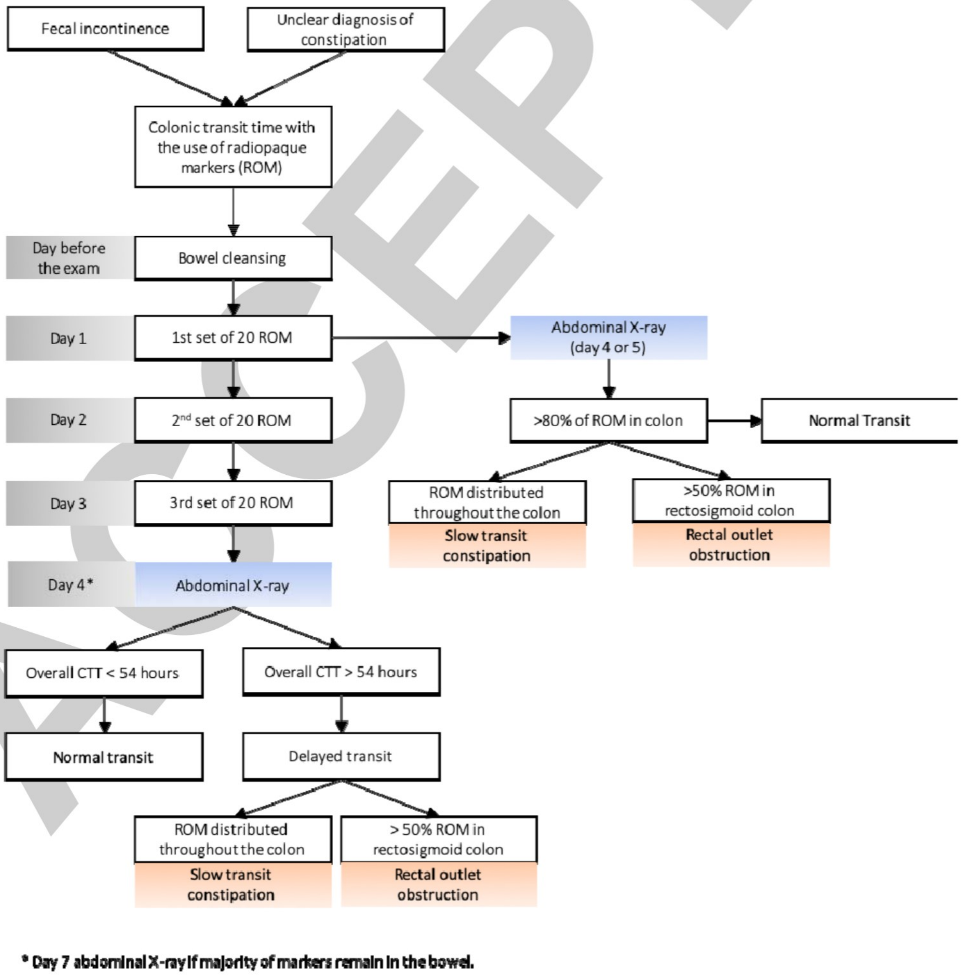

Figure 2. Colonic transit study. A – slow transit constipation; B – rectal outlet obstruction. R: right colon; L: left colon; RS: recto-sigmoid colon.

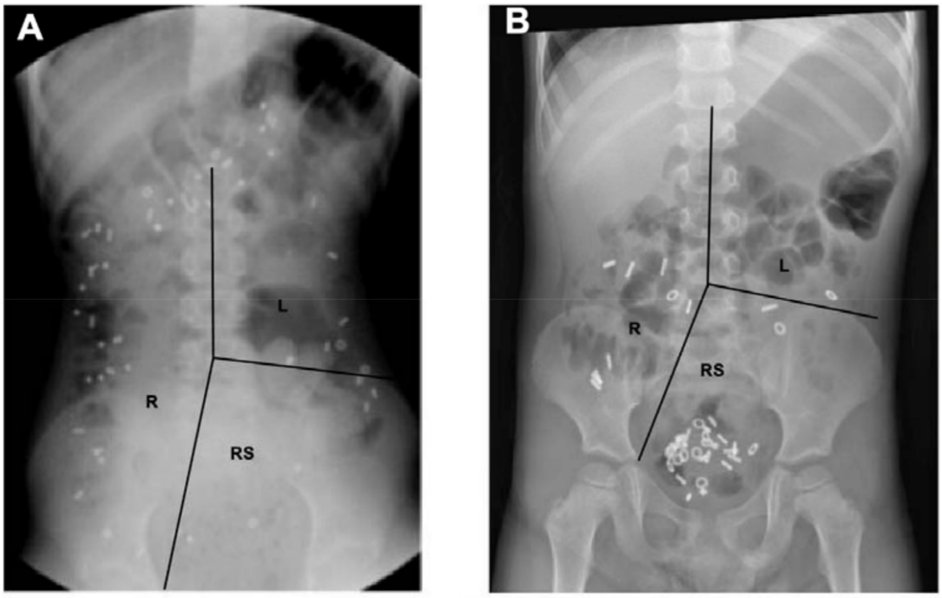

Figure 3. The investigation protocol and an example of normal colonic scintigraphy images (Courtesy of Dr Lorenzo Biassoni, Consultant in Nuclear Medicine, Nuclear Medicine Unit, Radiology Department, Great Ormond Street Hospital).

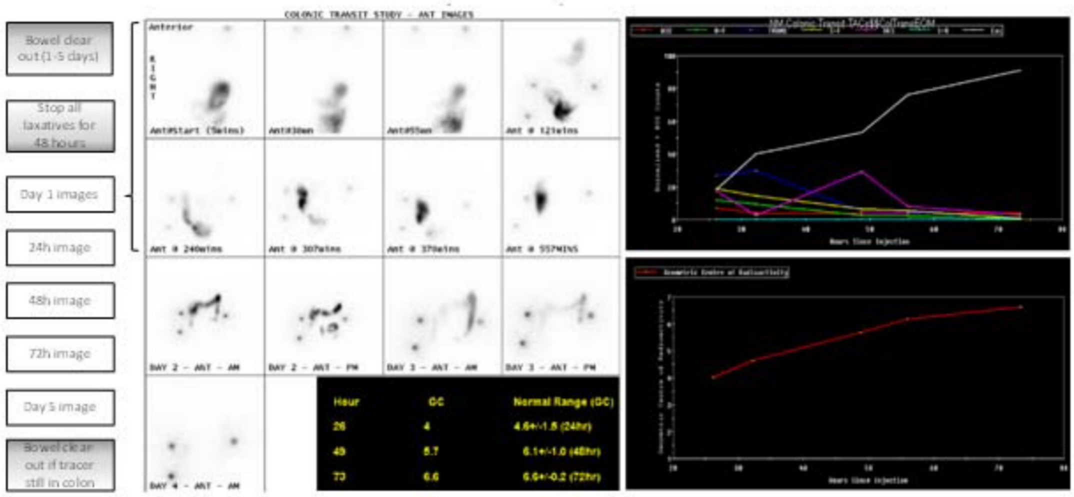

Figure 4. Colonic manometry – investigation protocol. A second day recording can be considered (see text).

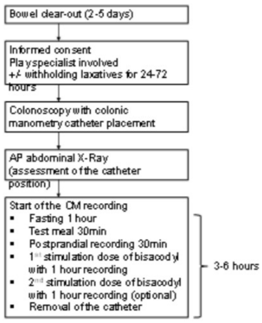

Figure 5. Manometry catheter placement in the colon. Arrow indicates hemostatic clips attaching the thread knotted on the catheter, to the colonic mucosa.

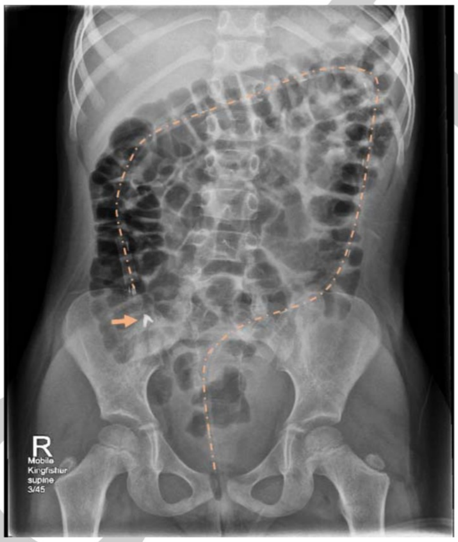

Figure 6. High-resolution and spatio-temporal plot of the colonic high amplitude propagated contractions (HAPCs). A – normal colonic motility; B – left colonic neuropathy; C – pancolonic dysmotility.

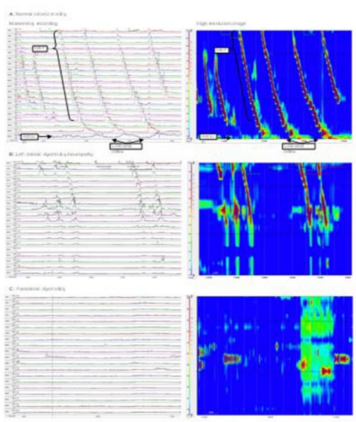

Table 1. ROM normative values for segmental colonic transit time in healthy children

1st author, year, ref	Age range (years)	X-Ray (day)	Right colon*	Left colon*	Rect/Sig*
Arhan 1981 (30)	2-15	Daily	7.7	8.7	12.4
Casasnovas 1991 (19)	10-14	4	10.8 ± 3.5	12.2 ± 2.7	14.7±2.1
Zaslavsky 1998 (21)	12-18	4	6.7 ± 3.9	7.9 ± 7.8	15.6±10.7
Gutierrez 2002 (24)	2-14	7	7.25 ± 5.75	6.6 ± 6.2	14.96±8.7
Wagener 2004 (31)	4-15	7	5.5 ± 4.4	6.1 ± 5.4	8.2±13.3
Park 2004 (25)	2-10	4	3.1 ± 4.2 *(ac)*	5.1 ± 4.9 *(dc)*	7.4±4.9
Vande Velde 2013 (26)	3-18	7	4.8 (0-28.8)	2.4 (0-31.2)	24 (0-64.8)

*Segmental transit times are expressed in hours as mean, mean ± 2 SD or median and range; ac: ascending colon; dc: descending colon; rect/sig: rectosigmoid colon; ref: reference

Table 2. Indications for colonic manometry assessment.

• Assessment of colonic motor activity in children with persistent constipation unresponsive to conventional therapy.
• Assessment of the presence of colonic involvement in children with pediatric intestinal pseudo-obstruction (PIPO) (40).
• Assessment of colonic motor activity in children and adolescent undergone surgery for Hirschsprung's disease with persistent symptoms lower GI symptoms.
• Assessment of colonic motor function prior to intestinal transplantation.
• Evaluation of the motor function of a diverted colon before possible closure of a diverting ostomy.
• Prediction of the response to antegrade enemas via cecostomy.